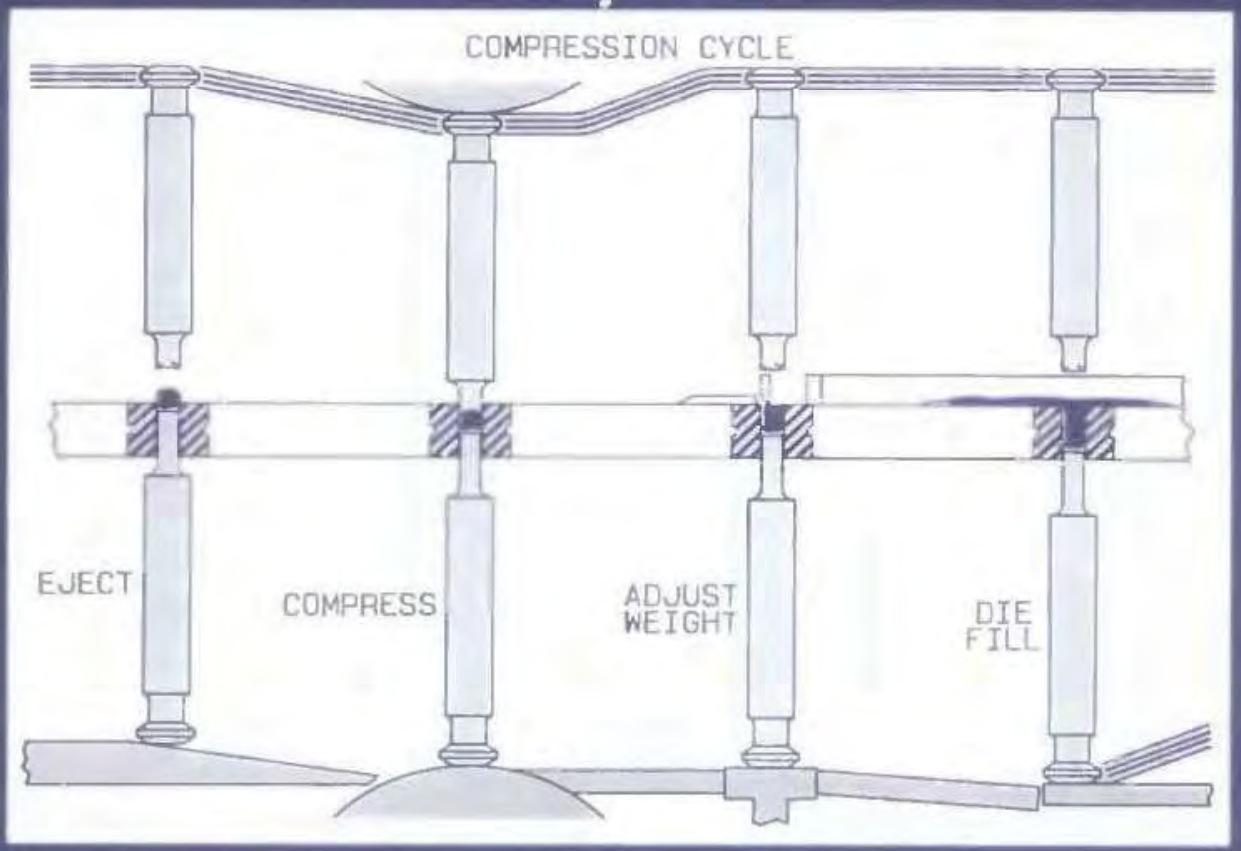
Copyrighted Material

Pharmaceutical Dosage Forms: Tablets Volume 1

Second Edition, Revised and Expanded

Edited by Herbert A. Lieberman, Leon Lachman, and Joseph B. Schwartz



CELGENE 2144
APOTEX v. CELGENE
IPR2023-00512

Copyrighted Material

PHARMACEUTICAL DOSAGE FORMS

Tablets

SECOND EDITION, REVISED AND EXPANDED

In Three Volumes
VOLUME 1

EDITED BY

Herbert A. Lieberman
H H Lieberman Associates, Inc
Consultant Services
Livingston, New Jersey

Leon Lachman
Lachman Consultant Services
Westbury, New York

Joseph B. Schwartz
Philadelphia College of Pharmacy and Science
Philadelphia, Pennsylvania



MARCEL DEKKER, INC. NEW YORK · BASEL · HONG KONG

Library of Congress Cataloging-in-Publication Data

Pharmaceutical dosage forms--tablets / edited by Herbert A. Lieberman, Leon Lachman, Joseph B. Schwartz. -- 2nd ed., rev. and expanded.
p. cm.
Includes index.
ISBN 0-8247-8044-2 (v. 1 : alk. paper)
1. Tablets (Medicine) 2. Drugs--Dosage forms. I. Lieberman, Herbert A. II. Lachman, Leon. III. Schwartz, Joseph B.
[DNLM: 1. Dosage Forms. 2. Drugs--administration & dosage. QV 785 P535]
RS201.T2P46 1989
615'.191--dc19
DNLM/DLC 89-1629
for Library of Congress CIP

Copyright © 1989 by MARCEL DEKKER, INC. All Rights Reserved

Neither this book nor any part may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, microfilming, and recording, or by any information storage and retrieval system, without permission in writing from the publisher.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

Current printing (last digit):
10 9 8 7 6

PRINTED IN THE UNITED STATES OF AMERICA

PHARMACEUTICAL DOSAGE FORMS

Preface

Several years have passed since the first edition of *Pharmaceutical Dosage Forms: Tablets* was published. During this time, considerable advances have been made in the science and technology of tablet formulation, manufacture, and testing. These changes are reflected in this updated, revised and expanded second edition.

The tablet dosage form continues to be the most widely used drug delivery system for both over-the-counter and prescription drugs. The term *tablet* encompasses: the usual compressed tablet; the compressed tablet that is sugar- or film-coated to provide dissolution in either the stomach or the intestine, or partially in the stomach and partially in the intestine; layered tablets for gastric and intestinal release; effervescent tablets; sustained-release tablets; compressed coated tablets; sublingual and buccal tablets; chewable tablets; and medicated lozenges. These various dosage forms are described in depth in the three volumes of this series.

In the first volume, the various types of tablet products are discussed; the second volume is concerned with the processes involved in producing tablets, their bioavailability and pharmacokinetics; and in the third volume, additional processes in tablet production are discussed, as well as sustained drug release, stability, kinetics, automation, pilot plant, and quality assurance.

The first chapter in Volume 1 describes "Preformulation Testing." This second edition of the chapter contains an extensive amount of new material on substance purity, dissolution, the concept of permeability, and some of the pharmaceutical properties of solids. In the second chapter, "Tablet Formulation and Design," the plan for developing prototype formulas has been revised and an approach, using statistical design, is presented. There is consideration given to those elements in tablet formulation that are of importance to the operation of tablet presses with microprocessor controls.

There have been so many advances in the technology of wet granulation and direct compression methods since the first edition that what had previously been one chapter has now been expanded into two chapters.

"Compressed Tablets by Wet Granulation" has been updated, and a new section on unit operations has been added. Information on the formulations of sustained-release tablets by wet granulation is included in the chapter. "Compressed Tablets by Direct Compression," a separate chapter new to this edition, contains: a table comparing all aspects of direct compression versus wet granulation; an extensive glossary of trade names and manufacturers of tableting excipients; a section on morphology of pharmaceutical excipients, including scanning electron photomicrographs; a discussion of direct compression of example active ingredients; and a considerably expanded section on prototype or guide formulations.

The chapter entitled "Compression-Coated and Layered Tablets" describes the current technology for making these types of tablets. The chapter "Effervescent Tablets" has been expanded to include fluid-bed granulation techniques, updating on stability testing methods, new packaging materials, and methodologies for checking airtightness of sealed packets. The chapter on "Special Tablets" now contains information on long-acting and controlled-release buccal tablets as well as new sections on vaginal and rectal tablets. The chapter "Chewable Tablets" has increased its coverage to include microencapsulation and spray coating techniques. This chapter includes an update of the information concerned with excipients, colorants, direct-compression chewable tablets, and current manufacturing and product evaluation procedures related to these tablets. "Medicated Lozenges," the final chapter in Volume 1, has increased its scope to include liquid-center medicated lozenges and chewy-based medicated tsblets.

Each of the tablet forms discussed requires special formulation procedures. Knowing how to make a particular type does not guarantee knowledge of how to make another. Since considerable expertise is required for the myriad tablet dosage forms, a multiauthored text seemed to be the only way to accomplish the editors' goals of providing knowledgeable and complete coverage of the subject. The editors chose authors to describe particular types of tablets on the basis of their experience, training, and high degree of knowledge of their subjects.

The authors were charged with the task of covering their technology in a way that would not be merely a review of the literature. Each chapter begins by assuming the reader is not very familiar with the subject. Gradually, as each chapter develops, the discussion becomes more advanced and specific. Following this format, we have intended the text to be a teaching source for undergraduate and graduate students as well as experienced and inexperienced industrial pharmaceutical scientists. The book can also act as a ready reference to all those interested in tablet technology. This includes students, product development pharmacists, hospital pharmacists, drug patent attorneys, governmental and regulatory scientists, quality control personnel, pharmaceutical production personnel, and those concerned with production equipment for making tablets.

The authors are to be commended for the manner in which they cover their subjects ss well as for their patience with the editors' comments concerning their manuscripts. The editors wish to express their special thanks to the contributors for the excellence of their works, as well as for their continued forbearance with our attempts to achieve our desired level of quality for this text. Although there has been a great deal written about various types of tablets, it is only in this multivolume treatment that this subject is completely described. The acceptability and usefulness

of these volumes is attributable to the efforts and skills of all of the contributing authors.

The topics, format, and choice of authors are the responsibilities of the editors. Any multiauthor book has problems of coordination and minimizing repetition. Some repetition was purposely retained because, in the editors' opinions, it helped the authors to develop their themes and because each individual treatment is sufficiently different so as to be valuable as a teaching aid. The editors hope that the labors of the contributors and our mutual judgments of subject matter have resulted in an up-to-date expanded reference that will facilitate the work of the many people who use it.

Herbert A. Lieberman
Leon Lachman
Joseph B. Schwartz

Contents

Preface		iii
Contributors		xi
Contents of	*Pharmaceutical Dosage Forms: Tablets, Second Edition Volumes 2 and 3*	xiii
Contents of	*Pharmaceutical Dosage Forms: Parenteral Medications, Volumes 1 and 2*	xv
Contents of	*Pharmaceutical Dosage Forms: Disperse Systems, Volumes 1 and 2*	xxx

Chapter 1.	Preformulation Testing	1
	Deodatt A. Wadke, Abu T. M. Serajuddin, and Harold Jacobson	
I.	Introduction	1
II.	Organoleptic Properties	2
III.	Purity	3
IV.	Particle Size, Shape, and Surface Area	5
V.	Solubility	12
VI.	Dissolution	18
VII.	Parameters Affecting Absorption	24
VIII.	Crystal Properties and Polymorphism	34
IX.	Stability	42
X.	Miscellaneous Properties	53
XI.	Examples of Preformulation Studies	57
	References	69
Chapter 2.	Tablet Formulation and Design	75
	Garnet E. Peck, George J. Baley, Vincent E. McCurdy, and Gilbert S. Banker	
I.	Introduction	75
II.	Preformulation Studies	77
III.	A Systematic and Modern Approach to Tablet Product Design	79
IV.	Tablet Components and Additives	88
V.	Regulatory Requirements for Excipients in the United States	121
VI.	References	128

Chapter 3. Compressed Tablets by Wet Granulation 131

Fred J. Bandelin

I. Properties of Tablets 132
II. Formulation of Tablets 133
III. Tablet Manufacture 135
IV. Granulation 148
V. Excipients and Formulation 151
VI. Multilayer Tablets 179
VII. Prolonged Release Tablets 181
VIII. Manufacturing Problems 188
References 190

Chapter 4. Compressed Tablets by Direct Compression 195

Ralph F. Shangraw

I. Introduction and History 195
II. Advantages and Disadvantages of the Wet Granulation Process 197
III. The Direct-Compression Process 198
IV. Direct-Compression Filler Binders 203
V. Factors in Formulation Development 214
VI. Morphology of Direct-Compression Fillers 220
VII. Coprocessed Active Ingredients 225
VIII. Modification and Integration of Direct-Compression and Granulation Processes 227
IX. Future of Direct-Compression Tableting 228
X. Formulations for Direct Compression 229
Glossary of Trade Names and Manufacturers 243
References 245

Chapter 5. Compression-Coated and Layer Tablets 247

William C. Gunsel and Robert G. Dusel

I. Compression Coating 247
II. Formulations (Compression Coating) 260
III. Inlay Tablets 273
IV. Layer Tablets 274
V. Formulations (Layer) 278
References 284

Chapter 6. Effervescent Tablets 285

Raymond Mohrle

I. Introduction 285
II. Raw Materials 286
III. Processing 294
IV. Manufacturing Operations 300
V. Tablet Evaluation 302

VI. Effervescent Stability 304
VII. Effervescent Formulations 320
VIII. References 326

Chapter 7. Special Tablets 329

James W. Conine and Michael J. Pikal

I. Drug Absorption Through the Oral Mucosa 329
II. Molded Sublingual Tablets 334
III. Special Problems with Molded Nitroglycerin Tablets 340
IV. Compressed Sublingual Tablets 354
V. Buccal Tablets 356
VI. Vaginal Tablets 359
VII. Rectal Tablets 360
VIII. Dispensing Tablets 362
IX. Tablets for Miscellaneous Uses 363
References 364

Chapter 8. Chewable Tablets 367

Robert W. Mendes, Aloysius O. Anaebonam, and Jahan B. Daruwala

I. Introduction 367
II. Formulation Factors 368
III. Formulation Techniques 371
IV. Excipients 382
V. Flavoring 387
VI. Colorants 392
VII. Manufacturing 396
VIII. Evaluation of Chewable Tablets 406
IX. Summary 415
References 415

Chapter 9. Medicated Lozenges 419

David Peters

I. Hard Candy Lozenges 419
II. Processing 445
III. Formulations (Hard Candy Lozenges) 497
IV. Center-Filled Hard Candy Lozenges 501
V. Formulations (Center Filled Lozenges) 509
VI. Packaging 511
VII. Chewy or Caramel Base Medicated Tablets 520
VIII. Formulations (Chewy Based Confections) 541
IX. Compressed Tablet Lozenges 543
X. Manufacturing: Compression Sequence 558
XI. Typical Formulations (Compressed-Tablet Lozenges) 565

XII. Quality Control Procedures 567
References 576
Suggested Reading 580

Index 583

9

Medicated Lozenges

David Peters*

Warner-Lambert Company, Morris Plains, New Jersey

Lozenges are flavored medicated dosage forms intended to be sucked and held in the mouth or pharynx [1,85]. They may contain vitamins, antibiotics, antiseptics, local anesthetics, antihistamines, decongestants, corticosteroids, astringents, analgesics, aromatics, demulcents, or combinations of these ingredients [2]. The oropharyngeal symptoms which lozenges are intended to relieve are commonly caused by local infections and occasionally by allergy or drying of the mucosa from mouth breathing.

Lozenges may take various shapes, the most common being the flat, circular, octagonal, and biconvex forms. Another type, called *bacilli*, are in the form of short rods or cylinders. A soft variety of lozenge, called a *pastille*, consists of medicament in a gelatin or glycerogelatin base or in a base of acacia, sucrose, and water. Confections (now obsolete) are heavily sugared soft masses containing medicinal agents [3].

Two types of lozenge bases have gained wide usage because of their ready adaptation to modern high-speed methods of product manufacture. These two lozenge forms, which will be discussed in detail, include hard (or boiled) candy lozenges and compressed tablet lozenges.

I. HARD CANDY LOZENGES

Hard candy is a mixture of sugar and other carbohydrates that are kept in an amorphous or glassy condition [4]. This form can be considered a solid syrup of sugars generally having from 0.5 to 1.5% moisture content.

Essentially, the preparation of hard candy lozenges can be considered an art. Many of the formulations used in confectionary manufacturing, and the rationale used for solving problem areas, are based on experience and intuition rather than scientific deduction. The confectionary equipment utilized by the manufacturer of lozenges is suitable for the preparation of

*Current affiliation: Treworgy Pharmacy, Calais, Maine

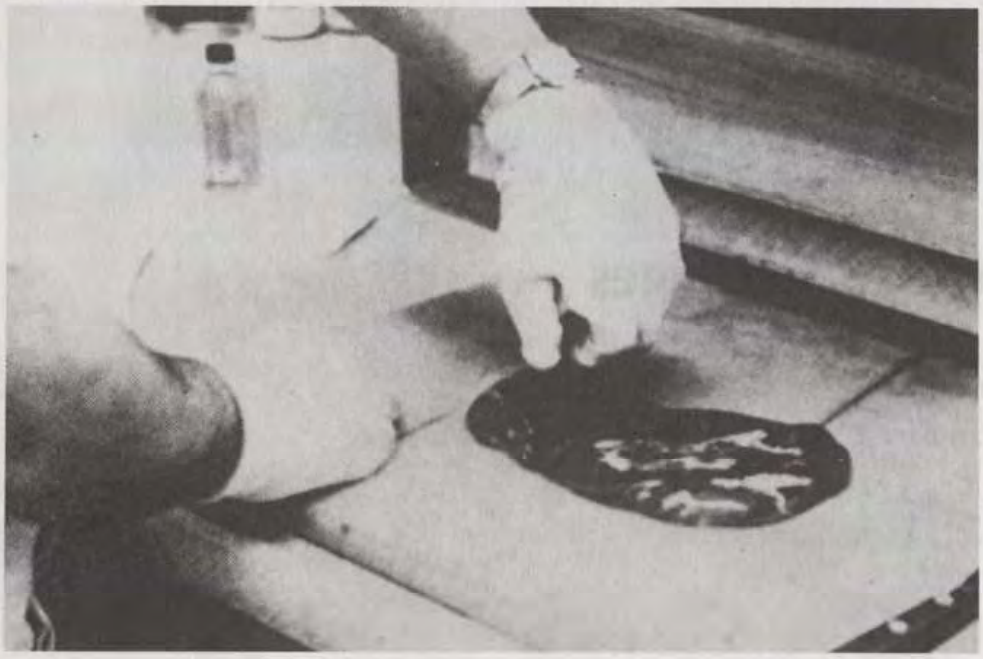
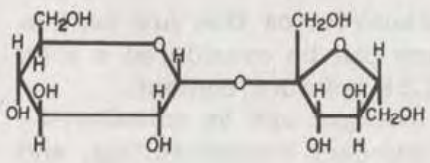


Figure 1 Mixing of flavors and medicinals by hand. Preparation of 1- or 2-kg laboratory batches enables the formulator to evaluate potential problem areas that may develop when flavor or medicament is incorporated into hard candy base. (From Ref. 24.)

candies but is not designed to produce a controlled and reproducible medicated candy with close tolerances as to size, weight, and quantity of drug concentration per unit dose. The formulator must gain a comprehensive knowledge of the physical and chemical qualities of raw materials in the product and become familiar with all aspects of candy base production in order to prepare a medicated product that conforms to the specifications for good manufacturing procedures (Figures 1 and 2). A review of possible shelf life problems must be determined through stability testing after the product is manufactured. The formulator, in essence, is required to bring a scientific approach to an empirical art.

A. Raw Materials

Sugar (Sucrose)



Various grades and types of sugars are available in commerce that may be suitable for incorporation into hard candy, but the two with the greatest utility are cane and beet sugars [4,80].

Sucrose is prepared commercially from sugar cane, beet root, or sorghum. The sugar cane is crushed and the juice (amounting to about 80%)

is expressed with roller mills, treated with lime to clear the syrup and then with carbonic acid gas to remove excess lime. The juice is then concentrated in vacuum pans until crystallization of sucrose is complete. The crystals and the syrup are separated by centrifugation—with the resulting syrup (a byproduct) known as molasses. Beet sugar is made by a similar process but is more difficult to purify.

Refined sugar from either raw cane or beet sugars is prepared by dissolving the sugar in water, clarifying, filtering, and finally decolorizing the solution by treatment with charcoal. The water-clear solution is evaporated under reduced pressure to the crystallizing point [5].

Cane and beet sugars are now chemically and physically identical and therefore cannot be distinguished from each other in the refined state. At one time, though, there were significant differences in the purity and shelf life among products prepared with each type of sugar. Beet sugar contained many impurities, producing a final product containing batch-to-batch differences in color. The candies had a tendency to grain (exhibit sugar crystallization) and pick up excessive moisture. Advances in sugar refining have led most manufacturers to indicate that these differences no longer exist, with only geographic considerations and availability determining which is used.

Today liquid sugar with a solids content of 67% w/w (Table 1) is used almost exclusively in the manufacture of confections, as all continuous candy base manufacturing equipment requires a constant supply of sugar syrup and corn syrup during cooking. Manufacturers can prepare the syrup as

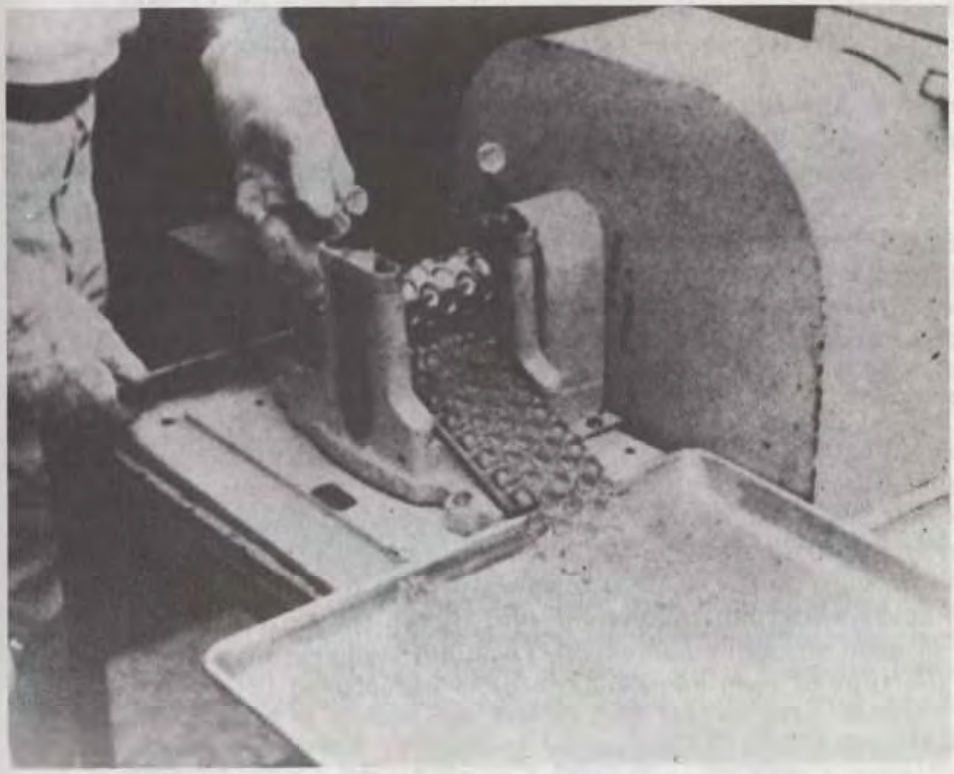


Figure 2 Motorized drop-former. Lozenges manufactured in the laboratory are suitable for stability evaluation of medicament, flavor, and color prior to manufacture of production batches. (From Ref. 24.)

Table 1 Physical Constants of Sucrose Solutions

Degrees Brix (% of sugar)	Degrees Baumé (modulus 145)	Index of refraction at 68°F	Specific gravity at 68°F	Weight (lb) of 1 US gal. at 68°F
67.0	36.05	1.4579	1.3309	11.08
68.0	36.55	1.4603	1.3371	11.13
69.0	37.06	1.4627	1.3433	11.18
70.0	37.56	1.4651	1.3496	11.23
71.0	38.06	1.4651	1.3559	11.29
72.0	38.55	1.4700	1.3622	11.34
73.0	39.05	1.4725	1.3686	11.39
74.0	39.54	1.4749	1.3750	11.45
75.0	40.03	1.4774	1.3814	11.50
76.0	40.53	1.4799	1.3879	11.55
77.0	41.01	1.4825	1.3944	11.61
78.0	41.50	1.4850	1.4010	11.66
79.0	41.99	1.4876	1.4076	11.72
80.0	42.47	1.4901	1.4142	11.77

Source: The Manufacturing Confectioner, Vol. 70, No. 7, July 1970.

needed from granular sugar or purchase liquid sugar directly from their sugar refiners.

Corn Syrup

Corn syrups are produced by either acid, enzyme, or acid–enzyme combination hydrolysis of cornstarch and are generally available in several grades, varying in degree of conversion [dextrose equivalent (DE)] and solids content (degrees Baumé) [4].

Manufacture

The manufacture of all corn sweeteners begins with the hydrolysis of cornstarch, a process involving the splitting of the starch molecules by chemical reaction with water. During the process, a thoroughly agitated slurry of purified starch granules containing the required amount of dilute acid is brought to the desired temperature by the injection of steam. A variety of acids will affect the conversion, but in the United States hydrochloric acid is used almost exclusively. Time and temperature are varied depending on the type of corn sweetener to be manufactured [6].

As the reaction progresses, the gelatinized starch is converted first to other polysaccharides and subsequently to sugars, mostly maltose and dextrose. The sugar content increases and viscosity decreases as the conversion proceeds. Complete hydrolysis produces dextrose.

The hydrolysis of the starch is halted when partially complete—to produce corn syrup, the exact degree depending on the type of syrup being made. Partial hydrolysis of starch converts part of the starch completely to dextrose; the remainder, which is not completely hydrolyzed to dextrose, consists of maltose and higher saccharides. The proportions of saccharides vary, depending on the extent and method of hydrolysis.

Two methods of hydrolysis are in commercial use for the production of corn syrup—the acid process and the acid-enzyme process. In the latter, acid hydrolysis is followed by conversion with an amylolytic enzyme, resulting in a syrup with a higher proportion of maltose than can be obtained by acid hydrolysis alone. The dextrose/maltose ratio can be varied, within certain limits, depending on the type of enzyme used and on the extent of the preliminary acid conversion.

In the acid hydrolysis process, the hydrolysis is stopped when the reaction has reached the desired DE range, by transferring the contents of the converter into a neutralizing tank where the pH is raised to the level necessary to stop the reaction. The acid acts as a catalyst and does not combine chemically with the starch. The acidified product is partially neutralized by adding a calculated quantity of sodium carbonate to the solution.

Fatty substances which rise to the surface are skimmed and then removed in centrifuges or by precoated filters. Suspended solid matter is removed by filtering the hydrolyzate in vacuum filters. The filtrate is then evaporated to a density of about 60% dry substance.

After this initial evaporation, the hydrolyzate is passed through either bone char or other carbon filters, which causes further clarification and decolorization so that the resulting syrup is clear and practically colorless. This process partially removes soluble mineral substances, which also can be removed by an ion exchange process.

After final filtration, evaporation is carried out in vacuum pans at relatively low temperature to avoid damage to the syrup. The syrup is cooled and can be stored or loaded directly in tank cars, tank trucks, steel drums, or cans.

In the production of high-conversion acid-enzyme or dual-conversion syrups, acid hydrolysis is carried to a level of 48–55 DE. The syrup then is neutralized, clarified, and partially concentrated, and the enzyme added. In other products the acid hydrolysis may be stopped at a level as low as 15 DE. When the enzyme hydrolysis has progressed to the desired degree, the enzyme is inactivated. Adjustment of the pH, further refining, and final evaporation follow as in the production of acid conversion syrup. A summary of the corn-refining process is described in Figure 3.

Dextrose Equivalent

Dextrose equivalent is a measure of the reducing-sugar content of a product calculated as dextrose and expressed as a percentage of the total dry substance [7,8]. Essentially, the dextrose equivalent is the percentage of pure dextrose that gives the same analytical effect as is given by the corn syrup. Certain sugars, such as dextrose, maltose, lactose, and levulose, are called reducing sugars because when a copper hydroxide solution (Fehling's solution) is warmed with these sugars, they react with cupric hydroxide to form cuprous oxide. Sucrose is not a reducing sugar; thus it does not react with Fehling's solution. Generally, dextrose equivalent indicates the degree of conversion in corn syrup. The higher the

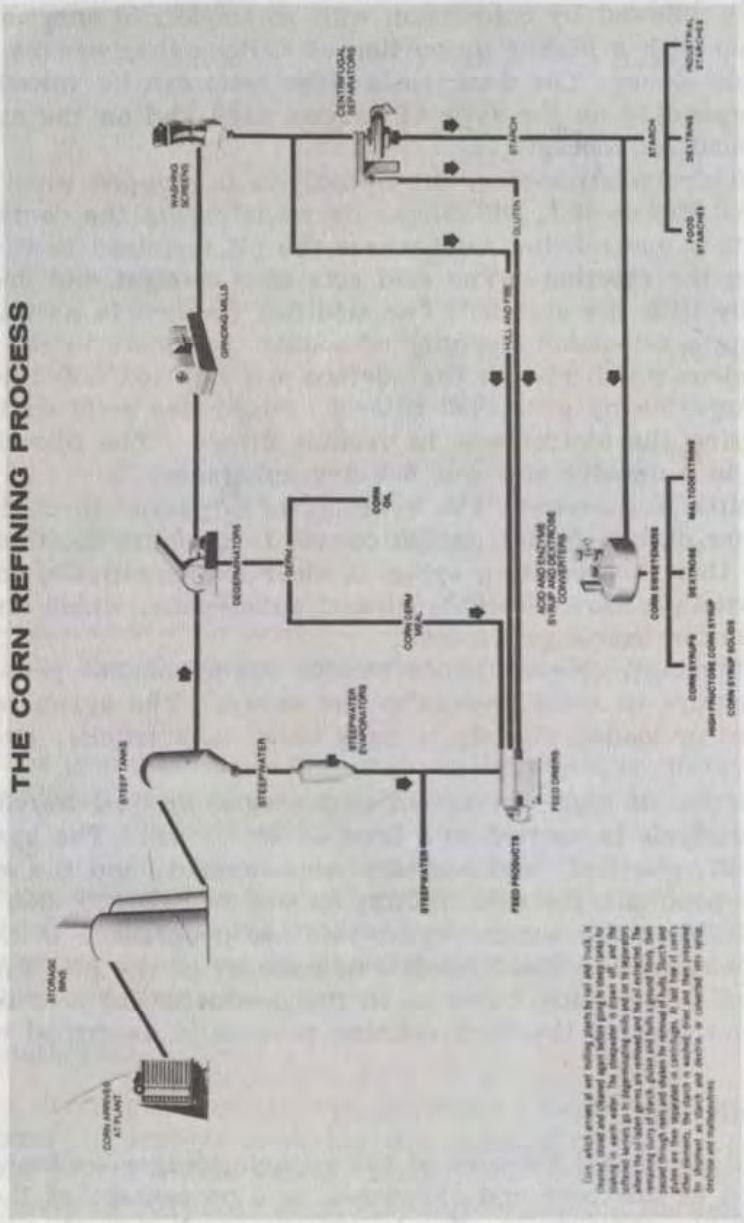


Figure 3 The corn refining process. (Corn Refiners Association, Inc., Washington, D.C.)

dextrose equivalent, the further the conversion has been carried out, resulting in less of the higher sugars (maltotriose and maltotetrose).

The classes of corn syrups categorized as to degree of conversion [8] include:

Low-conversion corn syrup	20–38 DE
Regular conversion corn syrup	38–48 DE
Intermediate-conversion corn syrup	48–58 DE
High-conversion corn syrup	58–68 DE
Extra high-conversion corn syrup	68–99 DE
Dextrose	100 DE

A typical analysis of corn syrup with representative carbohydrate composition and physical and chemical characteristics is included in Table 2.

Physical Characteristics

Corn syrups with 42–43 DE are called normal corn syrups; those with 37–38 DE, low-dextrose-equivalent corn syrups; and those with 58–62 DE, high-dextrose-equivalent corn syrups. Regular- or low-conversion dextrose equivalent corn syrups are widely used in hard candy. For caramels, low-dextrose-equivalent syrup is preferred because it prevents the product from "flowing" in the cold state because of the high viscosity that low-dextrose-equivalent corn syrups impart to products to which they are added. The high viscosity prevents the caramel from losing its shape when the product is stored at elevated temperature or high-humidity conditions. High-dextrose-equivalent corn syrups are generally used for filling where a low-viscosity and higher sweetness medium is required. Since the introduction of enzyme conversion, corn syrups can be varied to best suit their application. The properties and functional applications of corn syrups based on degree of conversion may be described as follows [6].

Browning reaction. The typical brown color that candy base may develop during cooking results from a reaction between reducing sugars and proteins (Maillard reaction). As the corn syrup conversion continues, more reducing sugars are produced. The higher dextrose equivalent syrups are more prone to darkening. Some reducing sugars are more active than others. For example, dextrose is more reactive than maltose. Therefore, the more highly converted products containing maltose are selected in preference to the dextrose-containing syrups. Fructose reacts more readily than dextrose and will give a greater amount of browning than dextrose at the same solids level.

Fermentability. Yeast-raised goods, particularly bread, require fermentable sugars to serve as food for the yeast, and also some residual sugars to give good crust color and add a mild sweetness to the finished product. Because fermentable sugars increase with dextrose equivalent level, the high-DE, dextrose-rich corn syrups are always utilized in making yeast-raised products with crystalline dextrose as the ultimate ingredient.

Foam stabilizer. Because the lower dextrose equivalent syrups have a greater ability to retain incorporated air, they are always chosen as the best foam stabilizer.

Table 2 Typical Analysis of Various Corn Syrup Grades

Representative carbohydrate composition			
Degree of conversion	Very low	Regular	Regular
Type of conversion	Acid-enzyme	Acid	Acid-
Dextrose equivalent (%)	26	35	43
Fermentable extract (%)	23	32	42
Dextrose (monosaccharides) (%)	5	14	20
Maltose (disaccharides) (%)	14	12	14
Maltotriose (trisaccharides) (%)	14	11	12
Higher saccharides (%)	67	63	54
Representative chemical and physical data			
Baumé at 100°F (degrees	42	43	43
Total solids (%)	77.5	79.9	80.3
Moisture (%)	22.5	20.1	19.7
pH	5	5	5
Acidity as HCl (%)	0.015	0.015	0.015
Viscosity (poises at 100°F)	220	220	125
Boiling point (°F)	222	226	227
Weight (lb gal at 100°F)	11.70	11.81	11.81
Percentage ash (sulfated) of resin-refined corn syrup, less than 0.02%.			
Percentage ash of vegetable-carbon refined corn syrup, 0.3%			

Source: A. E. Staley Manufacturing Co., Decatur, Illinois (Tech. Data Sheet No. 110).

Freezing point depression and osmotic pressure. Because freezing point depression and osmotic pressure are directly related to the number of molecules present, the highest dextrose equivalent products give the greatest freezing point depression and the highest osmotic pressure.

Hygroscopicity. The more highly converted syrups have the greatest ability to take up water and the low-conversion products the least. If a base product for preparing a dry powder with low hygroscopicity is desired, then the lowest dextrose equivalent products are used, sometimes extending below the 20-DE range into the maltodextrins.

Regular Acid-enzyme	Intermediate Acid	High Acid-enzyme	High Acid-enzyme	Very High Acid-enzyme
42	54	64	64	68
58	54	76	76	79
7	30	39	39	40
34	18	33	33	39
27	13	12	12	4
32	39	16	16	17
43	43	43	44	43
80.5	81.0	81.8	83.8	82.0
19.5	19.0	18.2	16.2	18.0
5	5	5	5	5
0.015	0.015	0.015	0.015	0.015
125	75	55	155	55
227	229	233	234	233
11.81	11.81	11.81	11.93	11.81

Nutritive solids. Since the caloric value of starch hydrolyzates is based primarily on carbon content, there is no significant difference among the various corn syrups when nutritive value is based on solids content. If a controlled rate of assimilation is required for specialty applications, such as infant foods, the lower converted products with lower rates of assimilation are used. In a special application, there could be preference for a corn syrup containing dextrose, maltose, or fructose.

Control of sugar crystallization. In the preparation of hard candies, control of the number and size of sugar crystals is required. The higher

polysaccharides of the low converted corn syrups are effective agents for this purpose. By selecting syrups with the correct higher polysaccharide content and distribution, control of crystallization can be obtained.

Sweetness. Fructose is sweeter than dextrose, which is sweeter than maltose, which is sweeter than higher polysaccharides. Since the sugars, fructose, dextrose, and maltose are all reducing sugars, the higher dextrose equivalent corn syrups are generally sweeter than the lower dextrose equivalent products. However, at any dextrose equivalent level, the corn syrup containing a given amount of fructose will be sweeter than a syrup containing an equal quantity of dextrose or maltose. Where sweetness is the major functional property desired, the high-dextrose-equivalent corn syrups, especially those containing fructose, should be selected.

Viscosity. This property is basically dependent on the average molecular size. The most viscous syrups are the lowest dextrose equivalent products.

Miscellaneous. Corn syrup is transported from the manufacturer to customers or to distribution points in rail tankers as a thick, viscous, water-white syrup. The tankers are usually insulated to maintain the temperature of the syrup at 90–140°F, depending on the type of syrup being shipped. A summary of the physical characteristics available with various corn syrups appears in Figure 4 [6].

Degrees Baumé

Corn syrups are sold on a Baumé basis, which is a measure of specific gravity or dry substance content [8]. Since corn syrups are viscous at room temperature, Baumé determination is made at 140°F (60°C) with an arbitrary correction of 1.00° Baumé added to the observed reading to correct the value, which would be reported at 100°F (37.7°C). This is called *commercial Baumé* [9]. Specific gravity is an important consideration when choosing a grade of corn syrup (43° Baumé corn syrup having about 20% water, 45° Baumé about 15% water, and 37° Baumé about 30% water). For transport by tank cars, a corn syrup of 43° Baumé is preferred over one of 45° Baumé because of its superior flow characteristics. Forty-three degree Baumé corn syrup, even with improved flow vs. 45° Baumé syrup, still must be heated to 100°F to effect acceptable flow. Use of 41° Baumé corn syrup (77% solids) eliminates the heating of corn syrup during storage. This requires longer heating during candy base preparation, thus resulting in longer cooking time and possibly more browning [10]. The overall advantages of 43° Baumé corn syrup make this the syrup of choice in the preparation of hard candy lozenges.

Applications

The primary functions of corn syrup in hard candy base are (a) to control crystallization; (b) to add body; (c) to supply solids at a reduced cost; (d) to adjust sweetness level. Control of sugar crystallization is a primary application of corn syrup in hard candy. Since sugar is readily crystallized when the water of sugar solutions is boiled off, the presence of the noncrystallizable corn syrup is necessary to inhibit the *graining* or recrystallization of the sucrose. This inhibition of sugar recrystallization is accomplished by surrounding each molecule of sucrose with a film of



Figure 4 Properties and functional uses of corn syrup. (Corn Refiners Association, Inc., Washington, D.C.)

uncrystallizable corn syrup. Hard candy, in essence, may be characterized as a supersaturated sugar solution in corn syrup [4]. The sugar molecules are dissolved and separated in the corn syrup, and because of the high viscosity of the corn syrup solution, movement of sugar molecules in the corn syrup is slowed. Eventually, though, molecules of sugar meet and combine, causing the formation of larger sugar crystals or the phenomenon described as graining [4].

The viscosity of the internal solution (determined by the grade of corn syrup and the moisture content of the finished candy base after cooking) and the storage conditions under which the finished lozenges are subjected (e.g., protection from moisture) determine the product's shelf life and rate of crystallization that can be expected [11]. All hard candies do eventually grain, but the speed at which this phenomenon occurs depends on the aforementioned grade of corn syrup (viscosity), mositure content of the cooked base, and storage conditions. Modification of the ratio of sugar solids to corn syrup solids in candy base will also affect the rate of graining in the finished product.

Incorporation of corn syrup solids at greater than 50% decreases graining tendencies because of the lower percentage of sugar solids dissolved in

the syrup, but this increases moisture absorption, thus resulting in an increase in product stickiness and in the interactions of medicaments. Higher percentages of corn syrup reduce lozenge sweetness but allow longer processing time because of the slowed rate of candy base hardening. Addition of greater than 70% sucrose solids to candy base increases graining tendencies due to the high solids content in the corn syrup. Candy base crystallizes rapidly, thus decreasing mixing time, and increasing opacity and the brittleness of the final lozenge. Candy base formulations containing 55–65% sugar and 45–35% corn syrup solids offer the best compromise among these factors: resistance to graining, reduction of moisture absorption, and a realistic processing time period during manufacture.

Invert Sugar

Invert sugar is a mixture of two sugars (levulose and dextrose) in equal parts, produced by hydrolizing (inverting) sucrose. Molecules of sucrose combine with water to form smaller molecules during the cooking of the candy base [12].

Invert sugar has the power to absorb moisture from the air and at the same time retard crystallization. Controlling candy base cooking time will reduce the quantity of invert sugar. A standardized cooking time will result in the formation of uniform quantities of invert.

Reducing Sugars

The quantity of reducing sugar present in the corn syrup plus the quantity of reducing sugar formed during the cooking cycle determines the quantity of total reducing sugars in the final candy base. Controlling the total reducing sugars will determine how resistant the candy will be to graining and moisure absorption.

Production of hard candy base containing greater than 20% reducing sugars slows the rate of product graining by lengthening crystallization time. This attribute is advantageous during manufacturing since the candy base will harden at a slower rate. The result is a base that can be mixed longer to assure a complete distribution of medicament while entrapping less air. This allows formation of a piece of hard candy with a greater degree of clarity. Increased crystallization time also produces a candy base that is more pliable during the lozenge-forming operation. This reduces the number of rejects formed because of lozenges breaking due to candy base brittleness. The incidence of sugar dusting is also lowered, resulting in a cleaner product and a more sanitary operation.

Preparation of candy base with reducing sugar content below 14% leads to the formation of brittle candy that is susceptible to breakage, dusting, and formation of high quantities (greater than 20%) of lozenge rejects. This is the direct result of manufacturing difficulties caused from candy base hardening through rapid crystallization. The resultant lozenges, while possessing less hygroscopicity than product prepared with higher reducing sugars, are more susceptible to graining when exposed to moist conditions.

A final reducing sugar content in the 16–18% range brings to the formulator many of the advantages cited for low and high reducing sugar content while minimizing the disadvantages. Crystallization time is slow enough to assure proper incorporation of medicaments, but sufficient candy base plasticity is available for the forming and molding operation. The resultant

lozenges are not brittle, resist dusting during the packaging operation, and resist both graining and excessive moisture absorption.

When selecting a grade of corn syrup suitable for lozenge manufacture, the formulator should consider a corn syrup prepared at a *regular conversion* level (41–44 DE), dual-converted (acid-enzyme) to a high maltose content (above 42%). The regular conversion imparts the proper internal viscosity to control graining, while the high-maltose-containing syrup is designed for use in products where a sweetener with minimum dextrose (less than 10%) and a resultant decrease in lozenge hygroscopicity is desired. The reduced dextrose content imparts better color stability, expecially during heating and storage, when higher dextrose contents would cause darkening.

Lozenges containing high-maltose corn syrup have increased internal viscosity. This retards sugar movement and aids in controlling crystallization of sucrose, while the lower water-pickup tendency improves and extends the lozenge shelf life—both from the chemical aspect of reducing drug decomposition and from the physical aspects of reducing graining and sticking.

High-maltose syrups were originally developed for use in hard candy, the theory being that a manufacturer using 40–50% regular conversion corn syrup (dry basis) could go to 50–60% with high-maltose syrup [13,14]. While noticeable improvements resulted in the winter months, stickiness is still a problem in the summer. Many processors who ventured to the 60% level gradually cut back to the 40–50% level. The use of high percentages (above 50%) of high-maltose corn syrup produced lozenges that exhibited increased breaking or stress cracking becuase of the high viscosity imparted by the corn syrup.

Most lozenges manufactured today possess a sugar-to-corn syrup ratio in the range of 50:50 to 70:30, with the greatest number of medicated lozenges produced with a ratio of 55–65 parts sugar to 45–35 parts corn syrup. This ratio produces lozenges with adequate sweetness, resistance to moisture pickup (with resultant stickiness), graining, and reactivity with medicinal components [15].

Acidulents

Acidulents are generally added to candy base as fortifiers to strengthen the flavor characteristics of the finished product. Acids commonly used include citric, tartaric, fumaric, and malic; of these, citric is by far the most common.

A second use for acidulents in candy base is to control pH in order to preserve the stability of selected medicaments. Since hard candy base is considered a supersaturated solution of sugar in a corn syrup medium, and because of the presence of water in the medicated lozenge base, pH is an important factor in maintaining the stability of medicaments affected by an acid or alkaline medium. The reactivity of the corn syrup and reducing sugars, the presence of moisture in the candy base, and the presence of flavors and acidulents increase the reactivity of medicament in the vehicle—to the extent that the kinetics of drug decomposition is related to liquid (as opposed to solid) dosage forms.

Regualr hard candy base has a pH of 5.0–6.0. Addition of acidulents for flavor enhancement will lower the pH to 2.5–3.0. At this pH many

medicaments exhibit acceptable chemical stability, while others are subjected to rapid decomposition. A determination of the stability profiles of the medicaments intended for incorporation into the lozenge base should be carried out at various pH levels to determine that which is optimum. This determination may preclude the use of acidulents and the flavors with which they are most compatible.

In some special applications, addition of selected ingredients (calcium carbonate, sodium bicarbonate, magnesium trisilicate) to raise the lozenge pH to 7.5–8.5 will be necessary to effect the desired stability profiles.

Method of Addition

Addition of acidulents to candy base is not a random procedure. Acidulent addition should be performed under controlled conditions since, even under the best circumstances, the acidulent will react with the candy base. Addition of acid to sugar (sucrose) causes inversion, which yields by hydrolysis glucose and fructose (dextrose and levulose). As the percentage of invert sugar in the candy base increases, the internal viscosity of the lozenge decreases, and the moisture absorption characteristics increase. Both phenomena increase tendencies for lozenges to grain, absorb moisture, and become sticky [16].

A certain quantity of invert sugar is produced during the cooking cycle. The faster the cooking cycle, the lower the quantity of *cook invert* formed. Addition of acidulents to candy base during the cooking cycle—or the failure to neutralize excess acid in any salvage that may be incorporated—acts as a *sugar doctor* or inverting agent. This so-called doctor will markedly increase the quantities of invert sugar formed, negating the advantages of a low moisture content in the base preparation or the use of high-maltose corn syrup. The acidulents should be added at the completion of the cooking cycle at temperatures not exceeding 120°C. Final invert sugar levels in candy base should not exceed 2.0–2.5%.

The presence of acidulents in the completed lozenge will shorten the shelf life of the final product, since even at room temperature the acidulent will continue to invert the sugar. Thus, the rate of graining and degree of stickiness will be higher than in lozenges prepared at pH 5–6. Another drawback of acidulents in lozenges occurs with elevated temperature and humidity. Under these conditions, a localized discoloration or burning of the candy will occur. Use of finely powdered acids helps to reduce this problem but will not eliminate it.

Incorporation of the acidulents to the vehicle as a controlled procedure helps minimize the disadvantages acidulents can represent in reducing the extended shelf life of the products to which they are added. The acidulent should be added to candy base at the lowest possible workable temperature of the candy mass (100–110°C). At the same time, the acidulent should be added at the lowest effective concentration (0.1–0.5%) in a manner that will prevent direct contact of the acid with the mass. Incorporation of the acidulent as a mixture with dry, ground salvage and the flavorant will lessen contact of the acidulent with the base, and at the same time help distribute it uniformly throughout the mass. This uniform incorporation prevents reaction during the addition procedure and reduces the degree of localized discoloration or burning during storage. The use of granular acidulent instead of finely powdered material will result in localized discoloration if the lozenges are exposed to prolonged heating or high humidity

during storage. The reactivity of acidulent with candy base during product manufacture is reduced because of lower overall particle surface area.

The advantages that acidulents bring to lozenge formulations through pH control and flavor enhancement usually exceed the disadvantages of discoloration and sugar inversion during storage, if the degree of inversion can be controlled during lozenge manufacture by proper addition techniques.

Colors

Incorporation of powdered or micronized dyes is not practical because of the low moisture content (less than 1.5%) and the high viscosity of the cooked candy base. Not all the dye will dissolve in the base, resulting in a nonuniform and nonreproducible colored product containing particles of undissolved dye. A method used to circumvent this difficulty involves the incorporation of colors into hard candy base as pastes, in mixtures of sugar, dextrose, corn syrup, dextrin, and glycerin; as aqueous solutions; or as commercially prepared color cubes (Figure 5) [17]. When adding colors as aqueous solutions, no more than 30.0 g of water should be added per 100 lb of candy base. More than this quantity will result in localized sticking and lumping during the mixing cycle. If more liquid is required, combinations with glycerin or propylene glycol should be used.

The formulator, during product development, should investigate the compatibility of the colorants—both at ambient temperature and at 110–115°C, the temperature at which the colors will be added to the products—since many dye systems are altered when added at the elevated temperature. A second factor that should be considered is the product pH. Addition of acidulents to candy base at elevated temperature along with, or shortly after, color addition can result in a noticeable change in the final product color as well as color differences between batches. Stability of colors in



Figure 5 Colors may be added to candy base as pastes, as aqueous solutions, or as commercially prepared color cubes.

the final product (effects of moisture, sunlight, pH, and medicaments) is also a matter of concern since changes in product appearance with time are not uncommon.

Many in-process color changes result when colored liquid salvage is incorporated in the candy base. This color modification may occur because of the pH of the salvage solution before cooking or may be because of a color change effected during the candy base cooking cycle. Color changes that result from pH may be remedied by a change in salvage pH. The salvage solution pH may be adjusted anywhere in the range of 4.5–7.5. If a pH in this range can produce a stable color solution, then color change problems can be avoided. Color change problems caused by the cooking temperature of the candy base cannot be alleviated. If this problem occurs, the salvage solution may have to be decolorized before use [69]. Modification of the candy base color back to the original shade can be effected by the addition of more color to the cooked candy base. This is practical only if a uniformly color-modified product is produced each time the colored salvage solution is manufactured. Candy base colors that prove to be stable when added to candy base during the cooking cycle may be added to salvage solutions before the cooking cycle instead of to the cooked candy base during the mixing cycle.

Flavors

The addition of flavors to cooked candy base can pose a variety of problems to the formulator. These include flavor losses during processing, flavor incorporation difficulties, flavor and candy base interactions, and flavor–medicament interactions. The specific flavor-related difficulty must be determined, and remedial actions taken, if a stable and reproducible product is to result.

Addition of flavors to candy base usually takes place at temperatures from 120 to 135°C. At these temperatures, flash-off is the primary problem. Addition of flavors to the base also results in distribution difficulties because of the high viscosity of the candy base and the fact that the cooked candy base does not readily absorb liquids without rapid and continuous agitation. Separation of flavors from the cooked base will markedly increase the incidence of flavor loss, since the flavors present at the surface of the hot mass are most likely to volatilize. The ideal situation is to incorporate or surround the flavors with candy as rapidly as possible. Separation of flavors from candy base may result in the formation of bubbles of concentrated flavor in the completed lozenge. These lozenges may contain a "liquid pocket" of flavor which, when broken in the mouth, may produce excessive burning or discomfort to the user. The separation of flavor from the candy base may also cause processing difficulties because of an increase in the candy mass tackiness and a reduction in candy base elasticity. A final disadvantage of flavor separation may be a nonuniform flavor concentration among production batches. This is a negative factor, especially when flavors are medicinal in nature or are covering bitter principals. As a rule, no more than 450 g of flavor should be added to 100 lb of candy base.

A method designed to reduce the quantity of flavor flash-off and flavor separation at the surface of the candy base involves the addition of flavor components as a mixture with ground salvage. This ground salvage flavor mixture is added to the cooked candy base (125–135°C) on the mixing table and immediately folded into the hot mass.

As the ground candy melts, the flavor is drawn into the base and is rapidly mixed into the molten mass. Since the flavor is not exposed to the surface of the candy base for as long a time, flavor losses are reduced, and losses (5–15% of flavor added is lost, depending on each individual flavor) are reproducible. The resultant candy has a uniform distribution of flavors without formation of flavor pockets.

The particle size of the salvage used as a flavor carrier and extender should range from 20 to 50 mesh. If salvage particles are too large, the flavor will not be adsorbed on the surface of the candy. This will result in a separation of flavor from the salvage. If salvage is too fine, the resultant salvage-flavor mixture will set or harden, causing distribution problems.

Sufficient salvage must be utilized to adsorb the flavor in order to prevent separation from the salvage mixture—either during preparation or storage of the flavor-salvage mixture, or as the mixture is melting into the molten candy mass. The resultant mixture should consist of free-flowing, discrete granules that do not agglomerate or exhibit flavor separation during a 48-hr storage period. Depending on the type of flavor used, if the salvage is of proper particle size, 1 lb of ground salvage should adsorb 50–100 g of flavor.

A divergence from the usage of ground salvage occurs in the candy industry where the incorporation of ground salvage into a candy base is contraindicated. The explanation for this is that the addition of sugar granules or crystals to the cooling candy mass results in a medium that is suitable for crystallization of sugar (graining) [62]. The ground salvage addition may act as seed crystals which, under proper conditions (high moisture), will result in premature crystallization of sugar from the base.

The candy industry is concerned with manufacturing a product that is elegant in appearance. Refraining from addition of ground salvage produces a clear product free from excessive air entrapment and more resistant to graining than a lozenge prepared with ground candy.

Preparation of confections does not require masking of the bitter principals present in medicated products; therefore, the quantities of flavorants used are only 10–20% of those utilized in medicated lozenges. The small quantities of flavors are readily incorporated into candy base, thus minimizing losses. In instances where larger quantities of flavors are added, the candy manufacturer is not too concerned with flavor losses or nonuniform flavors between batches.

In the preparation of medicated products, the reduction in flavor losses through flash-off resulting from the use of the ground salvage is considered more important than a loss in clarity or a tendency toward premature graining. Flavors mask bitter principals and in many instances are medicinal themselves; therefore the manufacture of a product with uniform flavor content supersedes the appearance of the final product.

Another method to reduce flavor loss is the addition of selected solvents, where compatible, with the flavorants. Solvents most commonly used are propylene glycol, benzyl alcohol, polyethylene glycol [18], and glycerin. This method is most suitable when small portions (less than 100 g/100 lb candy base) of flavor are added to the product.

Use of natural or artificial flavorants [19] is left to the discretion of the formulator, but the compatibility of the flavor in the presence of heat and pressure should be evaluated. Incorporation of natural flavors containing terpenes or other materials with a low boiling point in contraindicated

in candy making because the temperature at which the flavorants are added to candy base, along with the added heat and pressure that occur when the mass is formed into lozenges, cause a charring or burning of these low-boiling-point materials. The result is a formation of black specks or black pockets of burned flavor. This phenomenon, called *dieseling* (Figure 6), does not occur in all batches, but when it does the organoleptic appeal of the product is reduced. Elimination of low-boiling-point flavoring components (especially terpenes) will alleviate this condition.

A third consideration in determining which flavor or flavor profiles should be used is the compatibility of flavors with the medicaments in the product. Different flavoring components (e.g., aldehydes, esters, ketones, alcohols) may react with the medicaments to produce a chemical decomposition or drug instability. Adjustment of lozenge base pH to accentuate certain flavors (e.g., citrus) may also result in a situation that would be in-

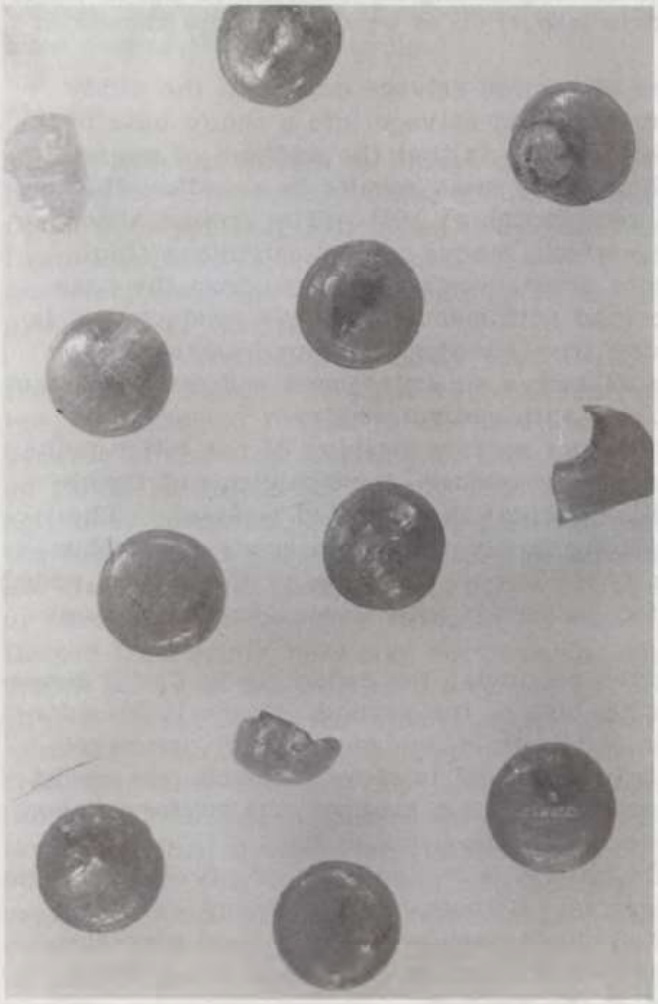


Figure 6 Lozenge diesels. Charring of low boiling point flavor components results in formation of black specks, burned areas, air pockets, and surface irregularities. Flavor adulteration also results when dieseling occurs.

compatible with various medicaments. The chemistry of both the flavor and active components must be studied before choosing flavors for any product. A classic example of flavor–drug interaction occurring in candy base is the interaction of benzocaine with cherry, lemon, or other aldehyde-containing flavor components. In a relatively short period (4 weeks at 45°C, or 12 weeks at 25°C), the benzocaine-aldehyde reaction causes a Schiff's base formation:

$$RCHO + RNH_2 - RCH = NR + H_2O,$$

resulting in drug decomposition and elimination of the local anesthetic efficacy. To further aggravate the condition, the citrus flavors are usually added with acidulants (citric or malic acid) to accentuate the citrus notes. The resultant lozenge pH of 2.5–3.5 forces this Schiff's base reaction, thus speeding up decomposition of the benzocaine. Elimination of the acidulant slows the reaction but reduces the organoleptic appeal of the citrus flavors.

Solid and Liquid Salvage

Preparation of a medicated product utilizing equipment that was fashioned for production of confections requires constant control of both machinery and production workers. Manufacture of products that require the close tolerances and tight specifications of a medicated lozenge on machinery that does not lend itself to these specifications leads to a high percentage of dosage rejects.

A large number of oversized and undersized pieces are formed during the lozenge-forming operation. Some lozenges break during the cooling operation while others are rejected because of excessive air bubbles, cracks, or excessive sugar dusting. Still other lozenges may be rejected because of a high or low initial drug assay. Excess material may be produced during the cooking cycle of candy base manufacture (cooker salvage) that cannot be immediately used. The quantity of candy base and lozenge material rejected during normal production may range from 5% to as high as 25%, with 15% representing a realistic figure. The necessity of discarding up to 25% of the material produced would pose a severe financial hardship on a manufacturer and the consumer because of a significant increase in cost of raw materials. In order to alleviate this situation, a system of salvage reclamation has been developed [69].

The salvage, if properly treated, can be reused in finished product without altering color, texture, candy base composition, or drug concentration [20]. Before any salvage can be incorporated as part of medicated lozenge base; (a) lozenge salvage must be adjusted to a pH of 4.5–7.5 to prevent excessive and uncontrolled inversion of sugar during the cooking cycle; (b) stability of the active ingredients in the candy base during the cooking cycle must be determined (some medicaments are lost through steam distillation, some by reaction with flavors or candy base, while others are decomposed during the candy base heating cycle); (c) heat-sensitive colors or reactive medicaments must be removed before salvage usage. Activated charcoal or diatomaceous earth added to the salvage mixture, followed by filtration, will remove most color or active ingredients. If the medicament and colorants are stable during the salvage preparation and cooking cycle, the need for filtering the salvage is eliminated.

Salvage must be segregated as to product and incorporated only into the *same* product. If color and active ingredients can be added without treatment, a determination of how much salvage is incorporated into the candy base will also determine how much additional drug and color need be added to the completed candy base. (Flavor quantities in salvage need not be calculated as they are lost during the cooking cycle.)

Lozenge rejects can be ground and used as a carrier for flavors. Ground lozenges need not be incorporated in the final lozenge calculations for medicament, flavor, or color since the ground rejects are complete dosage entities; the addition of 5 lb of ground reject lozenges into the candy base is the same as adding 5 lb of finished lozenges. When salvage is added as ground candy, flavor loss is not a factor since the material is not involved in the cooking process.

Medicaments

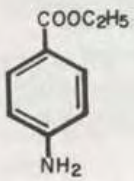
The type of medicament that can be added to candy base and administered to the patient via a lozenge is restricted only by flavor, dose limitations, or chemical incompatibility. Some materials are so unpalatable or irritating to the mucous membrane that they are unsuitable for this type of administration; some active ingredients must be given at a dosage level sufficiently high to preclude their use in a hard candy lozenge; other medicaments are so reactive with candy base components that the development of a product with a reasonable shelf life is impractical.

Hard candy lozenges usually range in weight from 1.5 to 4.5 g and, depending on the solubility or the melting point of the raw materials, only 3–5% w/w can be readily incorporated. Specialized methods such as dispersing or dissolving drugs in polyethylene glycol [21] increase the quantity of medicament that can be included in candy base. These specialized procedures circumvent the normal procedures for manufacturing hard candy and tend to shorten the product shelf life. This limitation means that a maximum of only 225 mg can be incorporated into candy base using normal manufacturing procedures. The higher the concentration of active drug, the greater the problems of flavoring, mouth-feel, and processing of the candy mass. High levels of powders reduce candy base elasticity, making the lozenge-forming operation more difficult to control while at the same time increasing the percentage of lozenge rejects.

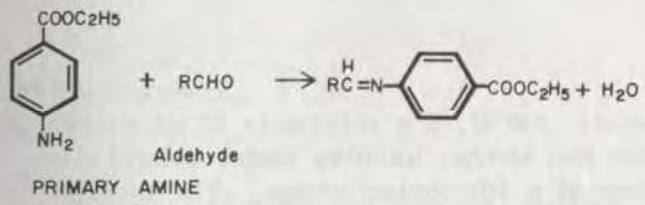
Certain medicaments may require special treatments for their addition or the use or deletion of certain raw materials to assure acceptable physicochemical stability profiles. Examples of certain classifications of medicaiments that can be incorporated into candy base (along with the particular problems of each type) include local anesthetics, antihistamines, antitussives, analgesics, and decongestants.

B. Local Anesthetics

Ethyl Aminobenzoate (Benzocaine)

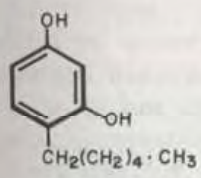


Usual dosage range: 5.0–10.0 mg per lozenge; melting point: 88–90°C; 1 g soluble in 2500 ml water; 1 g soluble in 5.0 ml alcohol. Benzocaine is extremely reactive with aldehydic components of candy base and flavor components. Addition of this material with liquid salvage is not feasible, since at 150°C (the cooking temperature of hard candy) the Schiff's base reaction is pronounced because of aldehydic components in candy and the formation of more reducing sugars during the cooking cycle [22]. As much as 90–95% of the available benzocaine will be lost if added to candy base.



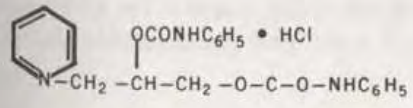
Addition of acidulants to the lozenge formulation promotes degradation via the Schiff's base reaction while drug addition at lower temperatures (110–120°C), along with maximum separation from flavor oils, provides an improved stability profile. Lozenges must be protected from moisture attack as formation of higher levels of invert sugar promotes drug decomposition. Benzocaine products are not difficult to flavor because of low dose and lack of bitter taste. (Insolubility in water and poor solubility in alcohol make the addition of benzocaine as a solution in flavors and organic solvents impractical.)

Hexylresorcinol



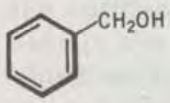
Usual dose: 2.4 mg per lozenge; melting point 67.5–69°C; 1 g soluble in 2000 ml water; soluble in alcohol. Hexylresorcinol is less reactive than benzocaine but is still susceptible to reaction with aldehydic components. There is a 10–20% loss of drug if hexylresorcinol is added with liquid salvage, but losses are mostly due to steam distillation occurring during the candy base cooking cycle and not a chemical decomposition problem. No flavoring or mouth-feel problems are associated with this medicament because of the low dose and lack of any appreciable flavor. Hexylresorcinol is relatively easy to incorporate with flavors since the normal dose is only 25% that of benzocaine. Hexylresorcinol can be classified as either an antiseptic or a local anesthetic.

Diperidon HCl



Usual dose: 10.0 mg per lozenge; 1 g soluble in 100 ml water: soluble in alcohol. Diperidon HCl is not used to any extent in current practice. The local anesthetic activity of diperidon HCl is about equal to that of cocaine. Although incorporation of this medicament in candy base poses little difficulty, flavoring problems are great due to a bitter, metallic aftertaste. Lozenges containing diperidon HCl tend to discolor with age.

Benzyl Alcohol



Usual dose: 10% w/w; boiling point: 205°C; 1 g soluble in 25 ml water. A liquid with a faint aromatic odor and sharp, burning taste, benzyl alcohol has an effective anesthetic dose at a 10% concentration. The incorporation of 10% benzyl alcohol into candy base is difficult but achievable since this material is a liquid at room temperature. Adequate (5–7%) ground salvage must be used to prevent separation during mixing and to effect proper addition and distribution. Forming lozenges is difficult because of reduced elasticity of the resultant candy base (due to the presence of the large quantities of ground salvage.) Also, reproducibility of benzyl alcohol content between batches depends on addition of this material at a uniform temperature to minimize losses from volatilization. Adequate ventilation is required during processing. The stability of benzyl alcohol in lozenges is acceptable. It is compatible with most flavors, although lozenges will discolor (to an orange hue) with age.

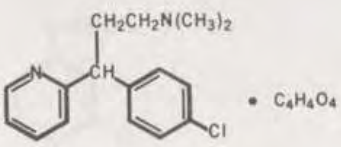
Dyclonine



Usual dose: 2–3 mg per lozenge: melting point 173–178°C, 1 g soluble in 60 ml water and 24 ml alcohol. Dyclonine products are not difficult to flavor because of its low dose and lack of bitter taste. The lozenge base should be adjusted to a pH between 3 and 5 to effect optimum stability of the medicament [91,92]. Some reactivity with aldehyde-containing flavor components. Dyclonine has a slow onset of anesthetic activity (5–6 min) but a long duration of action (45–60 min). Combinations with 5–10 mg benzocaine or menthol per lozenge will effect a rapid onset of anesthetic activity until the dyclonine begins to work.

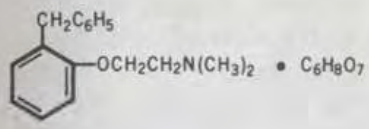
C. Antihistamines

Chlorpheniramine Maleate



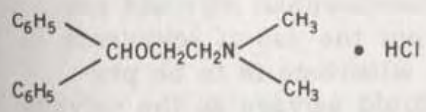
Usual dose: 2.0 mg per lozenge; melting point: 130–135°C; 1 g soluble in 35 ml water; 1 g soluble in 10 ml alcohol. This material lends itself to satisfactory incorporation and physicochemical stability in candy base. The usual dosage range (2–4 mg); safety and the acceptable stability profiles of this material with most flavorants make chlorpheniramine maleate an ideal ingredient when an antihistamine is required in the lozenge type of dosage form. Use of chlorpheniramine maleate does not produce problems with flavoring since this material has very little flavor of its own.

Phenyltoloxamine Dihydrogen Citrate



Usual dose: 22.0 mg per lozenge; melting point: 138–140°C; soluble in water. The usual therapeutic dose (22.0 mg) along with a high melting point makes the incorporation of phenyltoloxamine dihydrogen citrate in candy base difficult. This material exhibits a bitter and anesthetic taste along with considerable grittiness. The stability of this ingredient in candy base is acceptable.

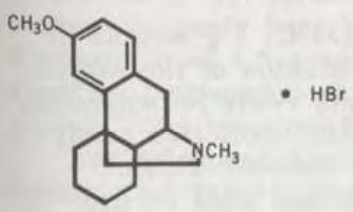
Diphenhydramine Hydrochloride



Usual dose: 10.0 mg per lozenge; melting point: 166–170°C; 1 g soluble in 1 ml water; 1 g soluble in 2 ml alcohol. Diphenhydramine HCl is a potent antihistamine. Incorporation of 5–10 mg of this ingredient in candy base is not difficult because of its good solubility. Diphenhydramine HCl also possesses antitussive action. It has a bitter, numbing taste that is best masked with citrus flavors. Lozenges tend to discolor (browning) with age.

D. Antitussives

Dextromethorphan Hydrobromide



Usual dose: 7.5 mg per lozenge; melting point: 122–124°C; 1.5 g soluble in 1000 ml water; 25 g soluble in 100 ml alcohol. The usual dosage range of dextromethorphan HBr in lozenges is 5–15 mg. Incorporation of this

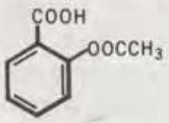
ingredient in candy base is not difficult because of its melting point and solubility; addition with liquid salvage is feasible as this compound is not subject to heat degradation or steam distillation problems. It is compatible with most flavors and is stable over a wide pH range. Dextromethorphan HBr has a bitter taste, an anesthetic mouth-feel, and an unpleasant after-taste. Masking greater than 2.0 mg per lozenge is difficult.

Dextromethorphan HBr is supplied as a 10% adsorbate (10% of dextromethorphan HBr adsorbed on 90% magnesium trisilicate) to avoid flavoring difficulty [71–75]. This adsorbate, which releases the dextromethorphan HBr at the pH of stomach fluids, renders the active ingredient almost tasteless. This results in a medicament that is easy to flavor but difficult to incorporate in candy base, as 10 times the amount of material must be added to achieve an equivalent dose of the regular dextromethorphan HBr. The magnesium trisilicate, being insoluble and having a melting point above that of candy base, will not readily incorporate in the candy mass. The material that does incorporate produces a grainy, rough lozenge texture with an unpleasant mouth-feel.

One method of incorporating the adsorbate into candy base is to prepare a granulation (Figure 7) of the dextromethorphan HBr adsorbate with either glycerin or propylene glycol. A ratio of one part solvent to three parts dextromethorphan HBr produces a free-flowing granulation. The resulting lozenge can be easily flavored and has a smooth mouth-feel. Use of the adsorbate limits incorporation of dextromethorphan HBr to 10 mg or less (usual range 5.0–7.5 mg per lozenge) unless a 4.0 g or higher weight lozenge is produced or an alternate manufacturing procedure is used. The product can be flavored as desired since dextromethorphan HBr will not degrade in the presence of flavor components, but the use of acidulants is contraindicated if the tasteless nature of the adsorbate is to be preserved. The adsorbate cannot be added with liquid salvage as the salvage pH would be 8.0 and addition of acid to lower pH would change the lozenge taste and mouth-feel. This is because a portion of the dextromethorphan HBr will be released from its magnesium trisilicate carrier.

E. Analgesics

Aspirin



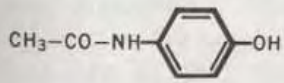
Usual dose: 175.0 mg per lozenge; melting point: 135°C; 1 g soluble in 300 ml water; 1 g soluble in 5 ml alcohol. A direct addition of the aspirin or a mixture of flavor and aspirin to candy base allows ready incorporation of 175.0 mg into a 2.5–3.5 g hard candy lozenge. This medicated candy possesses an acceptable mouth-feel and can be easily flavored without danger of medicament–flavor interaction. The candy base must be prepared at a very low moisture content (less than 0.5%), and all flavors and alternate raw materials must be moisture-free, as incorporation of even a small quantity of water will result in rapid hydrolysis of aspirin into acetic and salicylic acids.



Figure 7 Preparation of a free-flowing granulation of insoluble or high melting point medicaments with a suitable solvent and ground salvage eases incorporation into the candy base.

The hygroscopic nature of the candy base requires that protective packaging be employed if a reasonable product shelf life is to be expected. Use of lozenge rejects as salvage without filtration is not practical, as dissolving the salvage in water results in rapid decomposition of the aspirin.

Acetaminophen

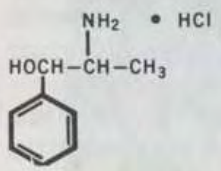


Usual dose: 175.0 mg per lozenge; melting point: 169–170°C; very slowly soluble in water; soluble in alcohol. It is difficult to incorporate this medicament in candy base because of its poor solubility and high melting point. Preparation of 4.5 g candy lozenges with up to 175.0 mg of acetaminophen requires preparation of a granulation with either 1–2% glycerin or propylene glycol. The resulting lozenge has a bitter taste with a metallic aftertaste.

Acetaminophen does not decompose when combined with most flavoring agents, but the *p*-aminophenol, present as an impurity in acetaminophen, will react with low levels of iron to cause the formation of a pink color. Addition of a chelating agent (citric acid) will improve acetaminophen color stability in candy base, but the iron content of the candy base (derived from the iron in corn syrup) should be kept below 2.0 ppm.

F. Decongestants

Phenylpropanolamine HCl

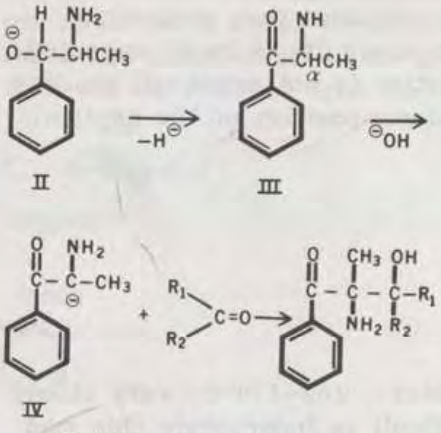


I

Usual dose: 18.5 mg per lozenge; melting point: 190–194°C; freely soluble in water and alcohol. The incorporation of 18–20 mg phenylpropanolamine HCl into 2.5–3.0 g lozenges results in a product with an acceptable mouth-feel. The formulation is not difficult to flavor because of the low level of medicament aftertaste. Phenylpropanolamine HCl will degrade via the aldol condensation in the presence of the aldehydes in candy base or with flavors containing aldehydes.

Aldol Condensation

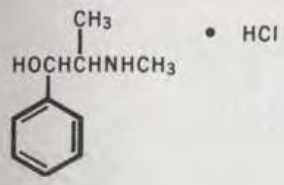
Under alkaline conditions, phenylpropanolamine hydrochloride (I) is stripped of HCl and loses its hydroxy hydrogen to form the anion (II). This anion is then capable of rearranging to a more stable ketone (III). The ketone, however, contains an active α hydrogen which can be extracted in the presence of $-OH^-$ to form the anion (IV), which can go on to react with aldehydes or ketones already present in the candy base or with flavors containing aldehydes or ketones.



(R1, R2 may be aryl, alkyl, H)

The addition of acidulent sufficient to lower the candy base pH to the range of 2.5–3.0 will improve phenylpropanolamine HCl stability in the lozenge—although even with this modification, the medicament will decompose if the lozenge is exposed to moisture during storage. Phenylpropanolamine HCl cannot be added to candy base with salvage solutions because of the reactivity of this medicament with the aldehydic portions in the candy base.

d-Pseudoephedrine Hydrochloride



Usual dose: 18.5–25.0 mg per lozenge; melting point: 181–182°C; soluble in water and alcohol. This compound is less bitter than phenylpropanolamine HCl and less reactive in the presence of candy base and with exposure to moisture.

II. PROCESSING

A. Cooking

Water is required to dissolve the sugar and to obtain the proper quantity of invert sugar. The batch then has to be boiled to remove the water. The higher the cooking temperature, the less water remains in the batch (Figure 8) [23,24].

Candy base cookers are divided into three classes: (a) fire cookers; (b) high-speed atmospheric cookers; and (c) vacuum cookers.

Fire Cookers

Cooking on an open fire (Figure 9) is the oldest method for preparing hard candy base. The fire cooker comes in two types: (a) the atmospheric gas cooker (Figure 10 and 11), which is a slow cooker and (b) the draft cooker (Figure 12), which cooks the candy at a faster rate. The use of fire cookers is declining in the United States but is still used for specialized items to produce a particular flavor, texture, or color.

In the tranditional method of manufacturing candy base on a fire cooker, the desired quantity of sugar is dissolved in at least one-third the amount of water by heating and stirring in a copper kettle until all sugar granules are dissolved. The sides of the pan are kept clean during the cooking operation by washing them continuously with water or by placing a lid on the pan so that the steam washes down any crystals above the level of the liquid. Corn syrup or inverting agent is added when the cooking temperature reaches 110°C. Cooking is then continued until a final temperature of 145–156°C is achieved, depending on the final solids and moisture content desired [23].

The formulator must add the correct quantity of water to the sugar, as insufficient water may result in incomplete dissolution of the sugar crystals, while addition of too much water may result in excessive sugar inversion because of increased cooking time. When boiling or dissolving sugar, a fundamental principle is that all solutions be heated and stirred until they are clear of residual crystals. Any undissolved sugar in the mass might act as a seed for crystallization or graining in the finished product. Heat is transmitted through the copper kettle into the sugar solution during

Assume it is desired to find the absolute (vapor) pressure at which a cooker should be operated in order to obtain finished candy with 88 percent solids and a final cook temperature of 75° C. (165° F.). An extended straightedge is placed at this solids content on scale C-C' (called point 2) and moved up or down until the sum of the values on scale B-B' (called point 1) and scale D-D' (called point 3) equals 75° C. (165° F.). This occurs at 58° C. (136.5° F.) (point 1) on scale B-B' and 11° C. (19.9° F.) (point 3) on scale D-D', and this shows there would be an 11° C. (19.9° F.) boiling point rise and a vapor temperature of 58° C. (136.5° F.). To determine the absolute (vapor) pressure or vacuum under which the cook would have to be operated, merely extend the 58° C. value on scale B-B' across to scale A-A', and this equals 135 mm Hg (point 4). This in turn corresponds to a vacuum of 24.6 inches Hg.

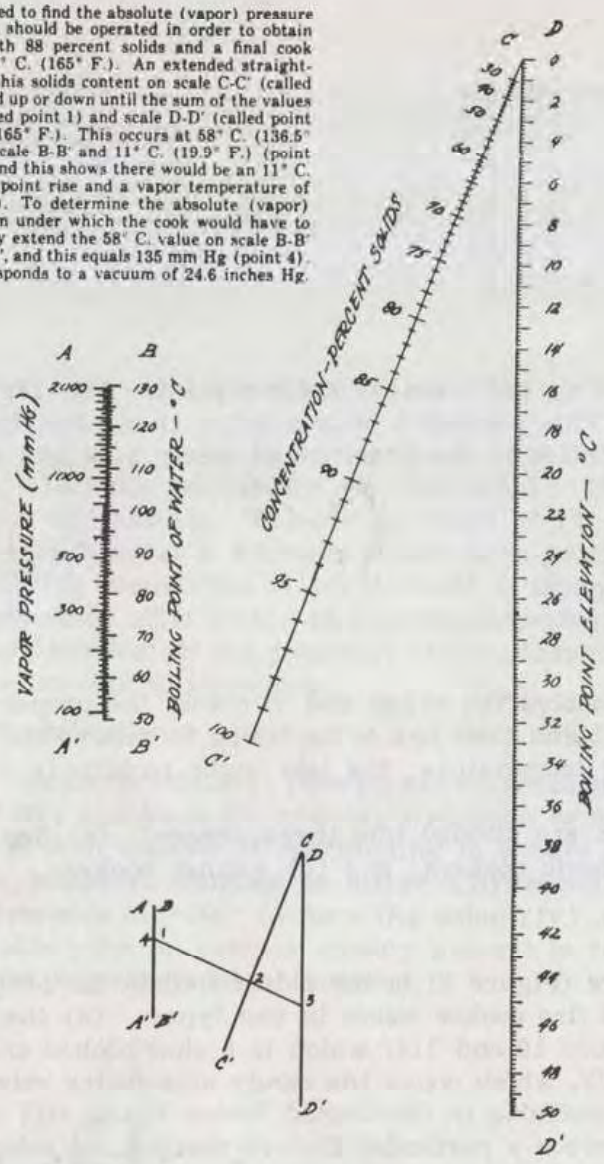


Figure 8 Calculating temperature, vacuum, and moisture content in candy cooking. (The Manufacturing Confectioner, Vol. 70, No. 7, July, 1970.)

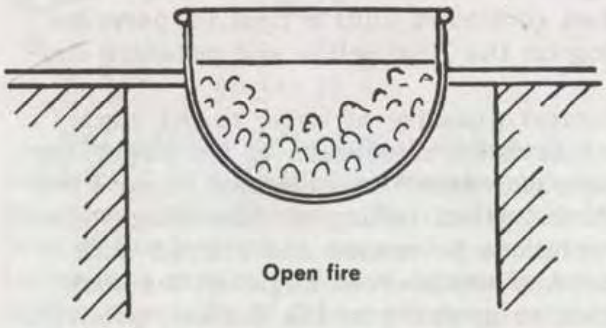


Figure 9 Schematic of open-fire cooking method for manufacturing hard candy base. Cooking temperature determines final candy base moisture content. (Robert Bosch GmBH, Div. Hamac-Höller.)

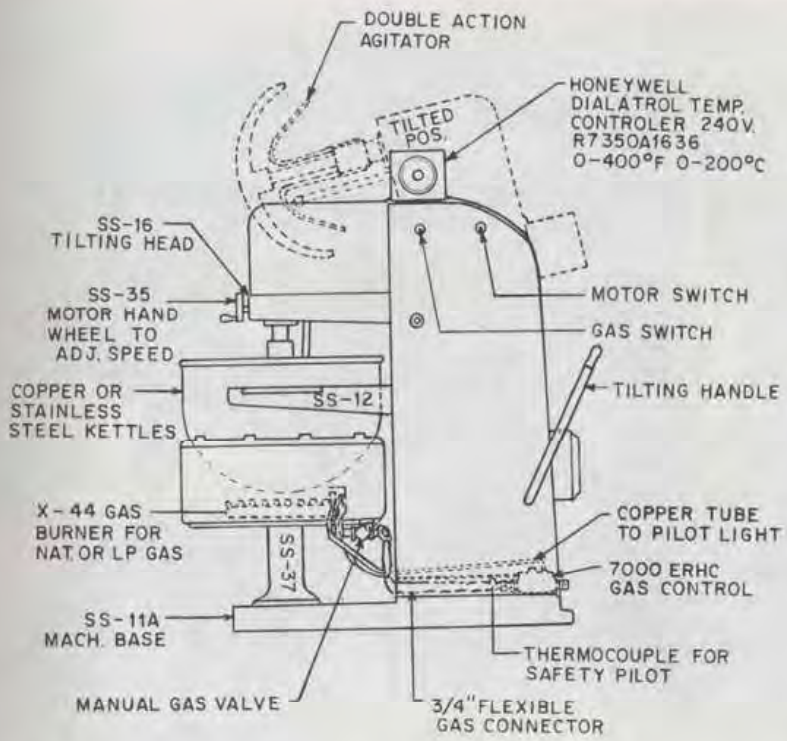


Figure 10 Schematic of atmospheric fire mixer. (Savage Brothers Co., Elk Grove Village, Ill.)

the cooking process. As cooking proceeds, the solution becomes more viscous until eventually the sugar particles near the wall of the pan are unable to change places rapidly enough with the cooler ones in the interior of the batch. As a result, the surface particles are overheated and burned, while particles in the interior are still below the necessary cooking temperature. This accounts for the yellowing or browning of open-fire-cooked batches. Browning also occurs if the fire is too hot; so when the temperature of the batch exceeds 125°C, the fire level should be reduced. Conversely, if the batch is cooked too slowly, it also becomes yellow and may become overinverted, particularly if an inverting agent is present. Use of large kettles with mechanical mixing action improves the efficiency of the fire-cooking process by increasing the rate of sugar particle movement, thus reducing the incidence of candy base yellowing or browning.

High-Speed Atmospheric Cookers

The high-speed atmospheric cooker (Figure 13) uses an efficient heat exchange surface and a swiftly rotating scraper, which spreads an almost microscopic film of candy on a heat exchange surface [4]. This results in a rapid exchange between the heated surface and the batch, the latter boiling more quickly and producing a lighter candy with controlled and lower inversion rate than when candy base is cooked on a fire cooker [25].



Figure 11 Atmospheric gas furnace. Features: single or double action agitation with scraping action; 30 to 60 rpm stirring speed; thermostatic control; 110,000 to 286,000 BTU heat output; removable agitator; copper kettle 24 in. × 12 1/2 in. × 16 in. deep. (Savage Brothers Co., Elk Grove Village, Ill.)

The steam developed by this type of boiling is flashed off to the atmosphere. The candy is brought up to 165–170°C in just a few minutes; however, candy cooked in this way comes out of the cooker at 160°C and must be cooled as rapidly as possible by being dropped onto a cooling slab where it is generally brought down to 100–120°C, so that it can be worked as a plactic-like mass, making it convenient for incorporation of flavor, color, acidulent, and medicaments.

Vacuum Cookers

Vacuum cooking was developed to overcome the disadvantages of cooking candy base on an open fire. The rationale for vacuum cooking is based on the principle that water at atmospheric pressure boils at 100°C but will boil at about 40°C under a high vacuum; therefore, a sugar solution can be boiled at a lower temperature and still result in removal of the water. With this process, a sugar solution and corn syrup are boiled to 125–132°C, vacuum is applied, and (owing to the heat in the batch) additional water is boiled off without extra heating. The resulting vapor is condensed and removed by the cooling water of the vacuum pump. Today vacuum cooking is the process of choice for manufacturing hard candy base [23].

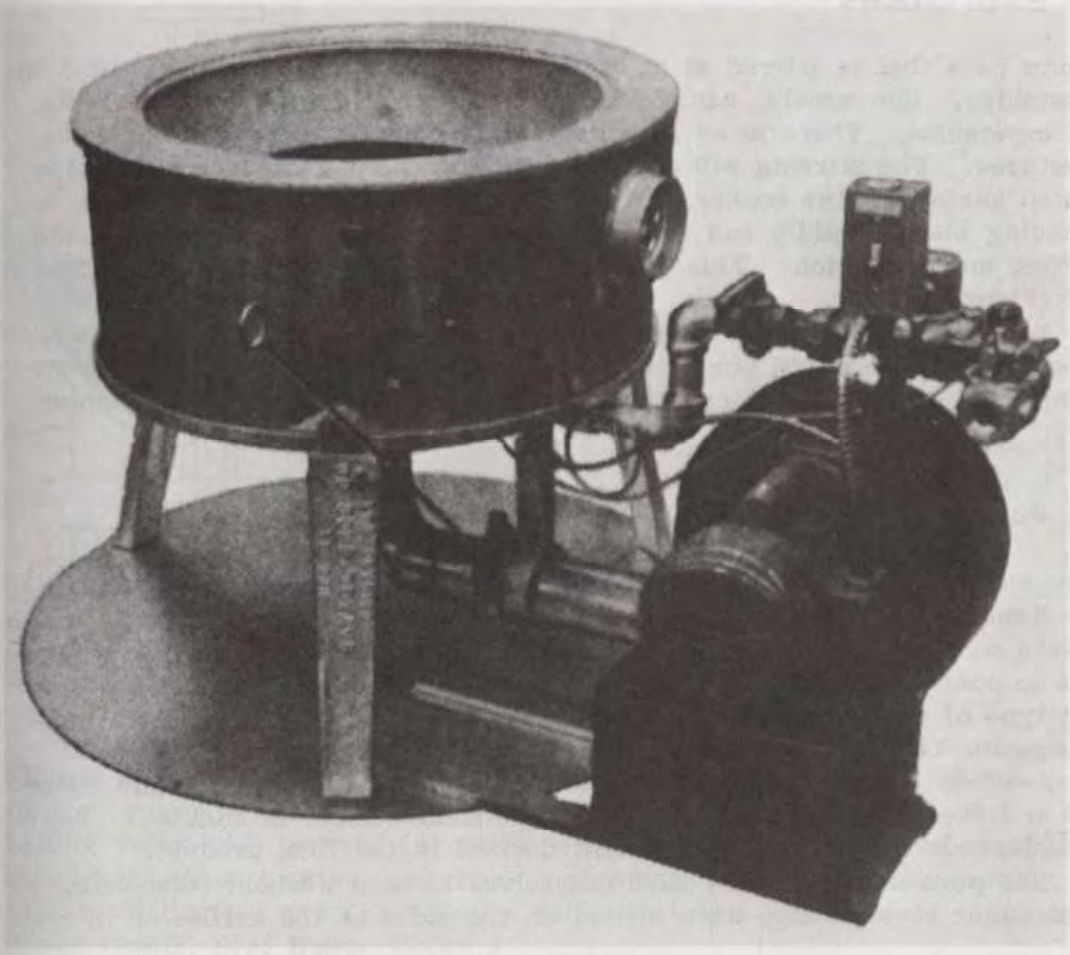


Figure 12 Forced-air gas furnace. Produces fast, high heat; can be used with mixed propane, or natural gas; 3,000-rpm blower speed; 25-in. outer diameter; 25-in. height. (Savage Brothers Co., Elk Grove Village, Ill.)

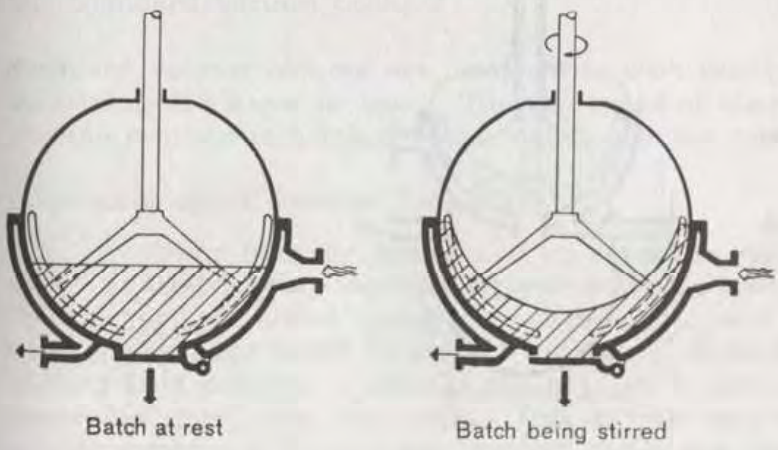


Figure 13 Schematic of high-speed atmospheric cooker with mixer. (Robert Bosch GmBH, Div. Hamac-Höller.)

B. Batch Cookers

Candy base that is stirred at a constant or falling temperature will tend to crystallize. Conversely, candy base stirred at a rising temperature will not crystallize. There is an advantage to stirring a batch at rising temperatures. The stirring will spread a thin film of sugar solution onto the heated surface of the cooker, resulting in the heated sugar particles changing places rapidly and causing a quicker heat exchange between the surface and the batch. This produces a lighter, more reproducible product (Figure 14).

Vacuum batch cookers have two major subgroups: (1) those that are capable of cooking 100% pure sugar down to about 65% sugar in the formulation, and (2) others which will cook 65% sugar down to about 10% sugar [4].

C. Pure Sugar Cookers

Pure sugar cookers are made to be operated in several ways. There is the Hamac-Hansella (Figures 15 and 16), Solich, or Hohberger types, which have a cooking kettle built above a vacuum kettle. The components separate to open with the bottom section dropping down and tilting. The second type of pure sugar kettle is the simplex cooker. These cookers have a separate kettle for precooking the hard candy formula, which is then dumped into the vacuum chamber where the vacuum is drawn on the chamber and the candy base is dried for a specified number of minutes. The time depends on the moisture content desired in the final product.

The pure sugar cookers lend themselves to easy washout (dissolving what sugar crystals may have formed on the sides of the kettles or in the

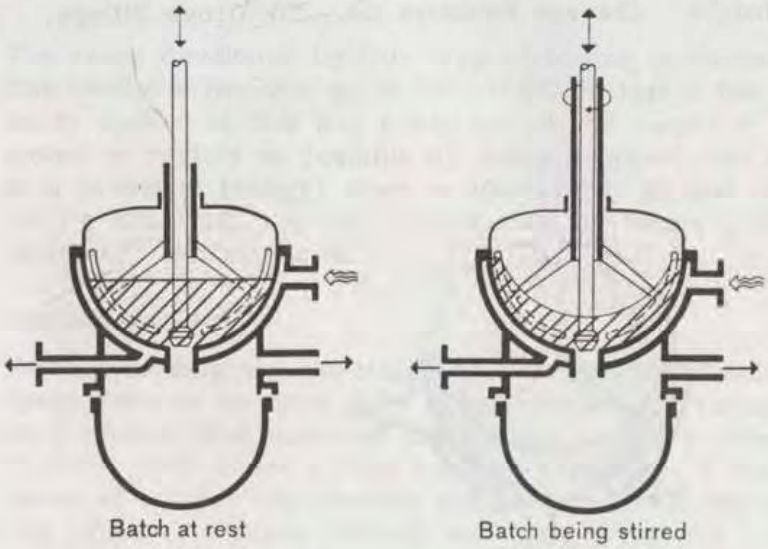


Figure 14 Schematic of batch vacuum cooker with mixer and receiving kettle. (Robert Bosch GmBH, Div. Hamac-Höller.)

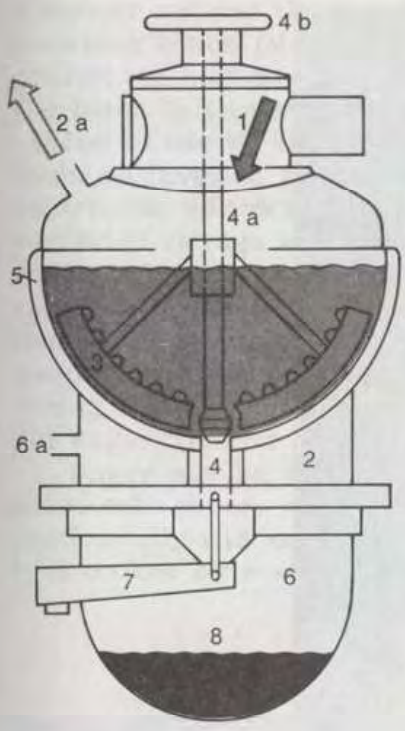


Figure 15 Schematic of Universal Batch Vacuum Cooker. (1) Filling (water, sugar, glucose, and possibly milk and fat), (2) batch cooker, (2a) boiling vapro, (3) beater, (4) valve, (4a) valve rod, (4b) valve operating wheel, (5) steam heating, (6) vacuum chamber, (6a) vacuum connection, (7) swivel device, and (8) delivery pan with boiled sugar mass. (Robert Bosch GmBH, Div. Hamac-Höller.)

vacuum chamber). It is essential that all crystals be dissolved and removed; otherwise the batch being cooked may grain in the kettle—or soon afterward on the cooling or tempering table.

D. Standard Vacuum Cookers

Standard vacuum cookers are designed to cook candy base formulations containing 65% sugar or less. The two types of standard vacuum cookers are the continuous batch process cooker and the continuous process cooker.

Continuous Batch Process Cooker

The installation normally consists of an automatic sugar dissolver, sugar syrup and corn syrup storage kettles, metering pumps, precooker, sugar feed pumps, the actual cooker, a vacuum pump, and a collection kettle. When a precooker kettle is used, it is common to have an intermediate holding tank between it and the cooker, and a pipeline connected to the sugar feed pump from this tank. This system requires an automatic dissolving machine which will continuously meter and dissolve sugar and add corn syrup [26].

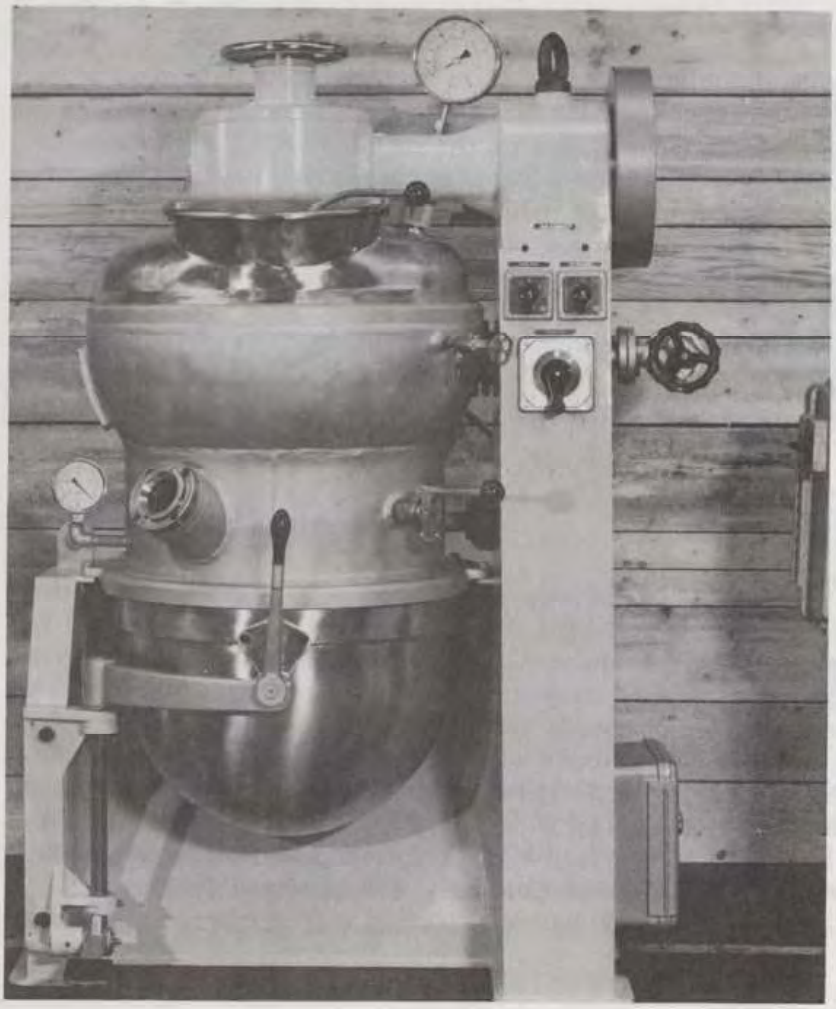


Figure 16 Universal batch vacuum cooker. Suitable for production of high- and low-boiled sugar masses up to 85 to 90% sugar. Output: 275 to 350 lb./hr.; batch size up to 90 lb. (Robert Bosch GmBH, Div. Hamac-Höller.)

Precookers

Precookers are steam-jacketed kettles equipped with celerity cookers (additional heat exchangers) placed in the unit in such a way that more energetic circulation can be obtained than when only the normal heat exchange surfaces are being used [4].

There are also continuous precookers which are called dissolvers (e.g., Solvomat-Hamac-Hansella) whereby an efficient heat exchange surface is used to boil, first, water and sugar which are added on a continual basis, and then the corn syrup which is also added to the machine on a continuous basis along with candy base salvage, if desired (Figure 17). Each component is added to the dissolver by way of a gear-metering system which is controlled by one gearing system so that the finished, precooked syrup can be brought up to the proper temperature (110–120°C) and used within 1 min or less of reaching this temperature. The short dwell time in the

dissolver reduces the quantity of invert sugar developed and reduces the browning action (Maillard browning) that occurred in the older type of precooking kettles. In the older models, cooking times necessary to bring the batch to temperature were as long as 15–20 min with another 10–15 min needed to use up the product. The hot mass in the precooking kettle could be inverted as much as an additional 1–2%. An optional gearing system can be installed for the continous, accurately metered addition of medicated salvage solutions, which must be added in a uniform and controlled manner. Quantities of salvage added can be altered by incorporating different change gears that can adjust the quantity of salvage solution added to the candy from a little as 1.5% to as much as 25% on a dry weight basis. Slip-on change gears enable the formulator to adjust the mixing ratio of sugar and corn syrup from 80% sugar:20% corn syrup to 45% sugar:55% corn syrup.

Sugar may be metered into the dissolver in a granulated form and mixed with water, or in a liquid syrup form (Figure 18). The sugar is continuously and automatically metered into the precooking chamber where it is cooked by a steam coil that passes almost completely around the bottom



Figure 17 Precooker for production of 650 to 2750 pounds of sugar plus glucose per hour. (1) Corn syrup line; (2) liquid sugar line; (3) precooker; (4) syrup flow valve; (5) intermediate holding container. (Robert Bosch GmBH, Div. Hamac-Höller.)

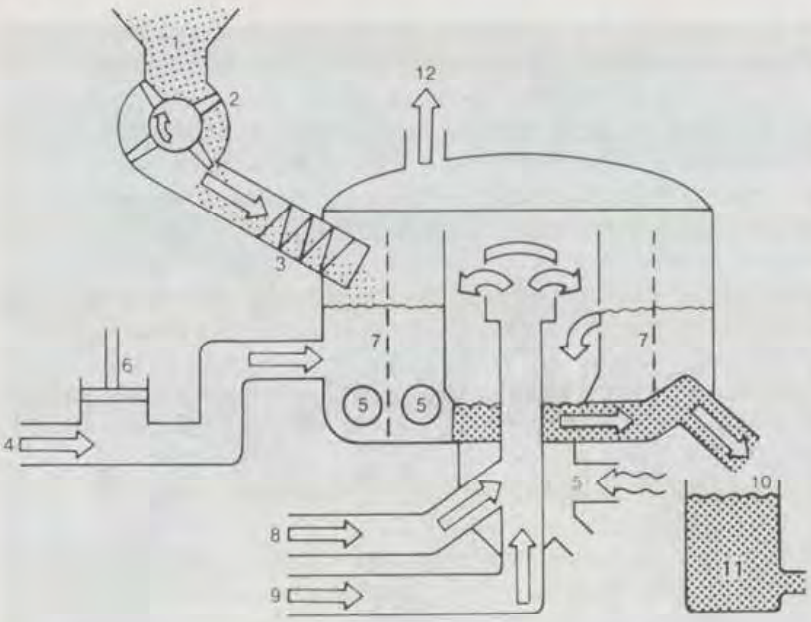


Figure 18 Schematic drawing of Hansella Solvomat precooker. Liquid sugar feed has replaced the granulated sugar feed and dissolving process. (1) Granulated sugar feed, (2) metering wheel, (3) worm, (4) water feed, (5) steam, (6) water pump, (7) sugar-water mixture, (8) glucose feed, (9) feed for other ingredients, (10) preboiled glucose-sugar solution, (11) intermediate container, and (12) boiling vapor discharge. (Robert Bosch GmBH, Div. Hamac-Höller.)

of the compartment, causing the liquid sugar to boil voilently without mechanical agitation. Liquid sugar precooking temperature can be adjusted between 100 and 110°C, depending on the desired output. The precooked liquid sugar then overflows into the central chamber where it is automatically mixed with the preheated corn syrup and any liquid salvage or other ingredients as desired in the proper proportion (Figure 19). The resulting precooked liquid sugar, corn syrup, and third ingredient (if required), after mixing and cooking, flow into an intermediate collection container before further processing (Figure 20). Automatic dissolvers have an output of 650–1750 lb of sugar per hour.

E. Cooking Machines

The precooked sugar–corn syrup solution, which has been cooked to a temperature of 100–120°C, now passes through an adjustable output syrup pump that continuously distributes the candy mass through cooking coils (Figures 21 and 22). These coils lead to an intermediate chamber where a thermometer is located, which measures the syrup temperature as it leaves the coil. The cooking coils and intermediate chamber are never under vacuum since the intermediate chamber is vented to the atmosphere. This feature enables all vapors from the batches to be vented, resulting

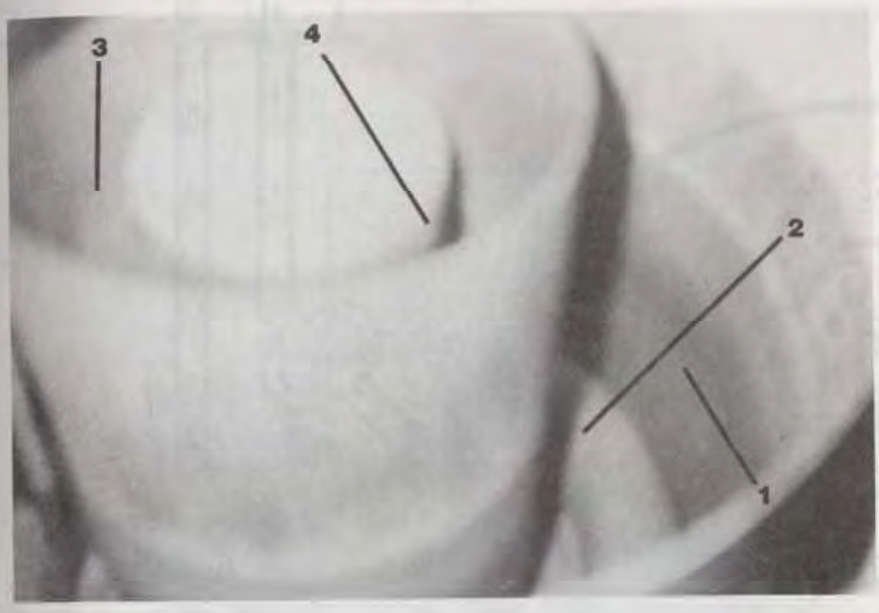


Figure 19 Internal view of Hansella precooker. (1) Precooking chamber; (2) steam coil; (3) central chamber; (4) addition of preheated corn syrup and third ingredient. (Warner-Lambert Co.)

in a dry and smooth-quality product, due to the absence of these vapors in combination with the turbulent vacuum effect that ordinarily exists in the cooking system. This principle also results in a savings of 80–90% in cooling water consumption normally required by the vacuum system to condense these vapors.

From the intermediate chamber, the finished cooked syrup (135–150°C) flows into the vacuum chamber. Flow from intermediate chamber to vacuum chamber is regulated by a metering valve, which is activated by vacuum and only opens when the vacuum chamber and receiving kettle are under full vacuum (635–762 mm Hg). The quantity of cooked syrup in the intermediate chamber must always be sufficient to seal the vacuum.

An adjustable timing device automatically changes the receiving kettles by opening an air valve the moment the required size batch has been cooked to the desired temperature. This action causes a stream of air to flow into the vacuum chamber, thereby breaking the vacuum and automatically closing the metering valve to prevent any syrup from dropping during the receiving kettle exchange. The filled receiving kettle drops from the vacuum hood and swings to the front of the cooker by means of a spring-activated turning device and is replaced by the empty one which, when in position, presses against the vacuum hood and is sealed by the vacuum. The process is repeated without any assistance from an operator (Figure 23).

The automatic kettle-changing timing device works directly from the strokes of the syrup pump; therefore, all batches are uniform in weight and quality and can be regulated from 50 to 100 lb as required. From 300 to 3000 lb of candy base can be prepared per hour of production, depending on the cooker model utilized (Table 3).

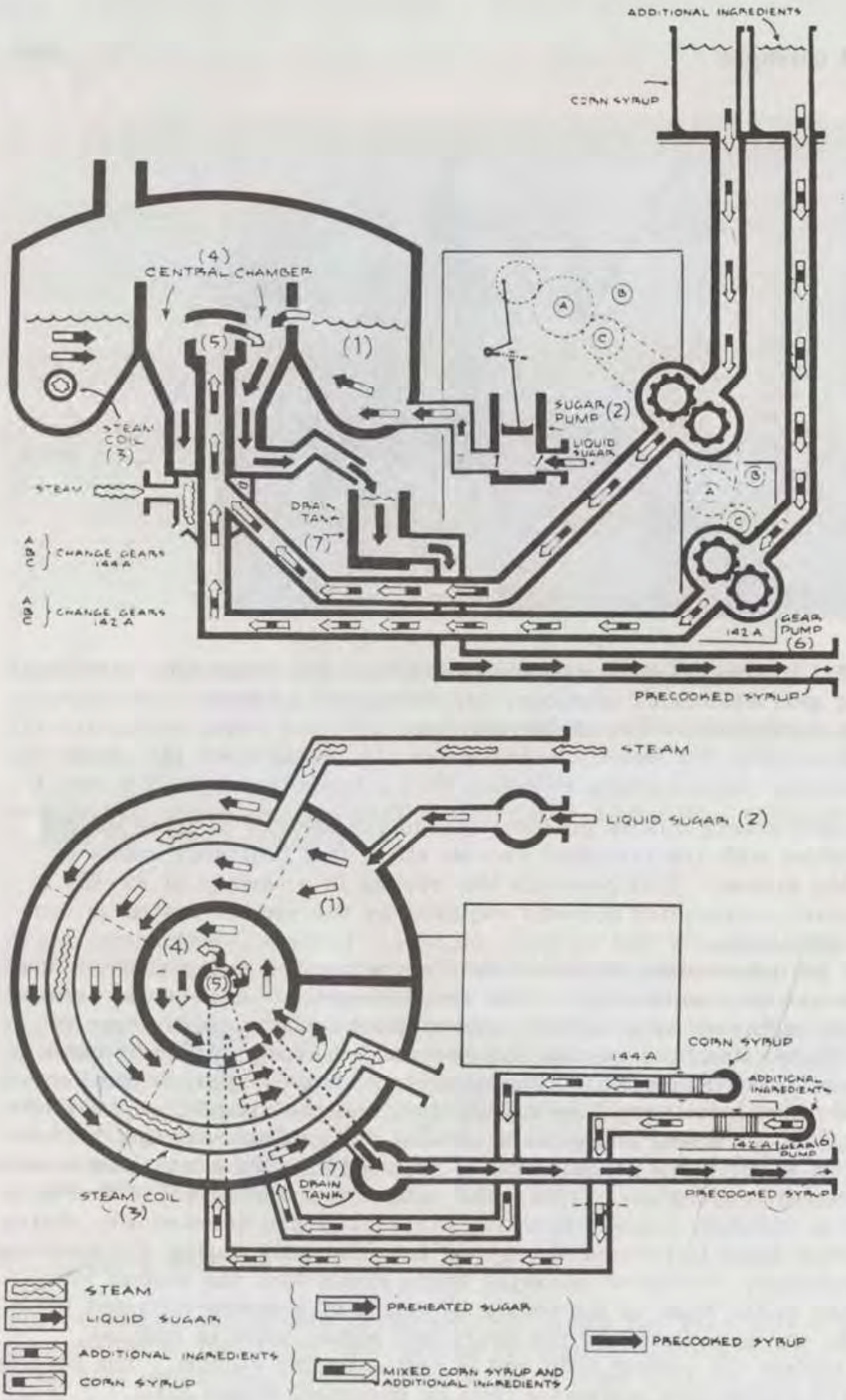


Figure 20 Hansella precooker. (1) Precooking chamber; (2) sugar pump; (3) steam coil; (4) central chamber; (5) preheated corn syrup; (6) third-ingredient pump; (7) intermediate drain tank. (Robert Bosch GmBH, Div. Hamac-Höller.)

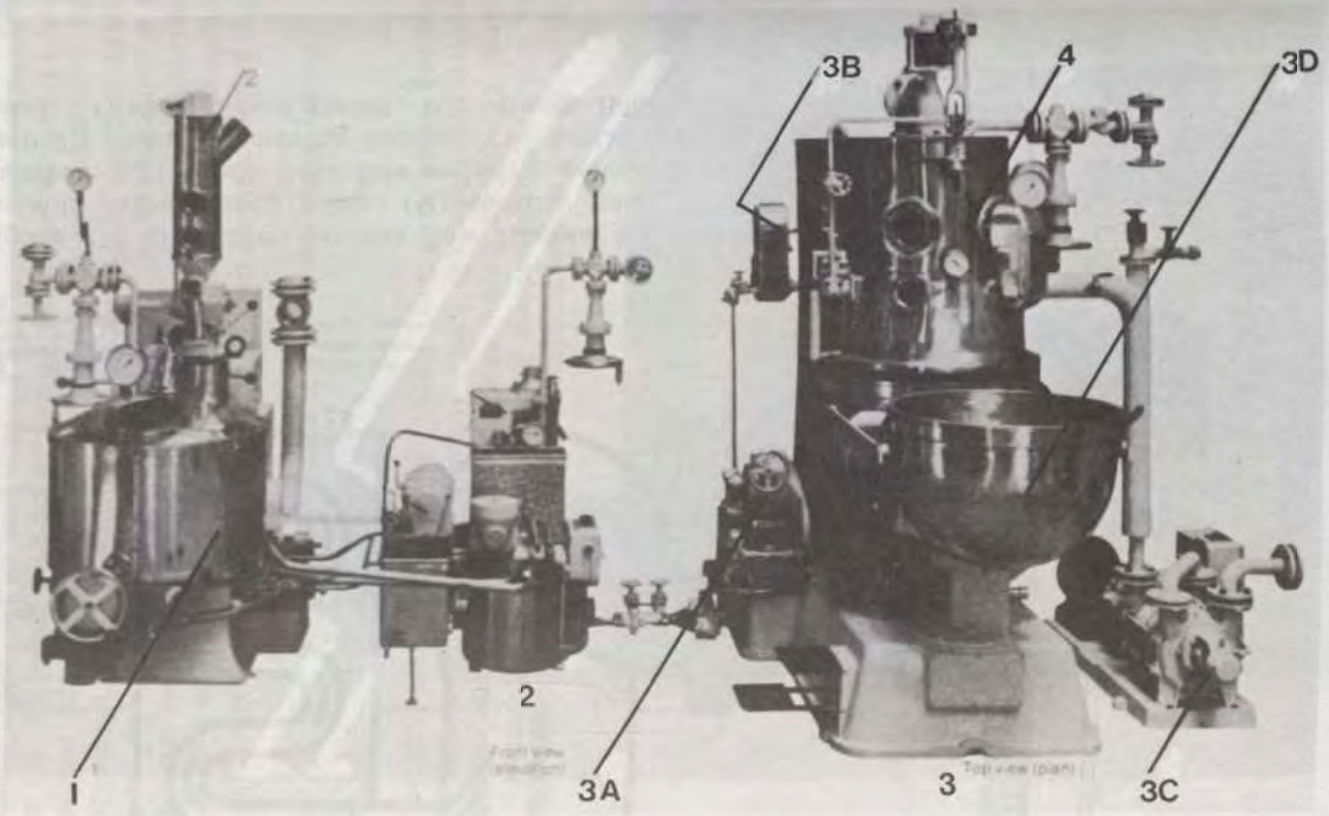


Figure 21 Complete candy base cooking setup. (1) Solvomat precooker; (2) intermediate container; (3) cooker; (3A) pump for sugar and glucose solution; (3B) metering gear; (3C) vacuum pump; (3D) delivery pan; (4) cooking chamber. (Robert Bosch GmBH, Div. Hamac-Höller.)

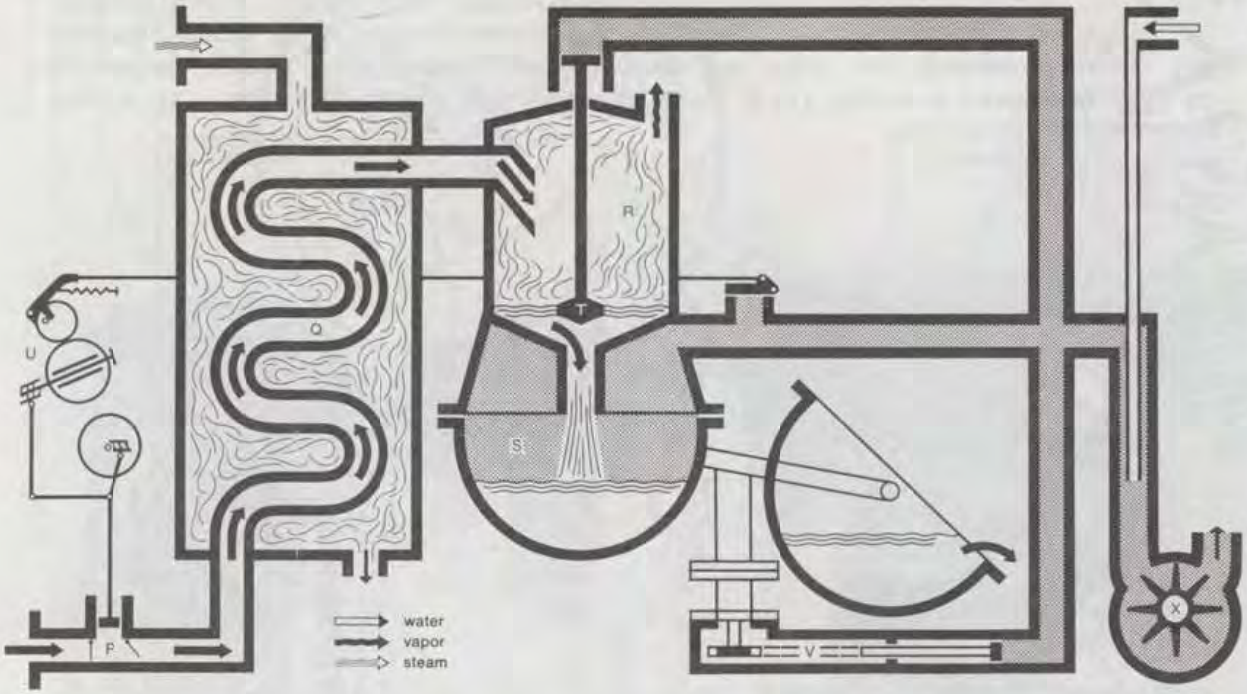


Figure 22 Simplified process flow diagram for continuous cooking system. (P) adjustable output syrup pump; (Q) cooking coils; (R) intermediate chamber; (S) vacuum chamber; (T) candy base flow metering valve; (U) adjustable timing device to automatically change receiving kettles; (V) kettle turning device; (X) rotary type vacuum pump. (Robert Bosch GmBH, Div. Hamac-Höller.)

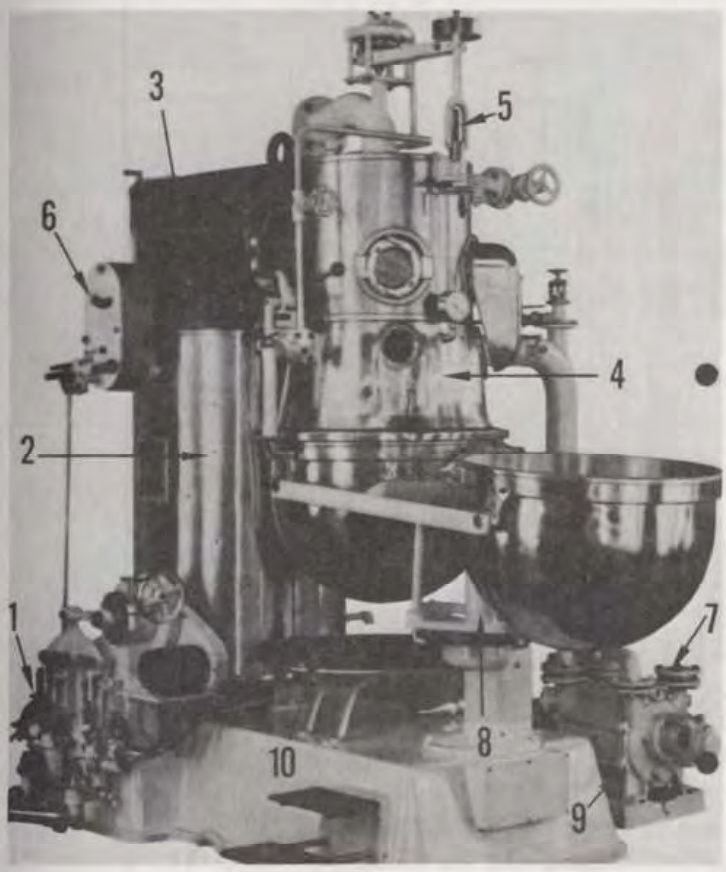


Figure 23 Vacuum cooking machine. (1) Adjustable sugar pump; (2) cooking coil; (3) intermediate chamber; (4) vacuum chamber; (5) flow metering valve; (6) timing device that automatically changes receiving kettles; (7) receiving kettles; (8) kettle turning device; (9) rotary vacuum pump; (10) washing drain. (Robert Bosch GmBH, Div. Hamac-Höller.)

F. Candy Base Manufacturing Principle

The entire cooking unit (Figure 24) is heated to the candy base cooking temperature by passing steam into and around the copper coil. The vacuum system is turned on and the steam pressure in the cooker adjusted by means of a reducing valve. Concurrently, the sugar syrup reservoir of the dissolver is filled and precooking is initiated. The precooking temperature has a considerable effect on the performance of the cooker. If the temperature is too low, more water has to be evaporated in the cooker; too high a temperature can affect the performance of the sugar pump because of the higher viscosity of the precooked mass.

The sugar pump is started and begins pumping the precooked solution into the heated coil where it is boiled and from which it is emptied into the intermediate chamber, where cooking vapors are removed to the atmosphere. The candy base then goes into the vacuum chamber where the final moisture is removed. The lubricated collection kettle is placed under the cooking dome, and the batch-size control mechanism is started. After a predetermined interval, the pan with the cooked batch is swung out.

Table 3 Typical Specifications for Three Hamac-Hansella Candy Base Vacuum Cookers

Specification	Type 135B	Type 145A	Type 155A
Capacity	1200 lb/hr to 3 tons in 8 hr	2000 lb/hr to 6 tons in 8 hr	3000 lb/hr to 10 tons in 8 hr
Drive	2 motors	2 motors	2 motors
For sugar pump	0.5 HP, 1200 rpm	0.5 HP, 1800 rpm	0.5 HP, 1800 rpm
For vacuum pump	7.5 HP, 1800 rpm	10 HP, 1800 rpm	20 HP, 1800 rpm
Steam pressure (permissible pressure)	150 lb/in^2	150 lb/in^2	150 lb/in^2
Working pressure (depending on output)	Up to 120 lb/in^2	Up to 120 lb/in^2	Up to 120 lb/in^2
Steam consumption	220 lb/hr max.	440 lb/hr max.	750 lb/hr max.
Water consumption	105 ft^3 per 8-hr day	210 ft^3 per 8-hr day	350 ft^3 per-8-hr day
Steam connection	1 in.	1 1/4 in.	1 1/4 in.
Condensed water connection	3/4 in.	3/4 in.	1 in.
Space requirements			
Width	6 ft 7 in.	7 ft. 5 in.	9 ft
Depth	8 ft	8 ft	8 ft 8 in.
Height	7 ft 5 in.	7 ft 10 in.	9 ft
Weight	Approx. 3650 lb (net)	Approx. 4500 lb (net)	Approx. 7340 (net)

Source: Robert Bosch GmBH, Div. Hamac-Höller.

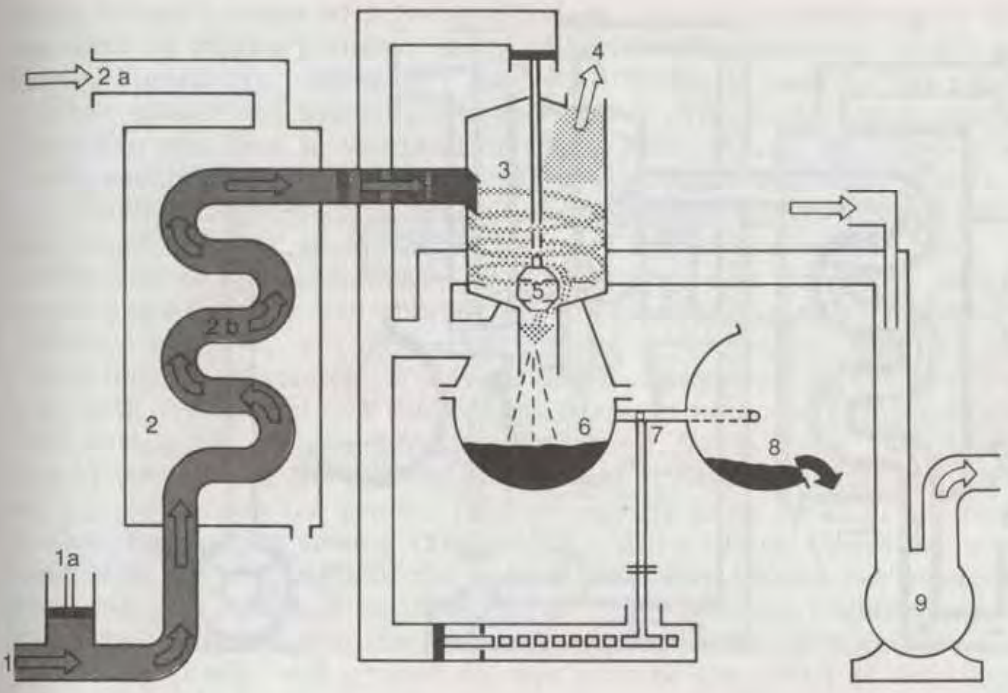


Figure 24 Schematic of candy base vacuum cooking sequence. (1) Precooked sugar-glucose solution; (1a) feed pump; (2) steam chamber; (2a) steam supply; (2b) cooking coil; (3) vapor space; (4) extraction of vapors; (5) valve; (6) vacuum chamber; (7) pan swiveling device; (8) discharge pan; (9) vacuum pump. (Robert Bosch GmBH, Div. Hamac-Höller.)

The sugar-corn syrup mixture boils violently as it moves along the relatively narrow coil surrounded by steam. The heating surface is large; therefore, rapid heat exchange results, and the mass is cooked for a very short time, through very intensely. This results in a lighter and clearer product with the potential for increased shelf life.

If the output of candy base production is increased, the steam pressure must be increased because more water must be removed over the same length of coil. Cookers should produce a candy with a final moisture content of about 1% after vacuum treatment (Figure 25).

The sugar pumps must always run in a water bath, insuring against the formation of crystals from friction. Such crystals could enter the batch and cause premature graining.

The advantages of continuous vacuum cooking are (1) a low final moisture content with little inversion—less than 2% (the inversion is kept even throughout the production run because cooking is rapid); (2) avoidance of caramelizing; and (3) a more pliable consistency of batches for subsequent processing.

G. Mixing

After the collection kettle is charged with the predetermined weight of candy base, the vacuum is broken and the kettle makes a 180° revolution, placing the second kettle in position for collection of the cooked candy base. The

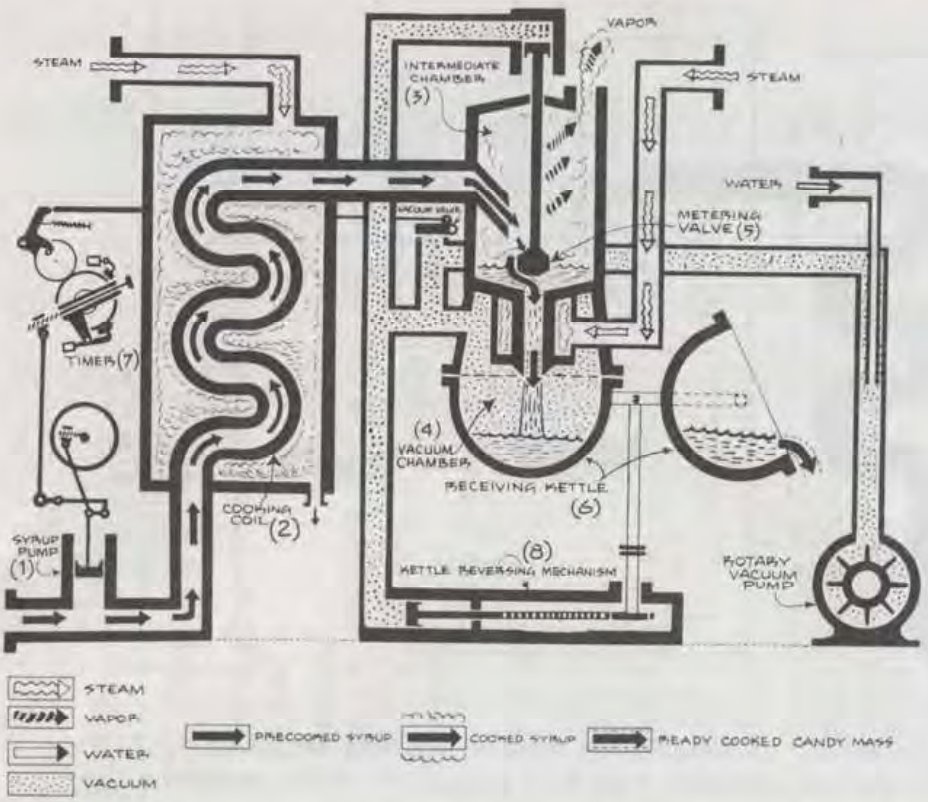


Figure 25 Complete process flow diagram for cooking system used in continuous and automatic cookers. (1) Adjustable sugar pump; (2) cooking coil; (3) intermediate chamber; (4) vacuum chamber; (5) flow metering value; (6) receiving kettle; (7) timing device that automatically changes receiving kettles; (8) kettle turning device. (Robert Bosch GmBH, Div. Hamac-Höller.)

filled kettle, heavier by the batch weight, presses the empty kettle against the vacuum hood where it is sealed by the vacuum. The cooking cycle may be completed every 3–5 min depending on the number of forming lines being serviced and the weight of the candy base collected per batch. About 1600–2100 lb of candy base can be manufactured per hour under normal batch process manufacturing conditions.

The temperature of the candy base is about 135°C, and the mass is a semisolid, having a plastic-like consistency when it is removed from the cooker. The candy mass is removed from the collection kettle into a lubricated transfer container mounted on a suitable weight-check scale (Figure 26). Here the weight of the candy base is checked and any adjustments for proper batch weight are made to the cooker (Figure 27).

At this point the colors, as solutions, pastes, or color cubes, are added and mixed into the candy base. Addition of the colors at this point (if the colors are heat-stable) allows for maximum retention time in the hot mass, assuring complete melting of the color into the base.

The candy base containing color is then transferred to a water-jacketed stainless steel cooling table for the mixing operation (Figure 28). This mixing can be either manual, using two or more operators, or mechanical,

using either a series of plows and rollers or a mixer consisting of two mixing arms, a mixing plunger, and a slowly rotating table top (e.g., Berks mixer; Figure 29). (The plow and roller mixing is used by the continuous process cooker and will be discussed later.) The Berks batch mixing machine can mix from 60 to 130 lb of candy base (Figure 30) while an experienced manual operator can efficiently mix only between 40 and 75 lb.

Throughout the mixing cycle, the temperature of the mixing table is maintained between 40 and 50°C. A table that is too hot will cause the candy base to stick, whereas a cold table will cause premature hardening. Premature hardening will shorten the effective mixing time, increase the tendency to grain, and reduce the efficiency of mixing. This will lessen the uniform incorporation of flavors and medicaments into the candy mass. With both the manual and Berks-type mixers, the operator uses a stainless steel mixing bar (Figure 31) to assist mixing and to speed the incorporation of medicament and flavors in the mass. The mechanical and manual mixing compresses the candy, thus presenting warm sides to the cool table surface for uniform cooling (Figure 32). When mixing cycles are short (less than 5 min), parts of the cooling table may become hot enough to make the candy base stick to the slab. Hydrogenated vegetable oil-based lubricant is spread onto the table surface to alleviate this condition.

Flavor, drug, and ground salvage mixture are added to the candy mass when mixing is initiated. The medicament can be dissolved in the flavor oils, then added to the ground salvage with the flavor, and mixed until uniformly distributed; or it can be added separately—with salvage or directly—to the candy mass, depending on solubility and stability characteristics of the medicament in flavor oils. The flavor, drug, acidulent (if required), and salvage mixture can be prepared on an individual batch basis

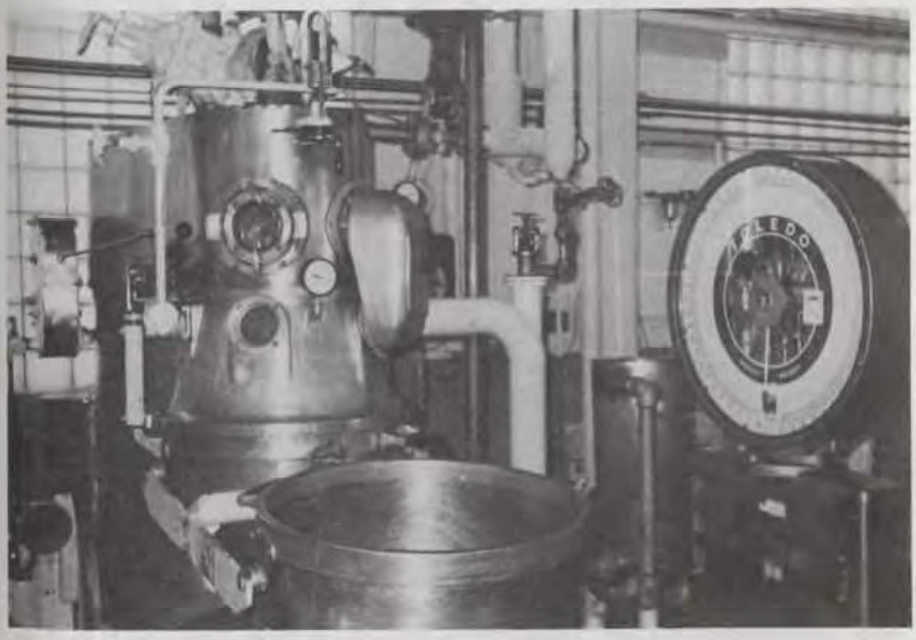


Figure 26 Candy base vacuum cooker. Scale is available to check weight each batch of candy base. (Warner-Lambert Co.)



Figure 27 Completed candy base being transferred to weighing container. All batch weights are double-checked. (Warner-Lambert Co.)

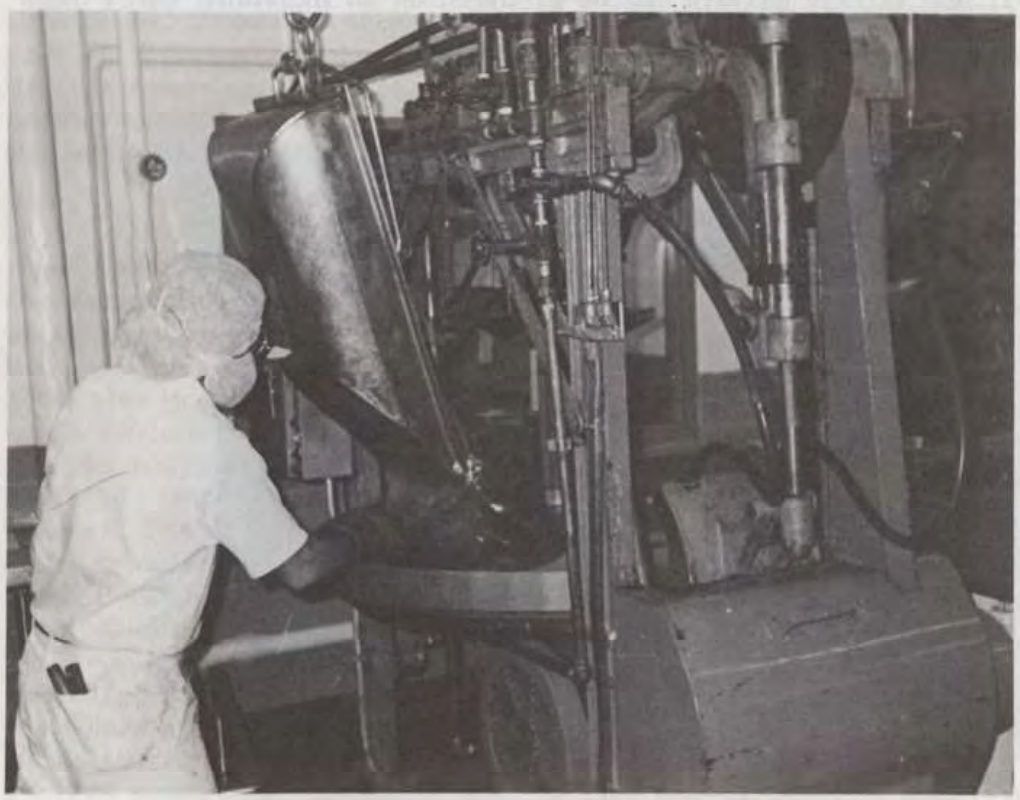


Figure 28 Operator transferring cooked candy base to mixer. (Warner-Lambert Co.)

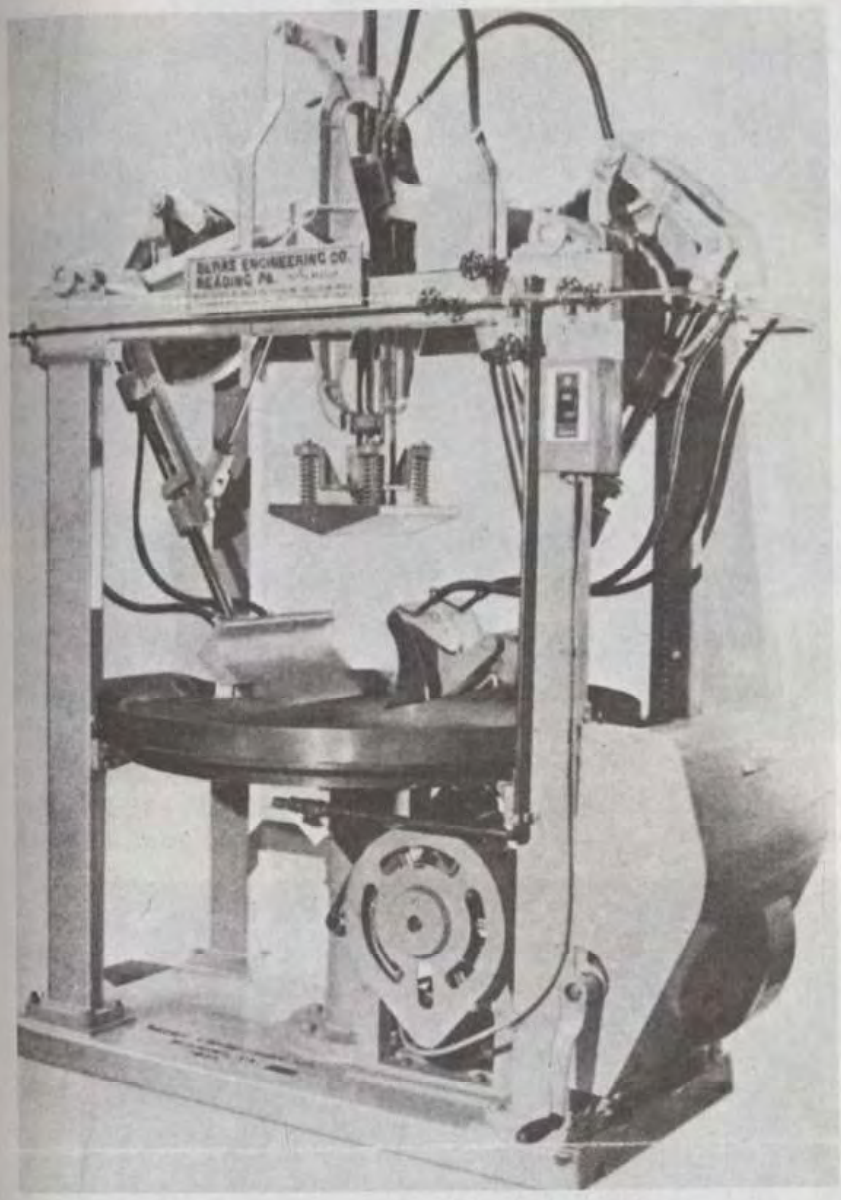


Figure 29 Plow-type batch mixing machine. Berks Co. mixer is capable of mixing 60 to 130 lb. of candy base. (Berks Engineering Co., Reading, Pa.)

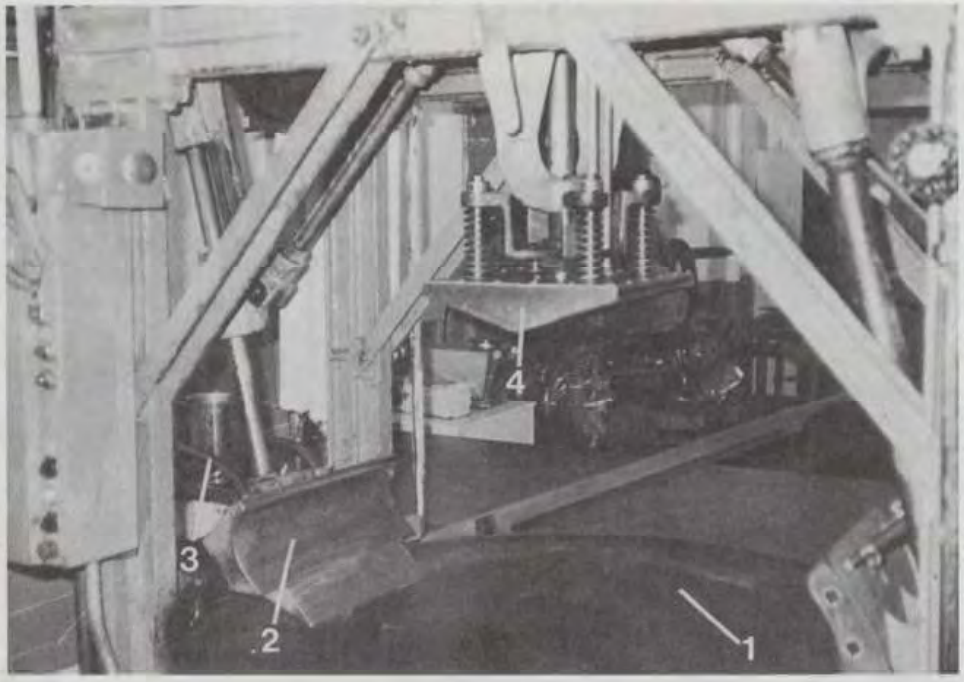


Figure 30 Plow-type mixer. (1) Water cooled and heated table that rotates one-quarter turn per mixing cycle; (2) mixing plow; (3) water inlet to plows; (4) top plow that flattens mixed candy mass. (Warner-Lambert Co.)

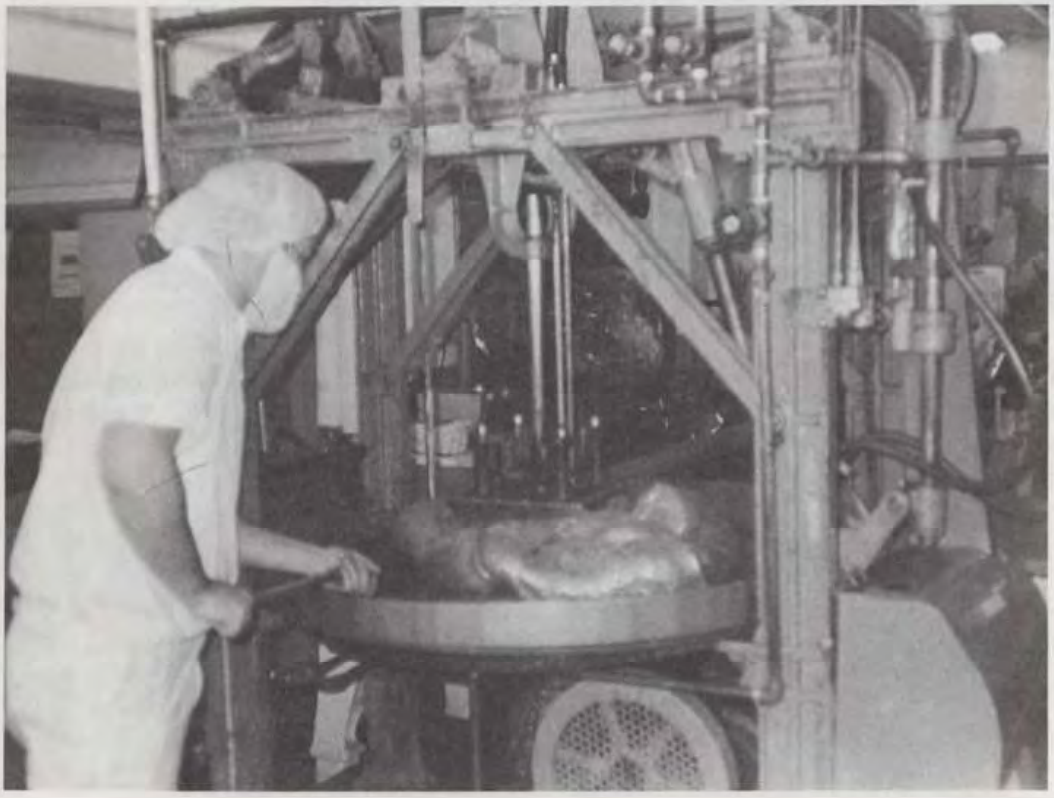


Figure 31 Operator-assisted mixing utilizing a stainless steel mixing bar. (Warner-Lambert Co.)



Figure 32 Candy base after side plows have compressed the mass. Top plow is now lowering to flatten the base. (Warner-Lambert Co.)

(Figure 33) or as a master premix (Figure 34) suitable for subdivision into individual premixes (Figure 35). This master premix can be prepared using either planetary, sigma blade, or ribbon blender. When premixes are prepared on a master batch basis, ground salvage [69] should be milled to a particle size range of 20–50 mesh (Figure 36). This produces granules that will adsorb the liquid mixture to prevent flavor and medicament segregation during granulation preparation and storage before use. If salvage is milled to a finer mesh size, the granulation will set or harden during storage, making distribution into the candy mass more difficult and requiring more operator assistance. Particles milled to the coarser mesh size will not adsorb flavor oils; such nonadsorption of flavor oils would result in problems of segregation and nonuniform distribution of flavor and medicament throughout the salvage mixture.

If the medicament cannot be added to the salvage granules in solution with the flavor oils because of incompatibility or solubility characteristics, either a direct addition of medicament to candy base on the mixing table can be made, or a separate solution of the drug in a compatible solvent can be granulated into a second salvage mixture and added to the candy mass before adding the flavor granulation. A slurry or free-flowing granulation with ground salvage using solvents such as glycerin or propylene glycol added in a ratio of one part solvent to three, four or even five parts medicament may be utilized for addition of insoluble medicaments.

The optimum mixing required to uniformly mix the flavor, salvage, and medicament into the candy base during the routine manufacture of medicated

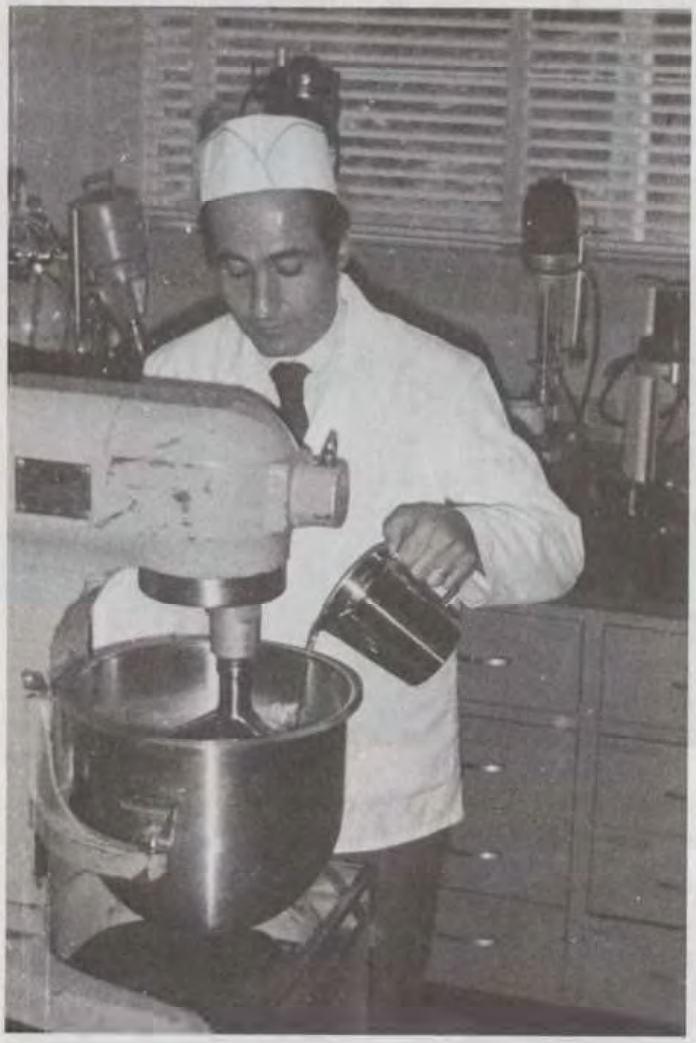


Figure 33 Preparation of flavor, medicament, and ground salvage mixture on an individual batch basis. Sufficient material is contained in the premix for incorporation into 100 lb. of cooked candy base. This procedure can be used to prepare experimental as well as production batches. Here the flavor is added to the ground salvage and medicament mixture. (Warner-Lambert Co.)

hard candy lozenges is determined by the time required to effect a uniform distribution of the materials in candy base. The time period required to cool the mass—or the speed of the cooker—determines how soon the next batch will be available for processing. The normal mixing cycle is 4–6 min.

After mixing is complete, the candy base is transferred to a warming table (Figure 37) where the batch is covered with a canvas cloth and allowed to temper (equilibrate so that it reaches a uniform temperature). This eliminates hot or cold spots in the mass, which hinder the lozenge-forming operation. Once tempered, the batch is divided into 35– to 50–lb portions that can be readily handled by the operators as they transfer the candy base to the batch former.

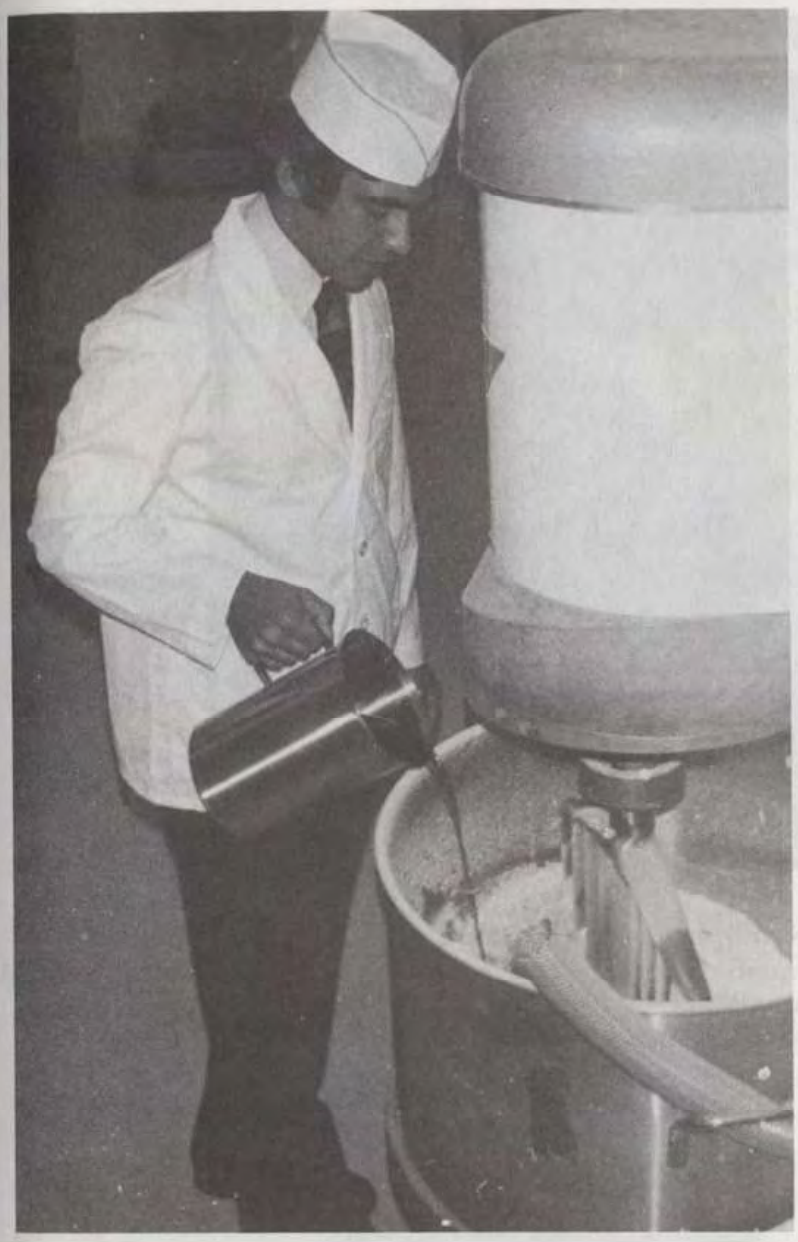


Figure 34 Preparation of flavor, medicament, acidulent, and ground salvage mixture as a master premix that can be subdivided into quantities suitable for incorporation into individual 100–lb. cooked candy base portions. The formulator is adding the flavor to the ground salvage, acidulent, and medicament mixture. This is followed by sufficient mixing to assure a uniform distribution throughout the batch. (Warner-Lambert Co.)



Figure 35 Flavor, ground salvage, acidulent, and medicament mixture being subdivided into quantities suitable for incorporation into the individual cooked candy base. All weights are checked during the subdivision procedure. Depending on the quantity of salvage required per batch, material sufficient for addition into 30 to 75 batches of candy base can be prepared as a single premix.

H. Batch Forming

After the candy mass has been properly tempered and cut into workable portions, it is transferred to the batch former (Figure 38) which is capable of holding 110–160 lb of candy base. The plastic-like sugar mass is formed by four rollers into a sugar cone that is tapered toward the front of the former (Figure 39). A pair of draw-off rollers in the rope sizer (Figure 40) draws the sugar cone from the batch former and transfers it at a uniform and predetermined rate to the sizing rollers. The operation of the batch former is synchronized with that of the rope sizer (Figure 41).

The four cone rollers are heated, usually by electricity or steam, to maintain the temperature of the batch (80–90°C) so that the outer jacket of the candy will not crack and will be uniformly shaped by the former. The rollers move in a counterrotating pattern that rolls the batch backward and forward so as not to distort any portion of the candy base in the former, expecially in the area where new material is added.

1. Rope Sizing

The delivery rate of candy coming from the batch former to the sizing rollers is determined by the height to which the batch former is adjusted, by the amount of material in the former, or by a combination of these two variables. The diameter of the sugar rope as it leaves the lower end of the former is adjusted by a hand wheel.

The rope sizer draws the sugar rope out of the batch former by means of the two draw-off rollers. The speed of the individual pairs of sizing rollers is matched so that a smooth and uniform material flow to the successive pairs of rollers is ensured.



Figure 36 Lozenges rejected due to manufacturing difficulties are milled to a particle size range of 20 to 50 mesh. This produces granules that will absorb the liquid-flavor mixture, to prevent flavor and medicament segregation during medicament-flavor premix preparation and storage. (Warner-Lambert Co.)



Figure 37 Mixed candy base on tempering table prior to batch forming. Cutting blade on right (1) is used to cut the mass into equal portions for ease of handling. (Warner-Lambert Co.)

The first pair of sizing rollers transports the candy rope, while each successive set reduces the diameter of the candy rope to the proper size (Figure 42). As the candy rope becomes smaller in diameter, the speed of the subsequent roller is increased. The thickness of the rope is determined by the diameter of the sizing rollers and by the gap between rollers. Any thickness of candy rope can be achieved by modifying the five pairs of

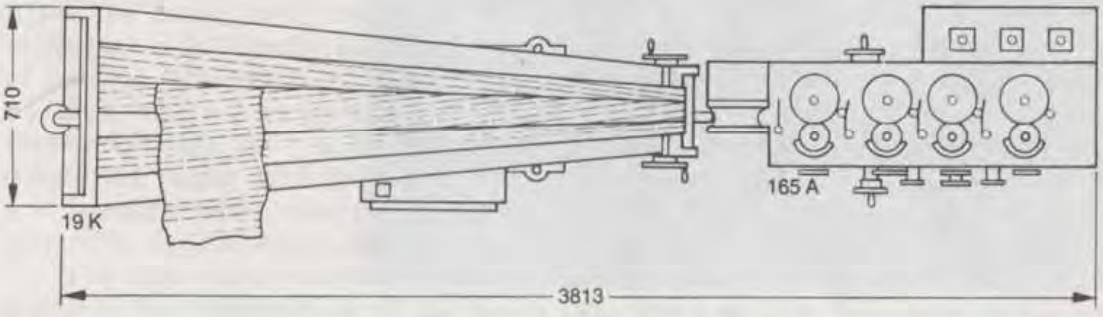


Figure 38 Schematic of batch forming operation. Candy base is fed into batch former. Between 100 and 160 lb. can be mixed. Formed batch is then passed through the 165A rope sizer to produce candy rope of uniform diameter. (Robert Bosch GmBH, Div. Hamac-Höller.)

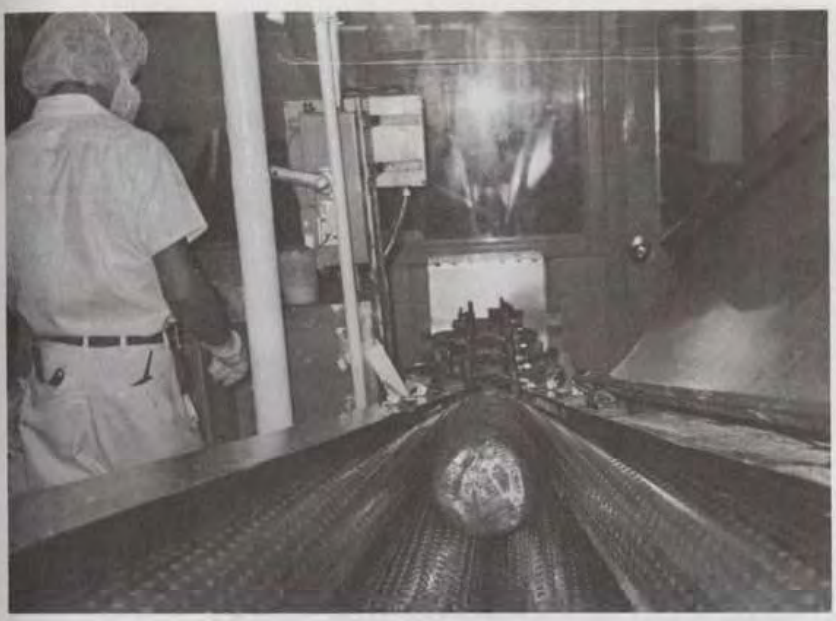


Figure 39 Candy base after forming is fed into sizing rollers from batch former. Note that candy mass has been formed into a cylinder. (Warner-Lambert Co.)

successively smaller forming rollers. The rollers are profiled to ensure satisfactory travel of the rope through the sizer. Electric heaters under the sizing rollers are thermostatically controlled to maintain the roller temperature a few degrees below the temperature of the batch (between 50 and 60°C). This prevents cracking at the surface of the rope.

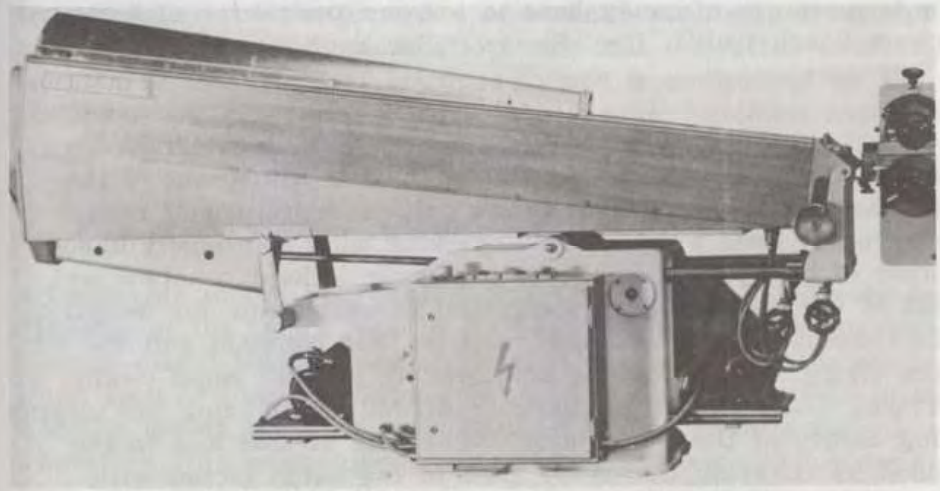


Figure 40 Hansella candy base batch former. Capacity 165 lb. of unpulled candy. Initial hand-adjusted sizing wheel is pictured at right. (Robert Bosch GmBH, Div. Hamac-Höller.)



Figure 41 Batch former and rope sizing unit. Rollers are heated a few degrees below temperature of candy base to prevent premature surface cooling. (Robert Bosch GmBH, Div. Hamac-Höller.)

The weight of the final piece is determined by the adjustment of the sizing rollers. Batch forming and sizing are critical operations if each lozenge is to have the same weight. The operator must continually check that the quantity of candy base in the batch former is kept constant and that the height of the batch former is adjusted to compensate for weight changes. The temperature of the batch must be held constant and the temperature of the sizing rollers must be monitored to prevent rapid cooling of the batch surface, which results in cracking as well as reducing the plasticity and forming ability of the candy mass. The rate of heat loss in the batch is reduced by covering the candy mass in the batch former with either the metal cover supplied with the former or a lubricated canvas cover. This also keeps the batch in a plastic-like state that is optimum for forming.

The speed of each set of sizing rollers should be individually adjusted throughout the sizing operation so that the candy rope is conveyed from



Figure 42 Candy rope is fed through the sizing rollers. Diameter of candy rope determines final lozenge weight. (Warner-Lambert Co.)

one set of sizing rollers to another rather than actually sized down. The sizing operation should taper the rope in such a granual manner as to not produce any unwarranted stretching or bulging of the candy rope. Overstretching or bulging may result from a sudden change in rope temperature (nontempered candy), candy base consistency or elasticity (undissolved or excessive solid salvage or medicament addition), or improper feed rate (too fast or slow) of candy from batch former to sizing rollers. These inconsistencies will cause the formation of a candy rope with a nonuniform diameter, resulting in the production of lozenges that are either overweight or underweight, as the weight of lozenges formed is determined by the diameter of the candy rope. The piece weight will remain uniform and within product specifications if the diameter of the rope is fixed (Figure 43).

J. Role of the Plastics Operator

Adjustments to the final lozenge weight can be effected only by altering the diameter of the candy rope or by changing the size or configuration of the lozenge dies. Manufacture of product with a uniform weight is assured when each of these conditions is held constant. The dies in the forming machine remain fixed for each product under normal production conditions. Therefore, the major concern is with maintaining a candy rope with a uniform and reproducible diameter. This function is the concern of the plastics operator, so-named because at the time the candy base leaves the batch former, it is in a doughy, plastic-like state. This operator must perform the initial and all subsequent adjustments to the sizing rollers based

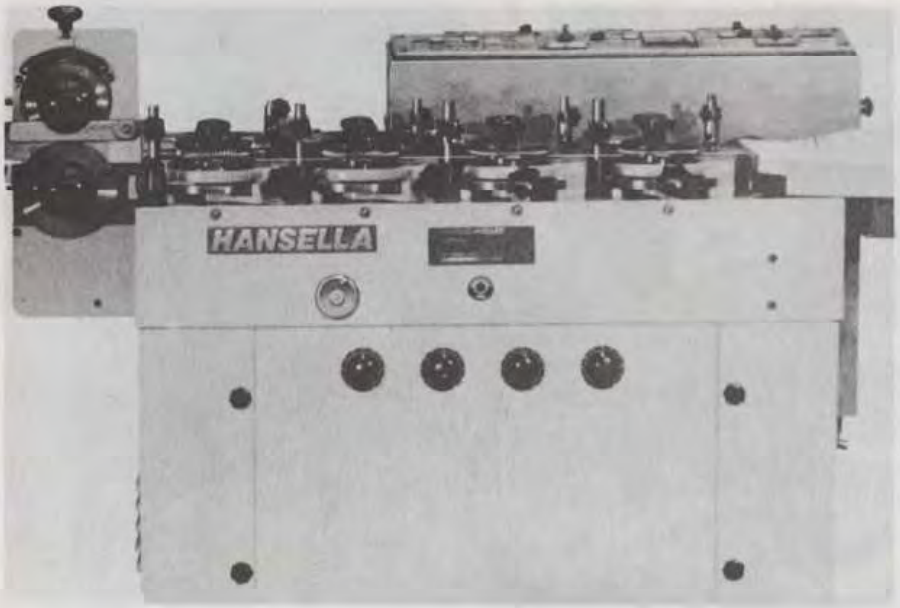


Figure 43 Hansella rope sizer. Feed capacity is variable from 28 to 400 ft. of candy rope per min. A clutch enables the operator to stop or slow the sizing rollers while the motor is running. (Robert Bosch GmBH, Div. Hamac-Höller.)

on the weight of the lozenges desired and by the condition of the candy base. The operator must also adjust the speed of the sizing rollers, depending on the temperature and flow of candy base from the batch former to the sizing rollers. The plastics operator, depending on the quantity of material present in the batch former, is required to adjust the height of the batch former to maintain a uniform flow rate to the sizing rollers. The operator, as the candy leaves the sizing rollers, must initiate the feed into the lozenge-forming machine as well as adjust the forming machine molding speed and pressure.

The plastics operator, monitoring the batch-forming, rope-sizing, and lozenge-forming operations, must be well trained, aware of all the variables that may affect production, and able to diagnose and remedy problems as they arise. Any efficient lozenge-making operation can be severely limited by an inefficient or untrained plastics operator. The efficiency of the forming operator is directly relatable to the quantity of lozenge rejects formed.

K. Lozenge Forming

The candy rope is fed into a final set of sizing rollers after it is discharged from the batch former and rope sizer (Figure 44), and from there into the rotating die head furnished with plungers and guiding cams (Figure 45) for the stamping and formation of the individual lozenges (Figures 46 and 47) [83]. The formed lozenges are then fed onto a distributor belt (Figure 48) which gives the lozenges their initial intensive cooling and shaking, in order to prevent any deformation of the still-plastic lozenges.

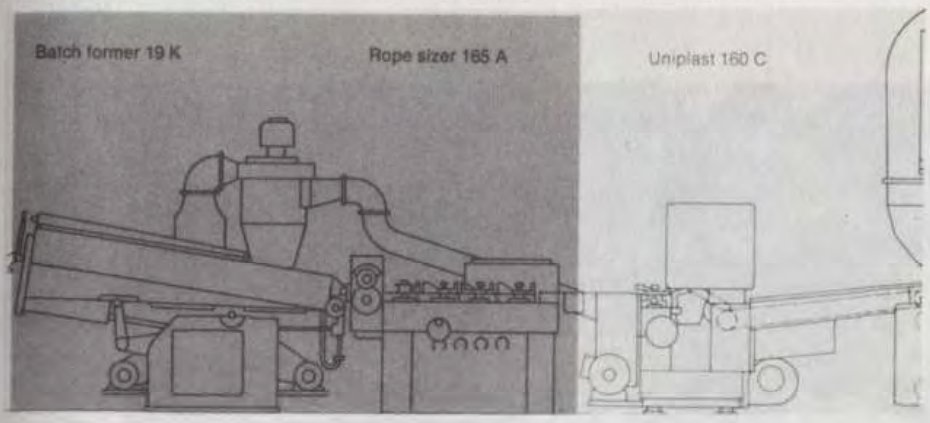


Figure 44 Schematic of batch forming, rope sizing, and lozenge forming operation. (Robert Bosch GmBH, Div. Hamac-Höller.)

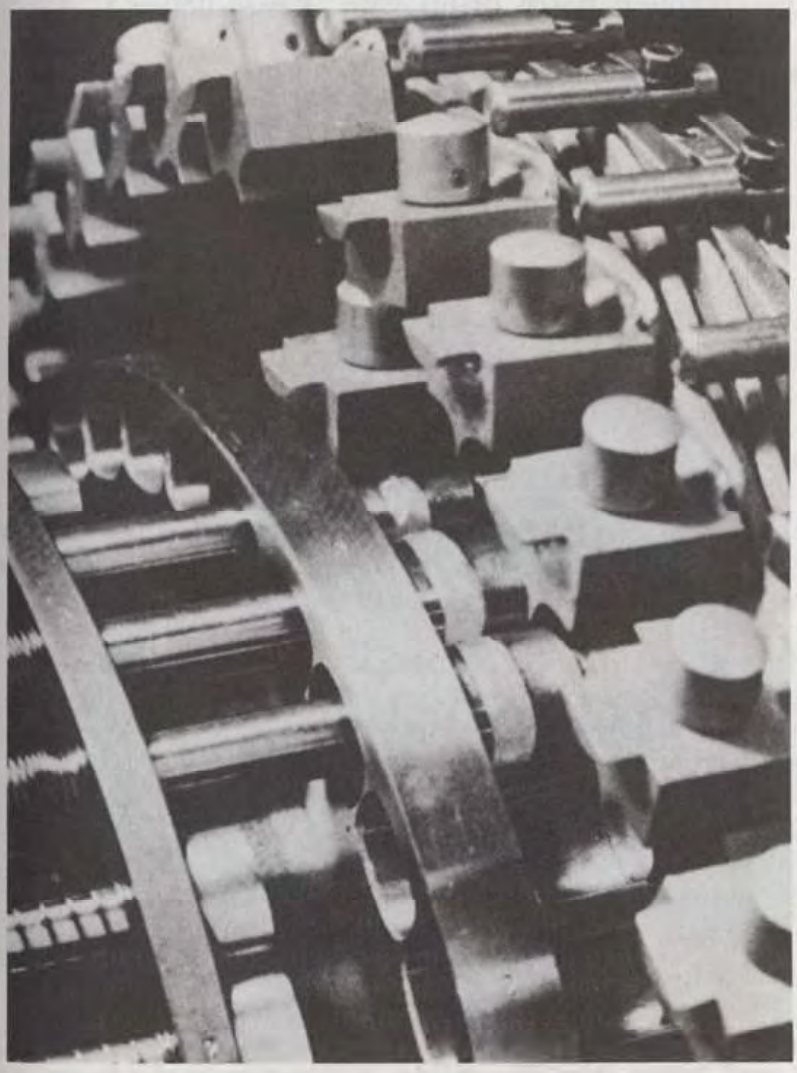


Figure 45 Lozenge forming dies furnished with plungers and guiding cams. (Robert Bosch GmBH, Div. Hamac-Höller.)

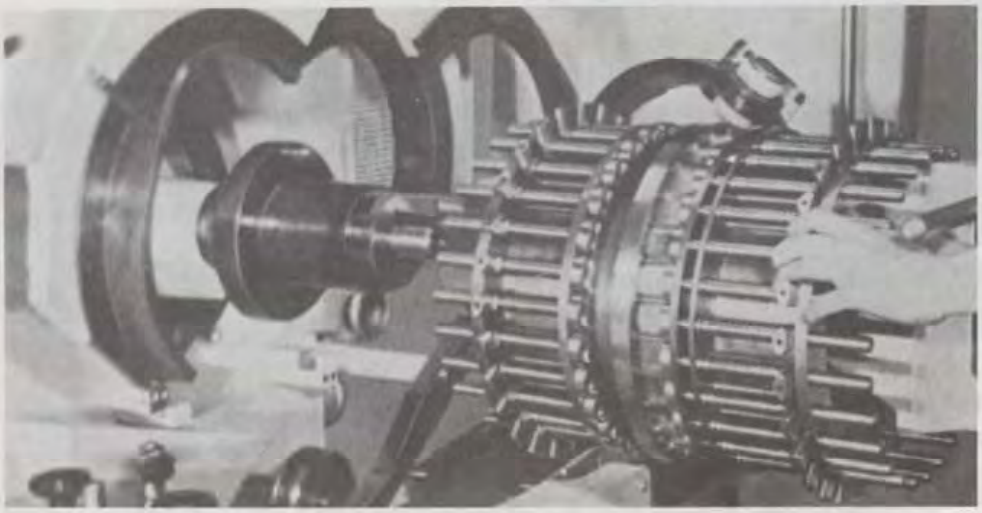


Figure 46 Installation of lozenge forming dies into Uniplast automatic lozenge forming machine. (Robert Bosch GmBH, Div. Hamac-Höller.)

Various forming machines produce candy at speeds ranging from 450 to 3000 lb/hr (Figures 49–52) depending on the lozenge weight, and in a multitude of shapes depending on the die configuration. The pressure on the dies is increased gradually and carefully as the forming operation commences, until well-shaped pieces of the desired gauge are formed. Extreme pressure must be avoided as this will cause premature wearing of the dies and the forming unit. Such excessive pressure may also cause expansion of the molded piece, with resultant distortion or cracking. Attempts to obtain a lower weight per piece by increasing the pressure without reducing the diameter of the rope results in failure, since candy piece weight can only be reduced by decreasing the rope diameter. Before the molding cycle begins, the dies must be warmed to prevent the surface of the formed piece from cooling too quickly and developing cracks (Figure 53).

L. Cooling

The candy piece must be cooled as rapidly as possible after it is formed to prevent it from losing its shape [4]. The cooling temperature should not fall below 15°C during this operation because air that is too cool will cause the lozenge surface to cool faster than the inside, a situation that places stresses and strains on the lozenge resulting in cracking and formation of air pockets.

After forming, the lozenges are ejected from the forming machine onto a cooling belt (Figure 54). This cooling line may either be a single- or multiple-belt conveyor [4]. Multiple-belt conveyors are preferred because they conserve space (Figure 55). The multiple belts are designed so that the first narrow belt (6–8 in. wide) will run as rapidly as the forming machine. At the end of this belt there is a breaker which will break up the candy if it is held together—and at the same time distribute the lozenges uniformly across a second belt (2–3 ft wide) that travels at a much slower speed than the first. At the end of the second belt, the product is transferred to a third belt, which is wider than the second (3–4 ft) and which travels at a still slower speed. The travel time for lozenges on the cooling belts is calculated so that when product reaches the end, it is cooled to below 35°C. The length of cooling time afforded the product depends on the thickness of the candy, as heat must be extracted from the inside to the outside. The thicker the product, the slower the release of heat. The cooling temperature must be controlled and the relative humidity should also be maintained at 35%. Any deviations from this value should also be

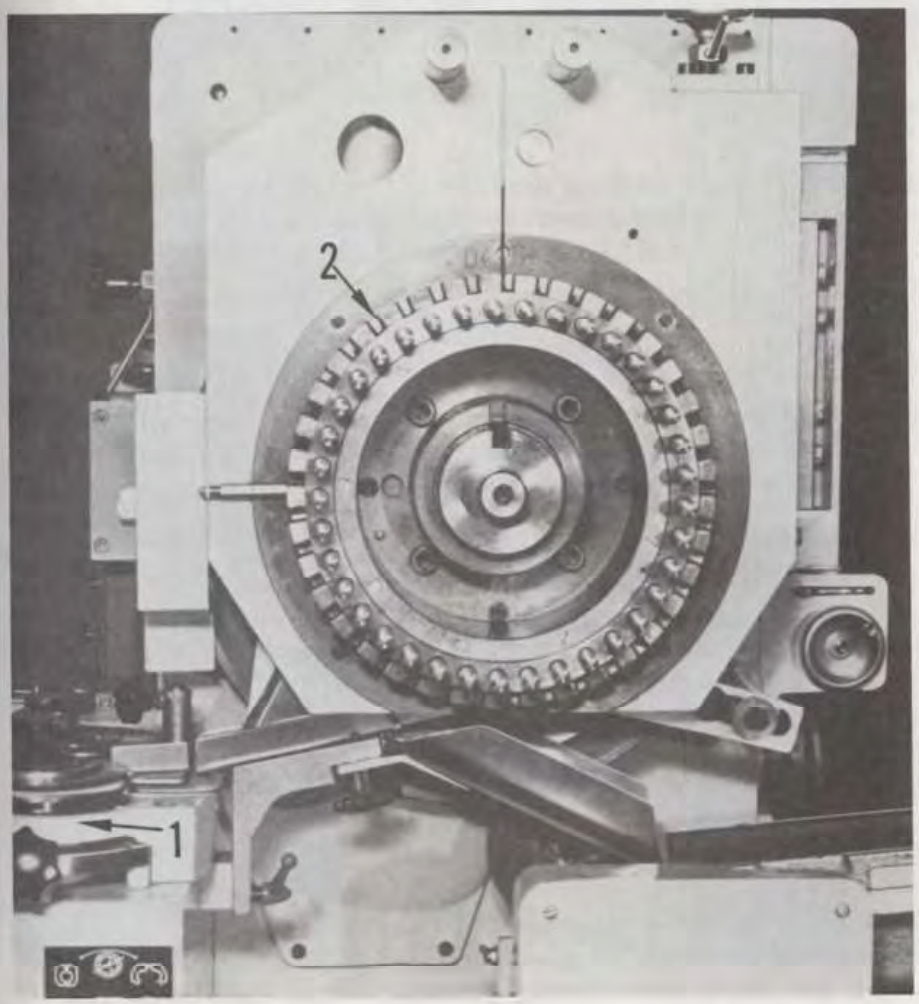


Figure 47 Uniplast 160C: automatic lozenge forming machine, open view. (1) Final rope-sizing rollers; (2) candy forming dies. (Robert Bosch GmBH, Div. Hamac-Höller.)

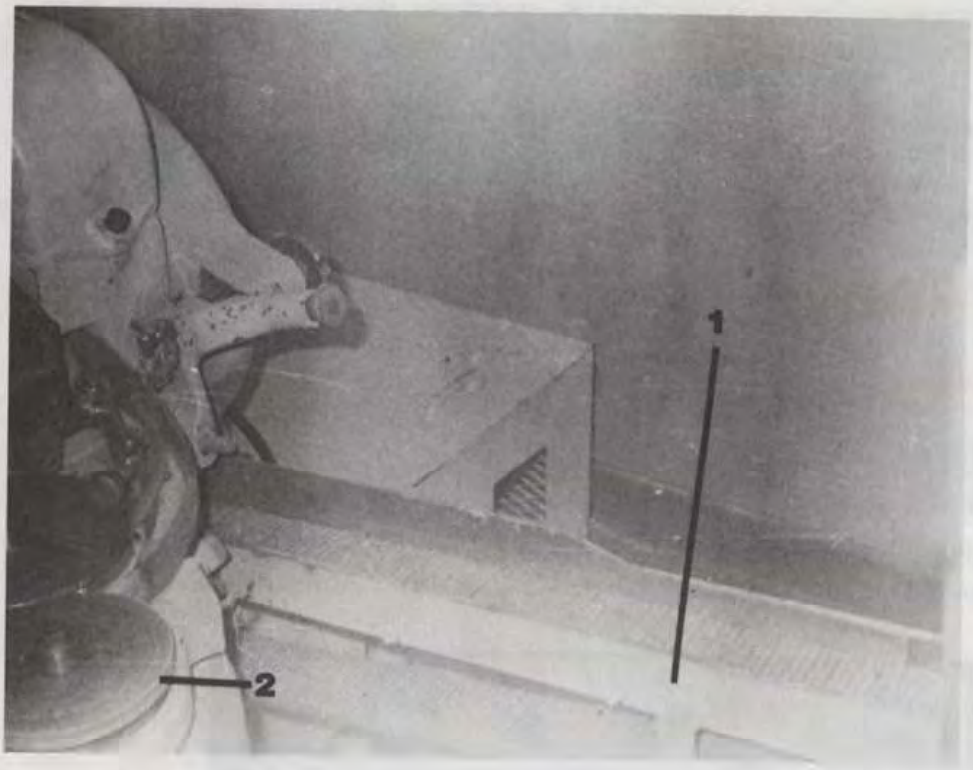


Figure 48 Automatic lozenge forming machine. (1) Ejection chute that carries lozenges away from forming machine to cooling tunnel; (2) final rope-sizing rollers positioned before candy base enters forming machine. (Warner-Lambert Co.)

considered when adjusting the cooling belt speed. All three aspects (lozenge thickness, cooling air temperature, and relative humidity) must be considered to produce lozenges with a minimum of flattening or stress cracking.

Air is blown over the product at a temperature of 15–20°C, at a velocity of 1500–3500 ft/min (normal velocity 2000 ft/min) as the lozenges pass through the cooling belts [4]. A gradual cooling temperature gradient along the belt can also be used instead of a uniform 15–20°C. This gradual reduction in temperature reduces lozenge stress cracking. The relative humidity in the cooling area should be maintained between 35 and 40%. Large differences in relative humidity may increase the incidence of moisture condensation on the surface of the lozenges.

M. Lozenge Sizing

Lozenge sizing is the operation whereby all oversized and undersized material is removed, leaving only that of the specified size. The sizing procedure (along with the candy base mixing process, which determines the uniformity of medicament distribution throughout the mass) is considered an extremely important operation, since proper lozenge weight dictates how much medicament is delivered to the patient per unit dose.

As described in Section II.K, the diameter of the candy rope, and not the force of compression, determines the final lozenge weight. Adjustments in compression force can modify the lozenge thickness (gauge) within certain narrow limits; but (unlike the preparation of tablets) adjustments for weight and size cannot be made on the lozenge former during the forming operation, as the forming machine will mold the candy rope into the shape of the die as it passes through—regardless of diameter. Stretching or compressing the candy during the rope-sizing operation before entrance into the forming machine results in the production of lozenges either too light or too heavy. Since the forming operation molds lozenges to size, control of the lozenge weight depends on control of the size of the piece. Lozenges formed in the desired size range also will be formed in a specified weight range. This relationship is the basis for the sizing operation; lozenge weight is related to its size.

The sizing operation consists of collecting the product as it leaves the cooling belt and transferring it (Figure 56) to a series of counterrotating rollers that are separated via a caliper adjustment (Figure 57). The first

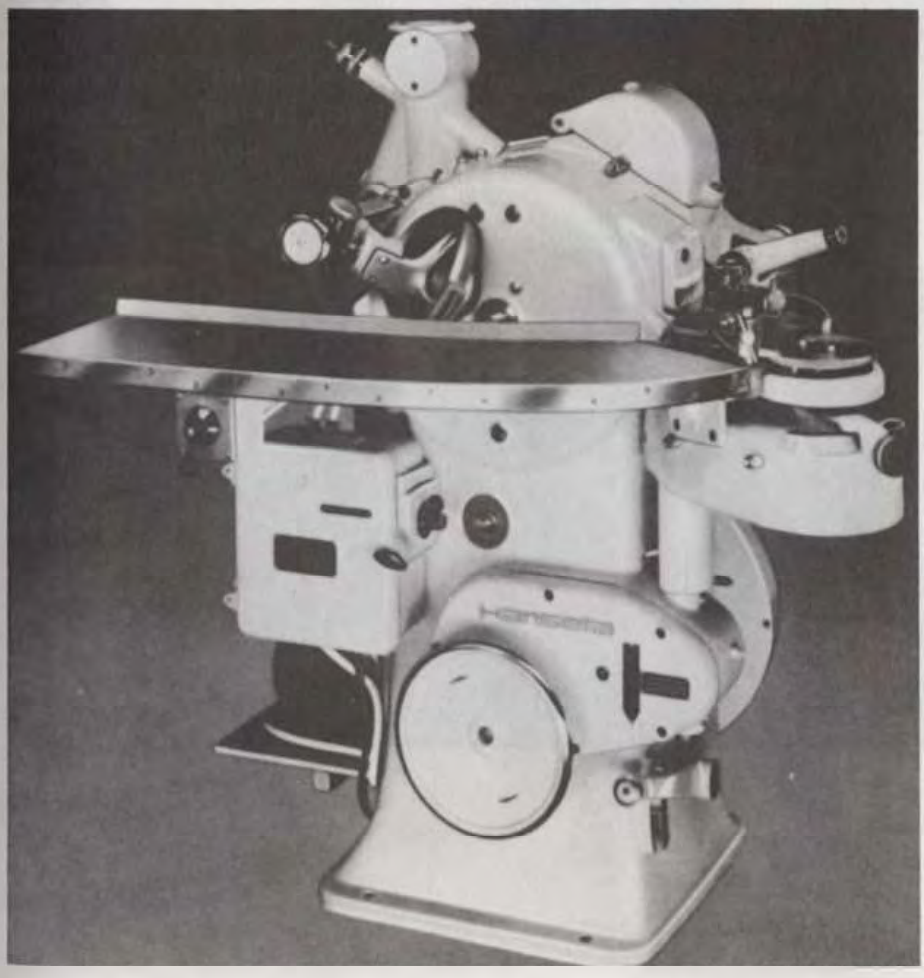


Figure 49 Super Robust lozenge forming machine produces lozenges of all shapes and sizes without seams. (Robert Bosch GmBH, Div. Hamac-Höller.)

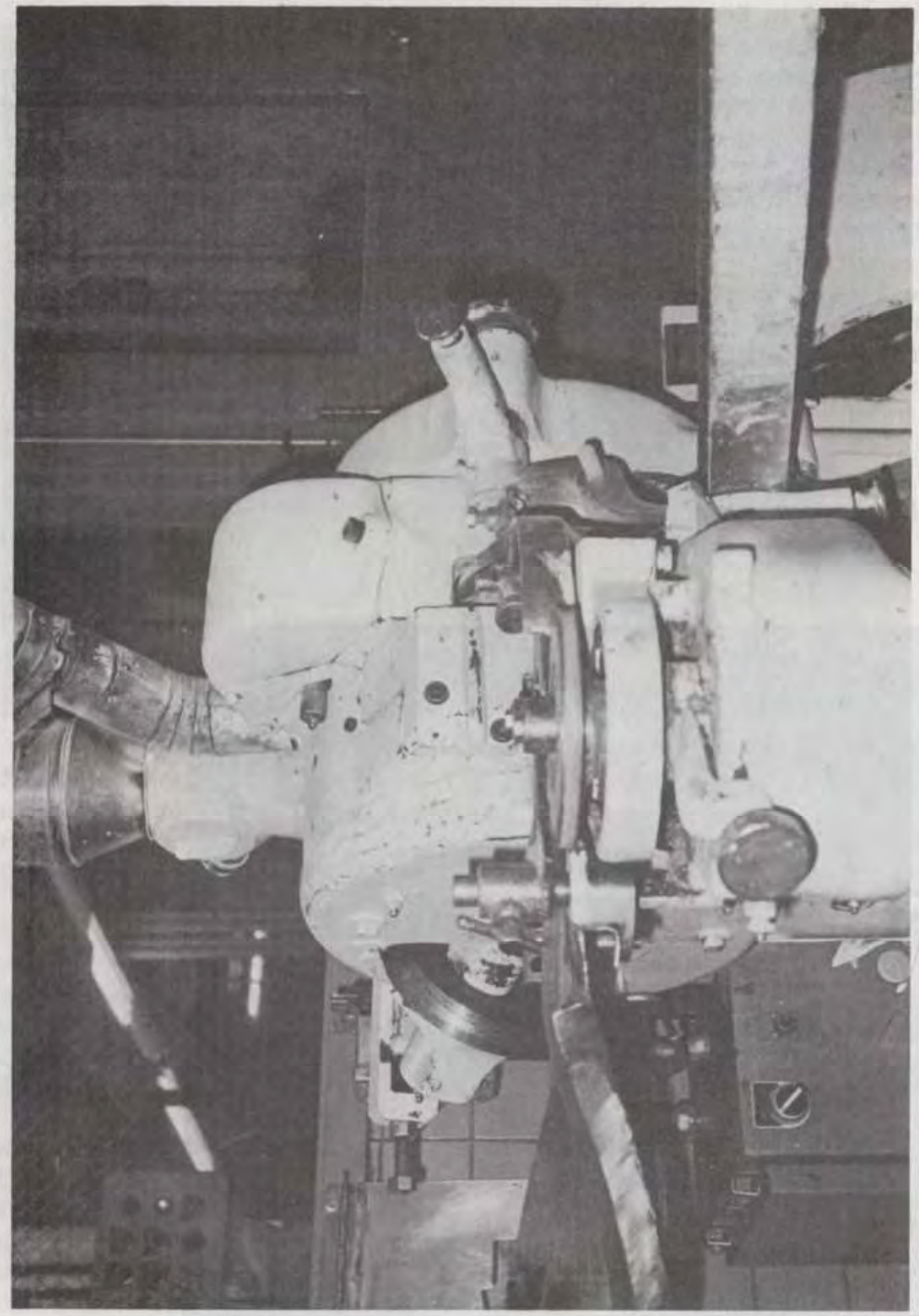


Figure 50 Super Robust lozenge forming machine. From 925 to 1675 lb. of lozenges can be formed per hour. The Super Robust has a 3-speed drive. (Warner-Lambert Co.)

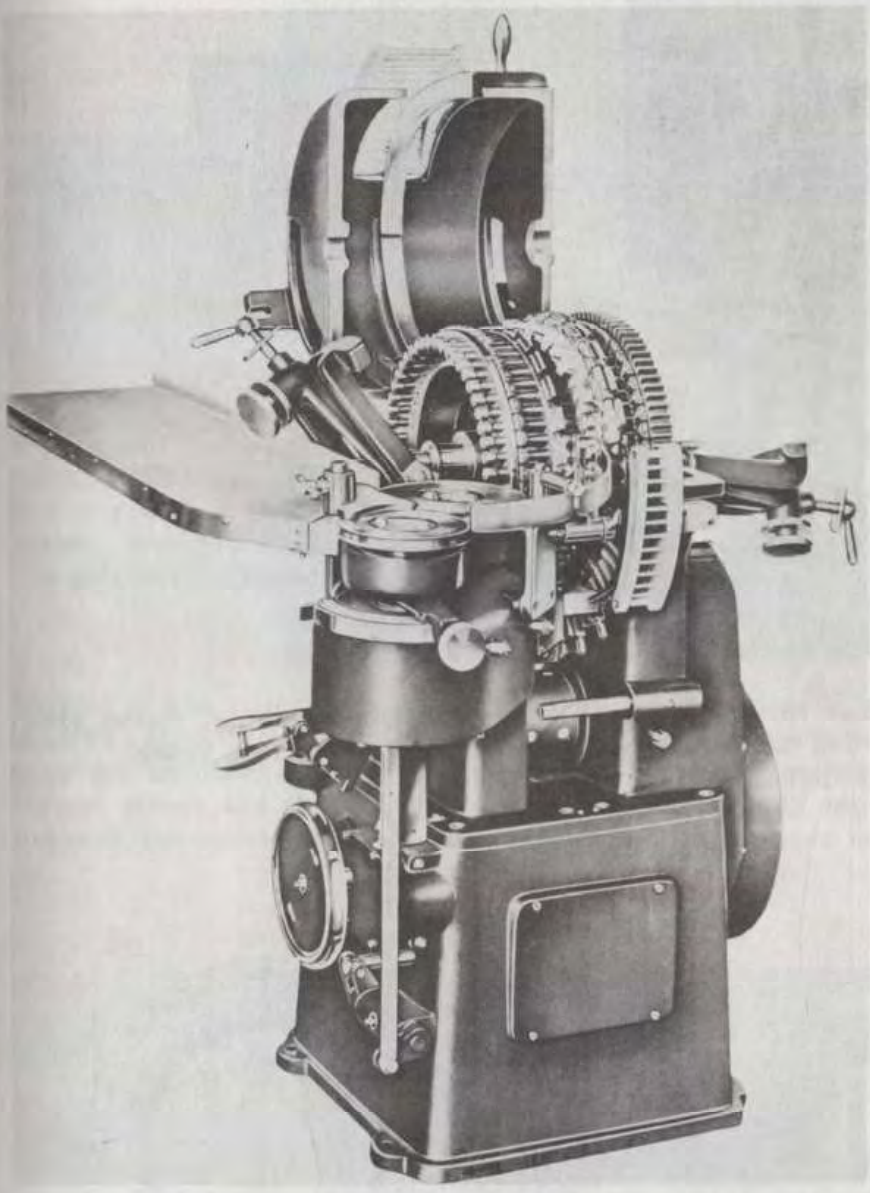


Figure 51 Super Rostoplast forming machine produces lozenges in a wide range of sizes and shapes. Output: 450 to 700 lb/hr. (Robert Bosch GmBH, Div. Hamac-Höller.)

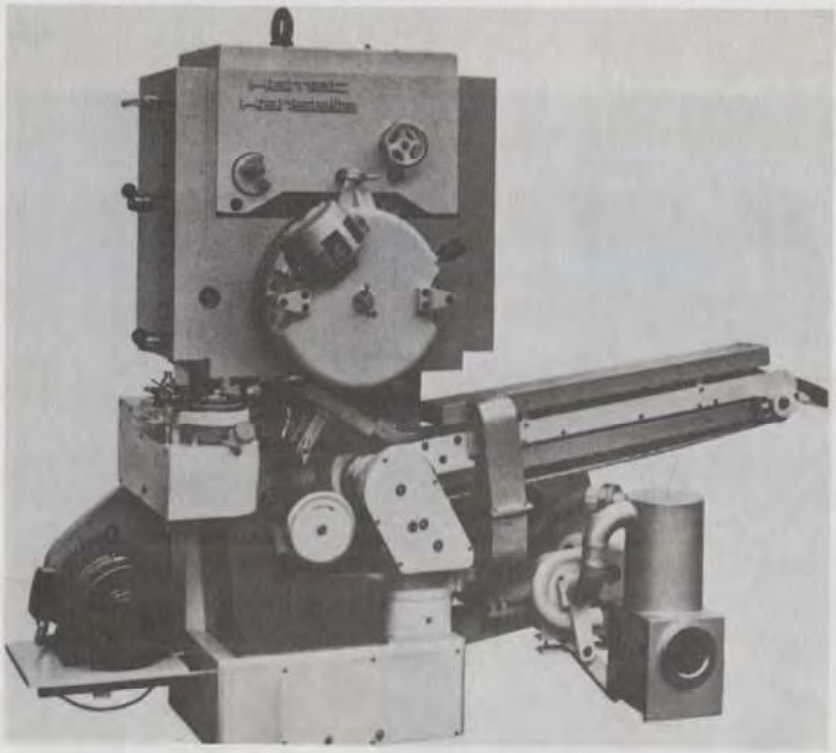


Figure 52 Uniplast 160C: automatic lozenge forming machine, closed view. Lozenge output: 745 to 2200 lb/hr; 4-speed motor. (Robert Bosch GmBH, Div. Hamac-Höller.)

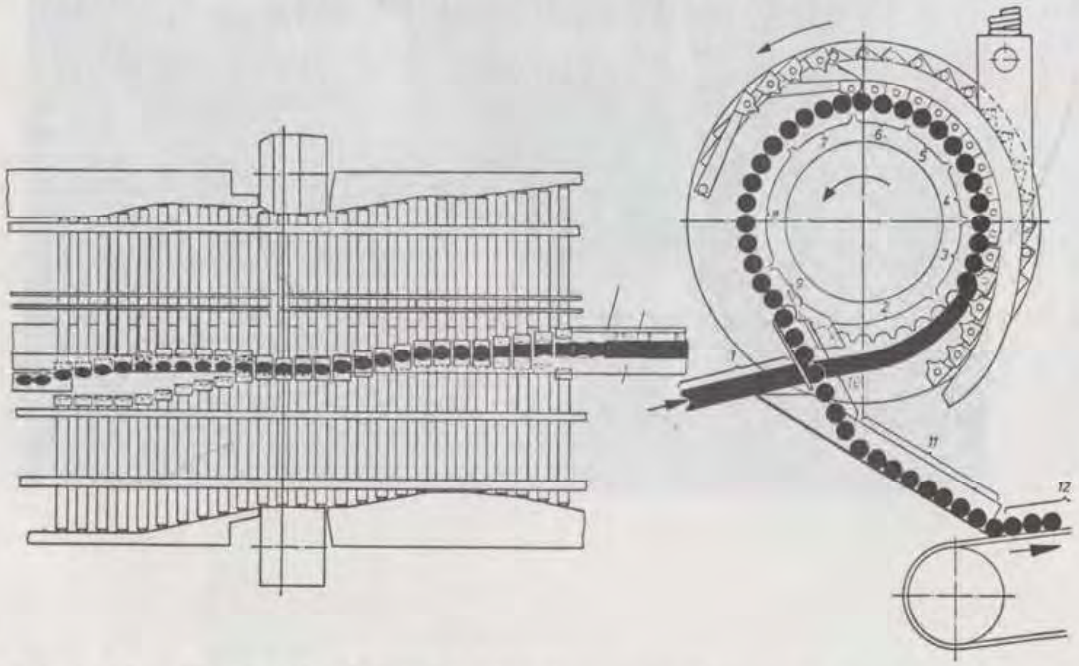


Figure 53 Schematic of lozenge forming operation. (1) Rope feed, (2) rope entry, (3) preforming of rope, (4) separation, (5) sweet preforming in flaps, (6) insertion into the die ring, (7) stamping in the die ring, (8) stress relief, (9) ejection, (10) chute, (11) feed trough to distributor belt, and (12) distributor belt. (Robert Bosch GmBH, Div. Hamac-Höller.)

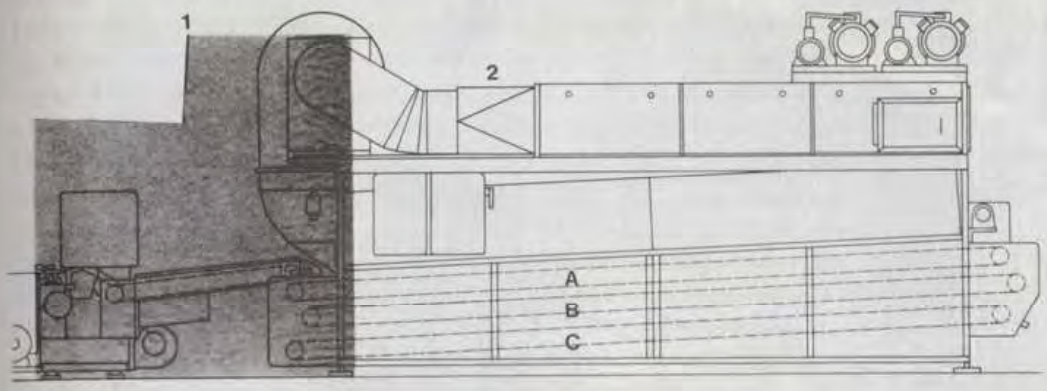


Figure 54 Schematic of lozenge forming and cooling operation. (1) Lozenge forming machine; (2) multiple-belt conveyor cooling tunnel. Belt A moves at the speed of the forming machine. Belts B and C each move at slower rates. The overall belt speed is dependent on the time necessary to cool the product. (Robert Bosch GmBH, Div. Hamac-Höller.)

portion of the rollers where the lozenges are deposited is separated only slightly, thus allowing only undersized lozenges to drop through, where they are collected in salvage containers. Scraps of broken or incompletely formed pieces are also collected, as is stretched candy rope. The opening between the rollers is gradually widened as the lozenges continue down the

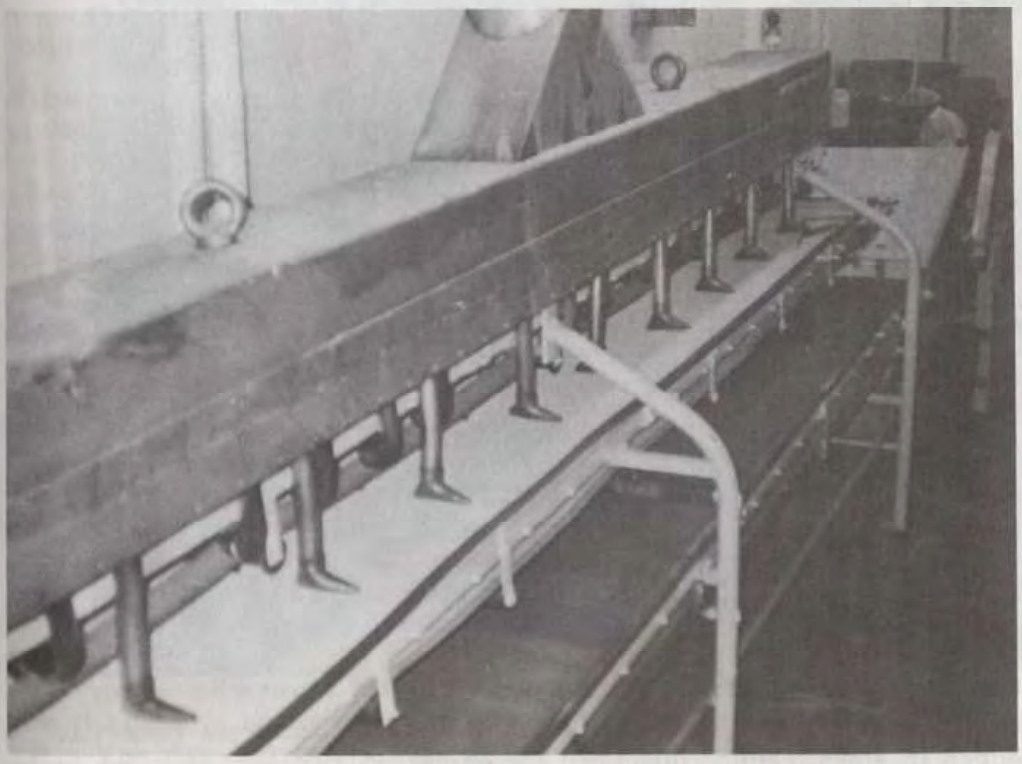


Figure 55 Multiple belt lozenge cooling tunnel. (Warner-Lambert Co.)



Figure 56 Cooled lozenges are transferred to an elevator for movement to the sizing rollers. (Warner-Lambert Co.)

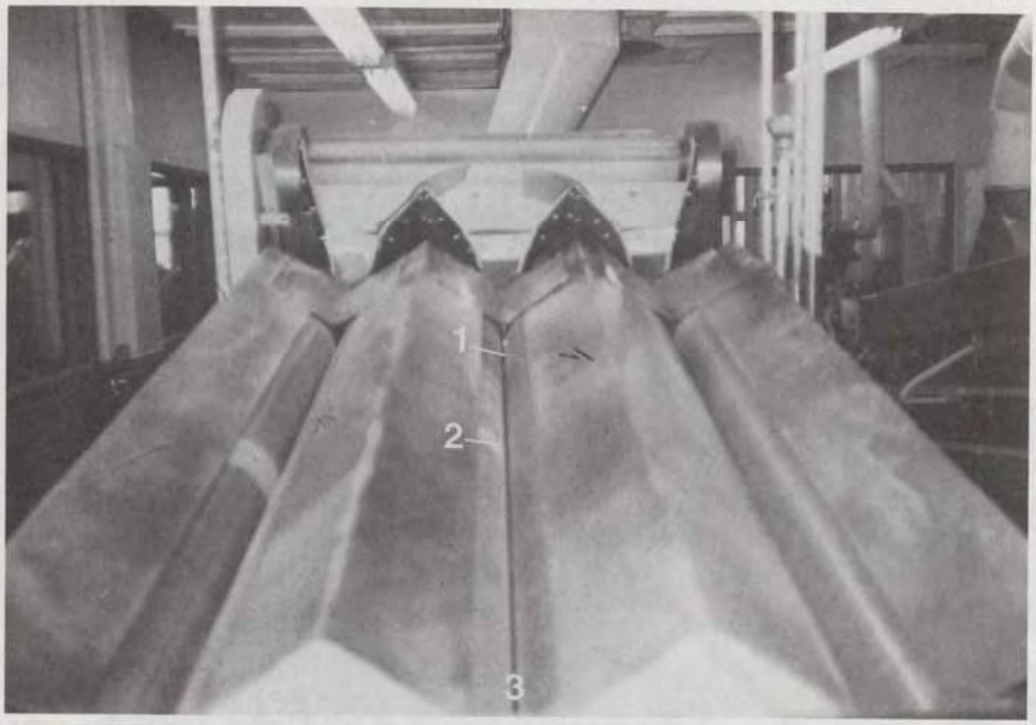


Figure 57 Lozenge sizing operation. (1) Undersized lozenges removed; (2) lozenges in specification collected; (3) oversized lozenges removed. (Warner-Lambert Co.)

length of the roller so that, in an area beginning about one-third the distance down the roller, the distance between the rollers is opened enough to allow lozenges within desired size specifications to drop through—whereupon they are collected in pans, identified as to batch designation, and held for assay and packaging. Lozenges that are oversized continue down the roller where they are collected at the end in another salvage drum. Lozenges that are distorted with surface air bubbles or with sugar granules adhering to the surface, lozenges with bubbles formed because of dieseling, "doubles" or any large, deformed pieces are also collected in this drum. The speed at which the lozenges are passed down the length of the sizing rollers must be adjusted so that undersized pieces are not carried over to the area where the properly sized product is collected and the lozenges of proper size are not carried out with oversized pieces.

N. Lozenge Storage

The properly sized lozenges are collected on an individual, identified batch basis in labeled containers. They are transferred to a conditioning area that is maintained at a temperature of 15–20°C and controlled relative humidity of 25–35%, for storage until the product is cleared for packaging by the quality control department.

O. Continuous Process Cooker

A recent modification of the continuous batch process cooker involves removal of the collection kettle and its replacement with a continually moving stainless steel belt calibrated to carry the candy base away from the cooker at a predetermined rate in a steady and unbroken stream (Figure 58).

Method of Operation

Figure 59 illustrates schematically the operation of the continuous process cooker.

Preparation of candy base—from the initial gear metering of sugar and corn syrup, precooking, collection in the center pot, pumping through the cooking coil in the steam chest, cooking and vapor draw-off in the intermediate chamber, to the vacuum drying—is identical to the process described for the continuous batch process method of candy base preparation. Unlike the candy base in the batch process, instead of being collected in a stainless steel or copper kettle, the candy base is continuously drawn off in a thin (6– to 8–in.-wide) strip by passage through two polished counterrotating draw-down rollers onto a heated delivery chute (Figure 60). The mass acts as a sealing agent between the vacuum chamber and the atmosphere as the candy base exits the cooker. It is through this design that a continual vacuum is maintained even through material is being released from the chamber. Concurrent with the removal of cooked candy base from the vacuum chamber, flavor is injected into the center of the candy base ribbon as it leaves the cooker, via two to four metered dosing pumps.

Precise adjustment of the injection ports is critical to assure surrounding the flavor with candy base, in order to minimize flavor losses through flash-off. The flavored candy base drops from the cooker onto a variable-speed rotating cone head, which effects an initial mixing of flavor into the candy

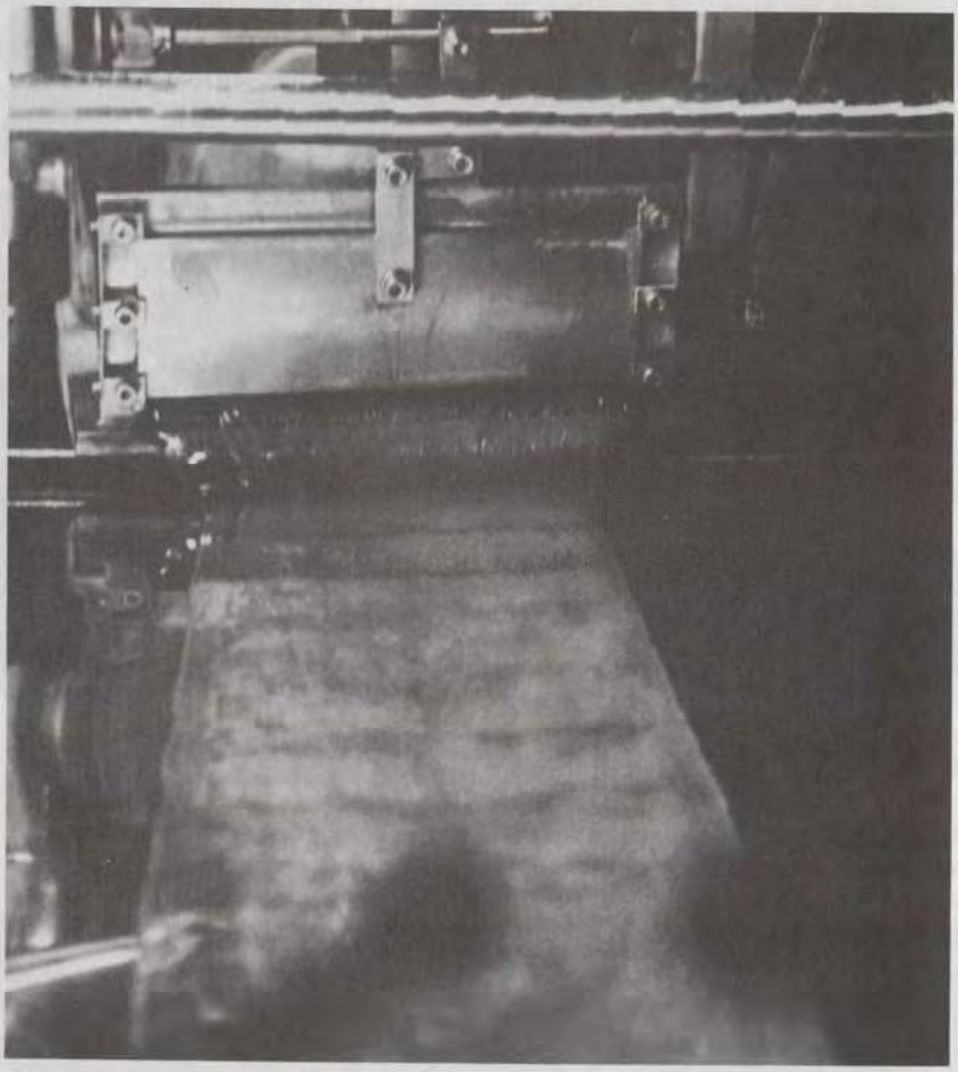


Figure 58 Continuous process cooker. Candy base entering cooling and mixing belt. (Robert Bosch GmBH, Div. Hamac-Höller.)

base. The speed of the cone head is adjusted according to the quantity of flavor added and the efficiency of flavor incorporation in the candy base. The candy, after this initial mixing is completed, slides down the steam-heated delivery chute onto a lubricated and continually moving stainless steel belt, where it is again mixed and sized by a series of three sets of plows and rollers (Figure 61). The candy is uniformly tempered as it moves down the conveyor belt, by the mixing action as well as by a spray of temperature-controlled water on the underside of the belt. Temperature gradients can be controlled by adjusting the water temperature.

The temperature of the base is 130–135°C as the candy leaves the cooker. The candy at this temperature is in a fluid state, so that after initial mixing via the cone head it is uniformly distributed along the width (18–24 in.) of the heated chute before being transferred to the belt. An acidulent (if desired) may be deposited onto the candy during its passage down the length of the steam-heated chute (4–5 ft) by way of a precalibrated

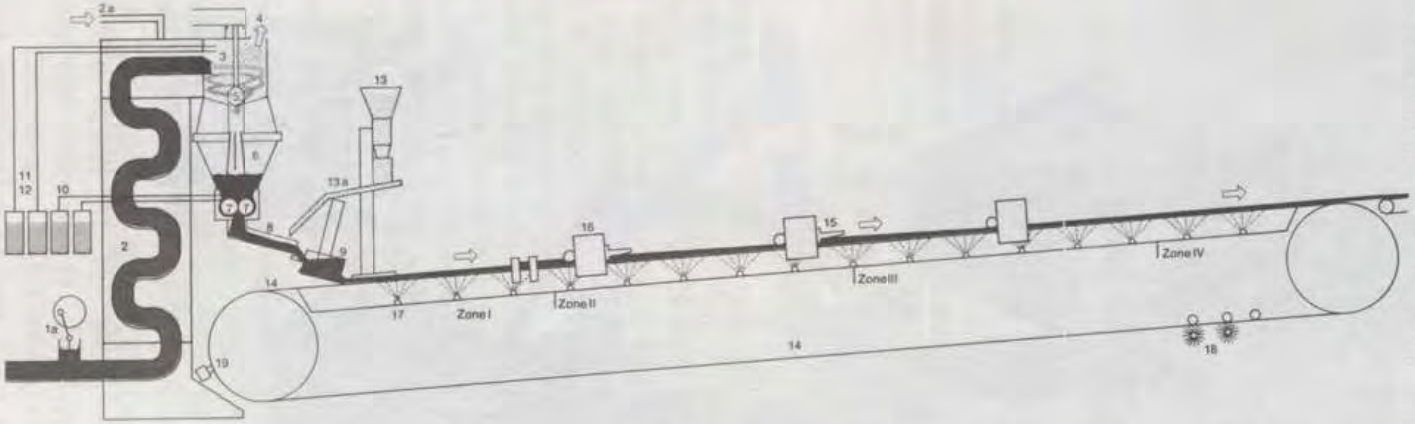


Figure 59 Schematic of continuous process cooker. Cooker: (1) precooked sugar-glucose solution, (1a) pump, (2) steam chest, (2a) steam feed, (2b) cooking coil, (3) intermediate chamber, (4) vapor draw-off, (5) valve, (6) vacuum chamber, (7) continuous sugar draw-off unit, (8) heated delivery chute, (9) mixing container, (10) dosing pump (addition, draw-off unit), (11) dosing pump (addition, intermediate chamber), (12) dosing pump (addition, intermediate chamber, (13) powder feeding unit, (13a) addition, delivery chute. Kneading conveyer band; (14) steel band (conveyor), (14a) profile ledge, (14b) mounting, (14C) guide wheel, (15) plough, (16) kneading station (reversing and kneading), (17) tempering device (water jets), (18) washing station, and (19) greasing station. (Robert Bosch GmBH, Div. Hamac-Höller.)

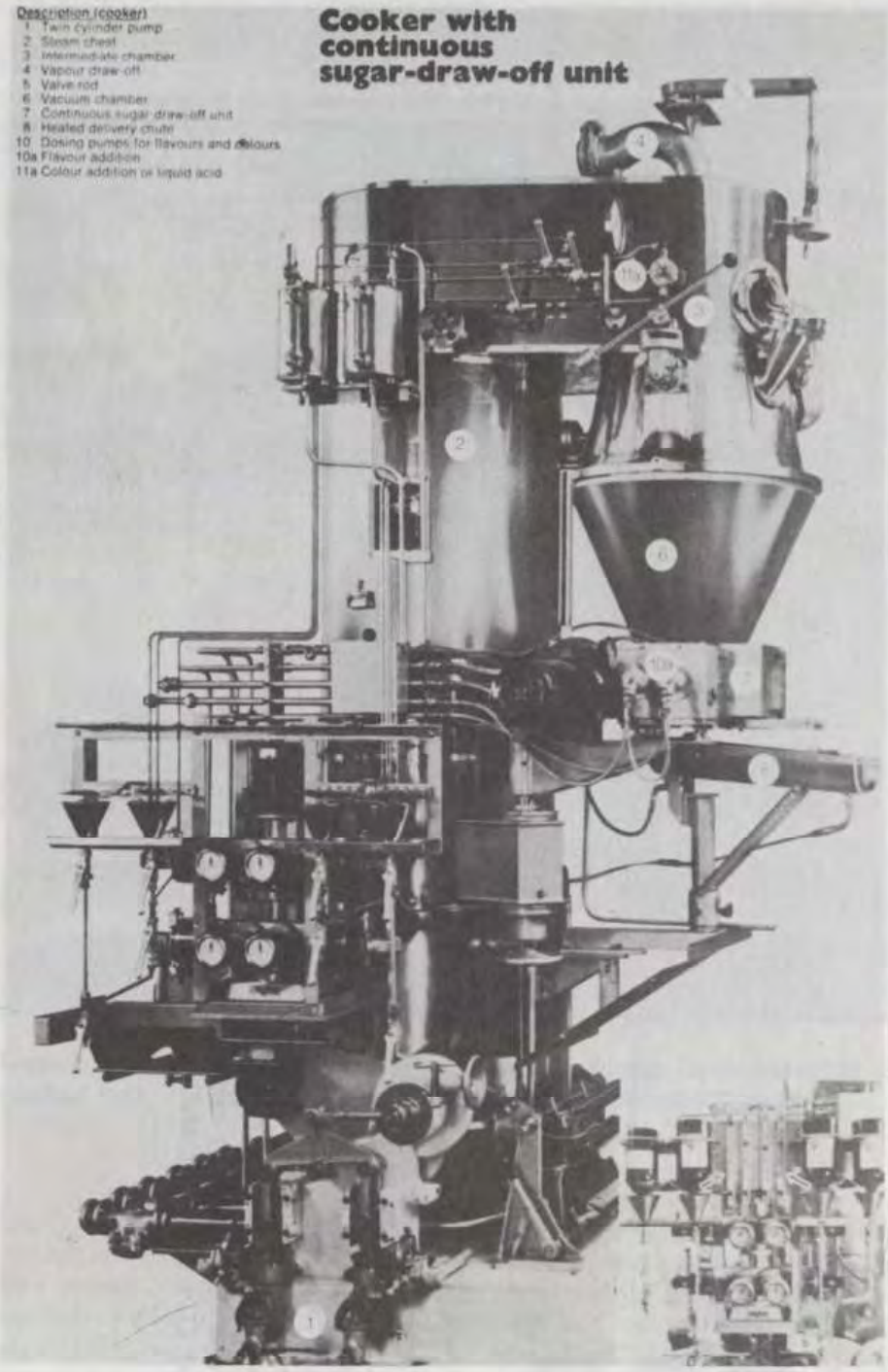


Figure 60 Cooker with continuous sugar draw-off unit. (Robert Bosch GmBH, Div. Hamac-Höller.)

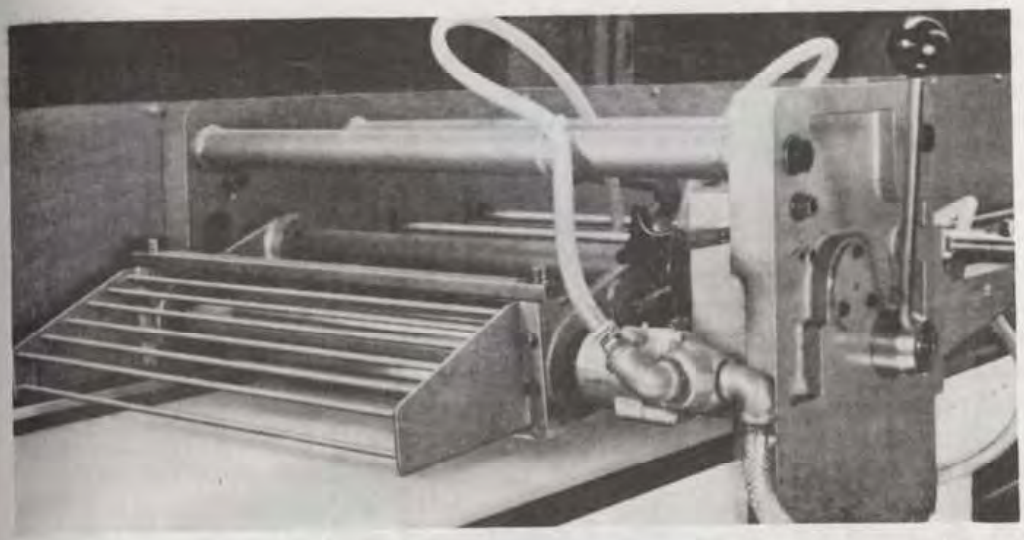


Figure 61 Plow and roller mixer. The unit is cooled by circulating water. The plows are fitted at their bottom edges with exchangeable Teflon strips to prevent damage to the steel belt. The rollers are adjustable in order to obtain a sugar mass of predetermined thickness. (Robert Bosch GmBH, Div. Hamac-Höller.)

vibratory dosing auger [27]. Once the candy base is on the moving and lubricated stainless steel belt, the acidulent and flavor are mixed and folded into it by way of series of three sets of plows and rollers stationed at uniformly spaced intervals along the belt. The ribbon is 6–10 in. wide when mixing has been completed, and the candy base is at the end of the belt where it is continually deposited into the batch former (Figure 62). All steps from this point until the end of the procedure are identical to those described for the batch process mode of manufacture. Lozenges are collected on a routine basis in storage hoppers labeled according to that portion of the batch from which the lozenges were manufactured. They are then held in a quarantine area until analytical and microbiological testing is complete.

Plow and Roller Mixing

Lozenges produced on the continuous process cooker are brighter in color and clearer in appearance than those produced by the batch process because the plow and roller mixing is more gentle. The mass is mixed at a higher temperature, thus entrapping less air than is associated with manual mixing or the Berks mixer type of mechanical mixing. Also, no solid, ground salvage is mixed into the batch—a procedure that rapidly cools the candy base and increases the incidence of air entrapment and candy base opacity. Conversely, the thoroughness of mixing resulting from the plow and roller combination is less than that obtained with batch process manual or mechanical procedures. This is not a disadvantage in instances where only flavor and acidulent (if needed) are added to the candy base after cooking is complete. The less energetic type of mixing encountered with plow and roller limits the quantity and consistency of material that can be efficiently mixed into the candy base (watery materials or materials

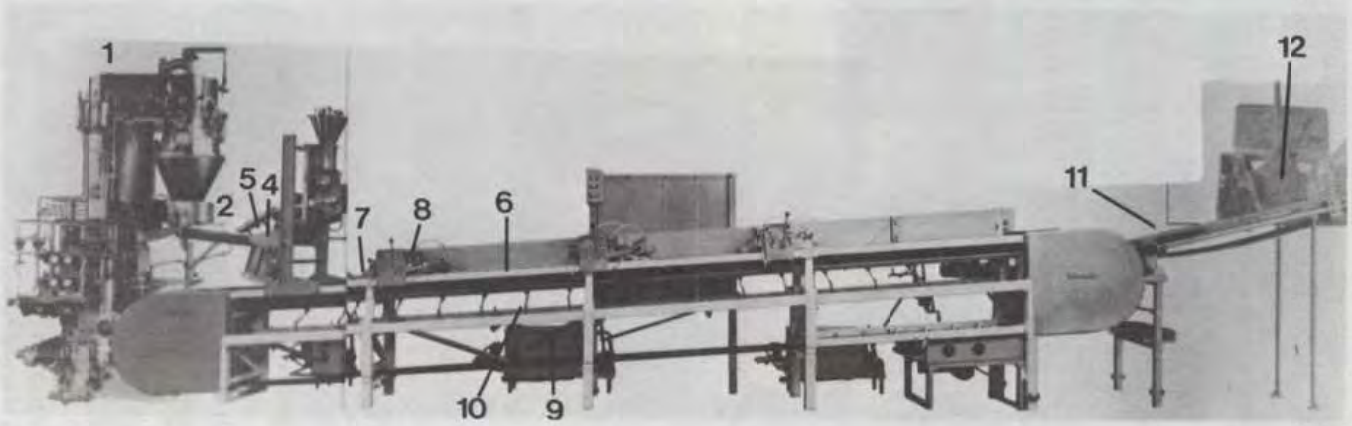


Figure 62 Continuous process cooker. (1) Continuous cooker; (2) heated delivery chute; (3) powder feeding unit; (4) mixing container; (5) powder delivery chute; (6) steel band (conveyor); (7) plow; (8) kneading station; (9) water-cooled tempering device; (10) water jets; (11) elevator to transfer candy base to batch former; (12) candy base entering batch former. (Robert Bosch GmBH, Div. Hamac-Höller.)

that are tacky are difficult to incorporate). To help alleviate this limitation, medicaments and colors are added with salvage through the cooker or pumped into the intermediate chamber. However, alternative methods of addition must be investigated if medicaments or colors are heat-sensitive or react with candy base.

Color and Medicament Addition Procedures

When the formulator must add dyes that exhibit color distortion or fading because of heat sensitivity or reactivity with candy base components, the dyes can be dissolved or suspended in glycerin and added to the candy base after cooking, through one of the metered dosing pumps available, to inject flavor into the mass as it leaves the cooker (see insert, Figure 60).

The addition of medicaments in the same manner as the addition of acidulents (sprinkling onto the surface of the candy base) is not practical because of lack of adequate control or sensitivity in the vibratory dosing auger mechanism. If the dosage of the medicament is at a low level (less than 5.0 mg per dose) and the solubility or dispersibility of the medicament lends itself to preparation of a high-solids but free-flowing solution or dispersion (solution or dispersion addition "rate" of medicament to candy base must be less than 2 lb/100 lb of finished candy base), the drug may be added through one of the metered dosing pumps, as the candy base leaves the cooker or slightly after the point of flavor addition. This reduces possible medicament–candy base or medicament–flavor interactions. Addition of active ingredients through the pumping system requires a pump that possesses a high degree of sensitivity to assure homogeneous addition of medicament into the candy base. This guarantees a uniform drug distribution throughout the manufacturing run. A flow meter or indicator for the liquid additions should be attached in order to control the consumption of the drug mixture, if the dosing pumps supplied with the continuous process cooker are to be used to deliver medicaments to the candy base.

The solution or dispersion containing the medicament, as well as any color solutions or suspensions, should be heated to 110–120°C before addition to prevent localized crusting or hardening of the candy mass at the point of injection. This crusting can result in a nonuniform distribution of color or medicament and can clog the pump injection ports, resulting in a retardation of medicament or color solution flow. Flavors need be heated only to 50–60°C (a flavor-heating glycerin system has been incorporated into the machine) before addition, since the quantities added are lower and the flavor components easier to incorporate in the candy base without the problems of crusting.

Candy Base Output

The speed of the forming machine and the size of the candy piece formed determine the speed at which the cooker and the belt are set. The candy base production rate and the speed of the belt are adjusted to deliver 20–25 lb of candy base per minute if one forming machine is being supplied. Up to 42 lb of candy base per minute can be manufactured if two forming lines are supplied. It is possible to divide the sugar rope by a cutting device in such a way that two batch formers, and consequently two forming lines, can be supplied with a single candy line.

Advantages of Continuous Process Cooker

Production of large quantities of candy base (10 tons/8 hr) is feasible using the continuous process cooker because components of the candy manufacturing and forming operation are used close to their designated capacities. The number of production workers (12 vs. 4), forming machines (4 vs. 2), candy base cookers (2 vs. 1), and cooling lines (4 vs. 2) needed to produce a given quantity of product in an 8-hr shift using the batch system is at least double whatever may be required to produce identical quantities on the continuous setup. The appearance of the finished lozenge is elegant since an almost clear piece, free from haze or air bubbles, results. Colors are vivid, and air entrapment and defects are reduced because of a uniform tempering of the batch, and deletion of solid salvage (plows and rollers cannot efficiently incorporate solid salvage) results in the formation of lozenges with a greater resistance to graining. This is because the base is not seeded with sugar dust or sugar crystals before the lozenges are formed. The result is the manufacture of a product that will maintain its original appearance from two to three times longer when stored under identical conditions and packaged in the same containers as batch process manufactured lozenges.

Disadvantages of the Continuous Process Cooker

The manufacture of medicated lozenges on the continuous process cooker is not without its drawbacks. The most severe fault—the one that requires rectification before a medicinal product can be manufactured using this process—is the lack of adequate controls during production and the ramifications that may result before human or machine errors are detected.

Unlike the batch system, which produces a predetermined quantity of candy base that is weighed and checked before the addition of flavors, colors, or medicaments, the continuous process cooker produces an unbroken stream of candy. The only adequate method for determining the quantity of candy base produced during any specified period of time is to break the candy ribbon before it enters the batch former and collect the product for a predetermined period of time, weigh it, and calculate the output of candy base per minute. Adjustments in cooker or belt speed are made as required. Normal quality-control compliance checking is carried out every 15–20 min throughout the run. An increase or decrease in candy base output during any specific time period will be reflected in a change in the concentration of flavor or acidulent present in the candy (a change in the organoleptic presentation), if medicament or color is added with salvage during cooking. If medicament or color is added after the candy base is formed, any significant increase or decrease in candy base output may result in production of lozenges with undersirable color or product that is out of specification when assayed for the desired medicament concentration. The manufacture of 30–40 lb of candy base per minute could result in 450–600 lb of lozenge rejects being formed before remedial actions are initiated—even though the routine checking of candy base output is mandatory. The production team responsible for maintenance of the cooker assembly must take precautions necessary to mitigate the chances of a nonuniform or faulty candy base output due to cooker, pump, valve, steam line, or vacuum malfunction or failure.

A second disadvantage associated with the production of lozenges via the continuous process cooker is the method of flavor addition. Injection

of the liquid flavors at the point where the candy base leaves the cooker exposes the flavor to the candy at a temperature exceeding 130°C. The ideal situation is to inject the flavor into the center of the candy ribbon as it leaves the cooker, by positioning the metered dosing-pump injection ports into the center of the mass. This would, in theory, surround the flavor with candy base, thus reducing flavor flash-off tendencies. In practice, though, it is not always possible to maintain the position of the injection ports in the center of the cooked candy mass, or to prevent portions of the flavor from leaking out of the base or being injected through the mass and being lost. (Generally such loss is prevalent when high concentrations, greater than 50.0 g/min, are being injected.) There is a tendency for the candy to separate or tear away from the injection ports, resulting in raw flavor being sprayed onto the surface of the mass. The incidence of flavor loss from this occurrence is greater than 75%. It is not practical to add flavors farther down the belt where temperatures are lower, as the mixing action of the plows and rollers is not energetic enough to assure uniform incorporation of the flavor in the base. The initial mixing as candy drops onto the chute as well as the action of the rotating cone head produces an acceptable initial mixing that complements the plow and roller action when flavor is injected at the point where the candy leaves the cooker. Flavor tends to collect on the surface of the base if it is added farther down the belt and is only folded into the center of the ribbon, thus increasing the percentage loss and producing lozenges with pockets of liquid flavor trapped in the center. Incorporation of flavors as a mixture with ground salvage and addition to the mass in the same manner that is used for citric acid powder (vibratory auger feed) is not practical since the wetted salvage will not flow uniformly from the auger. Agglomeration of the flavor-salvage mixture occurs in the hopper. Also, the material that is delivered by the powder-feeding unit will not be completely mixed into the base because of the inability of the plows and rollers to give the vigorous mixing required to incorporate the salvage mixture in the candy base.

The addition of selected solvents (benzyl alcohol, glycerin, propylene glycol) to flavors in order to raise the boiling point of the mixture will aid in reducing flavor flash-off, but the concentration of solvent necessary to achieve this condition will range between half to four times the required flavor quantity. The addition of sufficient solvent to lower flavor losses might not be a practical solution to the problem unless the quantity of flavor added to the base is low (less than 1.0 g/lb). This is because as the quantity of flavor added per minute increases, so does the percentage of flavor loss increase due to the inability of the mixing system to efficiently incorporate the liquid into the mass. The addition of 0.5–1.0 g of flavor per pound of candy base results in a loss of less than 10%, whereas addition of 1.0–2.0 g/lb produces 15–20% flavor loss, and more than 3.0 g of flavor added per pound could result in flavor loss in the range of 40–60%.

Lozenge Rejects

There are two reasons for the formation of higher levels of lozenge rejects when medicated products are manufactured on the continuous process cooker than when they are produced by the batch process: (a) difficulties of flavor addition, and (b) the possibility that nonuniform candy base production may produce lozenges with drug, flavor, or color levels out of

specification. As much as 1000–1500 lb of lozenges may be produced before a potential problem is detected or diagnosed and remedial actions are taken, since the cooker output is usually in the range of 40–42 lb of candy base being manufactured per minute. If an analysis of lozenges determines that high or low drug contents have resulted—that place the drug concentration out of the acceptable tolerances, through either improper weighing of medicaments, pump failure, or decomposition—it is possible that 12,000–20,000 lb of finished lozenges could be produced before analytical results determine that the lozenges are rejected for out-of-specification drug concentration.

The lozenge-forming and cooling operation probably produces the highest percentage of rejects on an ongoing basis. Product rejection during forming and cooling is an inherent weakness in all lozenge production, regardless of the type of candy base production, but it is proportional to the output of product manufactured per minute [69].

Forming equipment capable of manufacturing up to 2500 lb of candy lozenges per hour was developed concurrently with candy base cooking equipment capable of producing up to 2700 lb of candy base per hour. This high-speed production demands an unbroken supply of candy base, properly tempered and fed through the sizing rollers at a uniform rate. Any cold or hot spots that may develop in the mass, or any reduction in candy base elasticity from high concentrations of medicament or solvent or from improper positioning of the batch former (rate of feed into the sizing rollers), or any temperature variation in the rollers or batch former will place stress on the candy rope and form lozenges that are out of the specified range. Adjustments can be made to remedy this situation, but until this is done, as much as 200–300 lb of undersized or oversized lozenges can be formed. Continued variations in the quality of candy base produced will result in lozenge-forming problems, with an increase in the number of adjustments and rejects. The high-speed forming machinery also increases the incidence of lozenge chipping and sticking, as well as breaking of finished product during the cooling operation. The speed at which the lozenges pass through the final sizing rollers also produces a higher incidence of rejected lozenges. The quantities of lozenges that must be sized require that the sizing rollers be set at a high speed. This rate results in 5–10% of proper weight and proper size product being carried over the desired "drop-through area"—and out with the oversized lozenges. A time-consuming resizing operation is the only way to reclaim these lozenges.

Summary

The quantity of lozenge salvage produced may exceed the amount that can be readily returned to the process (18–22%) unless close controls can be instituted over all aspects of medicated lozenge production on the continuous process cooker. When this situation occurs, it is not practical—from a cost or raw materials standpoint—to manufacture medicated lozenges with this procedure. The quantity of salvage formed should not exceed 10% of product produced if rigid controls are maintained on the quantity of the candy base produced per minute, flavor, color, and medicament addition rates, as well as on the lozenge forming, cooling, and sizing operations.

The continuous process cooker offers many advantages in the high-speed production of medicated lozenges possessing improved organoleptic characteristics with extended shelf life. This method of manufacture

requires a closer surveillance over all aspects of product manufacture than does the batch method, since a human or mechanical error during production can turn 15,000–20,000 lb of finished product into that much lozenge salvage.

III. FORMULATIONS (HARD CANDY LOZENGES)

The following formulations represent various methods of manufacturing medicated hard candy lozenges.

A. Medicament-Flavor-Ground Salvage Method of Addition

Example 1: Antihistamine Lozenges (4.0 mg/2.5-g lozenge)

Ingredient	Quantity
A. Liquid sugar (67.5% w/w solids)	88.9 lb
B. Corn syrup 43°Baumé (80.5% w/w solids)	49.7 lb
C. Ground candy salvage (20–50 mesh)	3.0 lb
D. Chlorpheniramine maleate	72.75 g
E. Wild cherry flavor, imitation	75.0 g
F. Benzyl alcohol NF	75.0 g
G. Citric acid fine granular	300.0 g
H. Red color cubes	10.0 g

Liquid sugar and corn syrup are gear-metered into the dissolver and precooked at 125°C. Final cooking is performed at 148°C with a vacuum of 710 mm Hg to produce 100 lb of candy base with a 60:40 sugar/corn syrup ratio. The chlorpheniramine maleate is dissolved in a mixture of wild cherry and benzyl alcohol with the aid of heat. The mixture is uniformly mixed with the citric acid and ground candy salvage. Color is added to the cooked candy base in the collection kettle; flavor-drug-salvage mixture is added on the mixing table. Candy base is mixed, tempered, formed, rope-sized, molded, cooled, and sized.

B. Direct Medicament Addition

Example 2: Analgesic Lozenges (162.5 mg/4.0-g lozenge)

Ingredient	Quantity
A. Liquid sugar (67.5%) w/w solids)	88.9 lb
B. Corn syrup 43°Baumé (80.5% w/w solids)	49.7 lb

Example 2: (Continued)

Ingredient	Quantity
C. Ground candy salvage (20—50 mesh)	2.0 lb
D. Aspirin 100-mesh crystals	1.85 kg
E. Imitation orange flavor	35.0 g
F. Menthol crystals	50.0 g
G. Orange color paste	12.0 g

Liquid sugar and corn syrup are gear-metered into the dissolver and precooked at 120°C. Final cooking is performed at 148°C with a vacuum of 73 mm Hg to produce 100 lb of candy base with a 60:40 sugar/corn syrup ratio. The menthol is dissolved in the orange flavor and uniformly mixed into the ground salvage. Color is added to candy base in the collection kettle; the aspirin is added in the transfer kettle and folded into the mass; and the flavor-salvage mixture is added on the mixing table. Candy base is mixed, tempered, formed, rope-sized, molded, cooled, and sized.

C. Medicament Addition via Granulation

Example 3: Antitussive-Decongestant Lozenges (7.5 and 18.5 mg/3.5-g lozenge)

Ingredient	Quantity
A. Liquid sugar (67.5% w/w solids)	88.9 lb
B. Corn syrup 43°Baumé (80.5% w/w solids)	49.7 lb
C. Ground candy salvage (20—50 mesh)	4.0 lb
D. Dextromethorphan HBr, 10% adsorbate	1.0 kg
E. Pseudoephedrine HCl	241.0 g
F. Eucalyptus oil NF	150.0 g
G. Menthol crystals	170.0 g
H. Glycerin USP	2.0 lb

Liquid sugar and corn syrup are gear-metered into the dissolver and precooked at 125°C. Final cooking is performed at 150°C with a vacuum of 736 mm Hg to produce 100 lb of candy base with a 60:40 sugar/corn syrup ratio. The menthol is dissolved in the eucalyptus oil and uniformly mixed into a mixture of ground salvage, dextromethorphan HBr, adsorbate, and pseudoephedrine HCl. Glycerin is added and mixed until a free-flowing granulation results. The granulation is added to the candy base on the mixing table. Candy base is mixed, tempered, formed, rope-sized, molded, cooled, and sized.

D. Dual-Granulation Addition to Reduce Chemical Incompatibilities

Example 4: Decongestant Lozenges (15.0 mg/4.0-g lozenge)

Ingredient	Quantity
A. Liquid sugar (67.5% w/w solids)	88.9 lb
B. Corn syrup 43°Baumé (80.5% w/w solids)	49.7 lb
C. Ground candy salvage (20—50 mesh)	7.0 lb
D. Phenylpropanolamine HCL	172.0 g
E. Artificial berry-mint flavor	150.0 g
F. Berry shade color paste blend	15.0 g
G. Benzyl alcohol NF	100.0 g

Liquid sugar and corn syrup are gear-metered into the dissolver and precooked at 125°C. Final cooking is performed at 147°C with a vacuum of 736 mm Hg to produce 100 lb of candy base with a 60:40 sugar/corn syrup ratio. The phenylpropanolamine HCl is dissolved in benzyl alcohol with the aid of heat and uniformly mixed with 4 lb of ground salvage. The berry-mint flavor is separately and uniformly mixed with 3 lb of ground salvage. Color is added to candy base in the collection kettle. The phenylpropanolamine HCl-salvage mixture is added in the transfer kettle and folded into the mass, and the flavor-salvage mixture is added to the candy base on the mixing table after 60 sec of mixing has been completed. Candy base is mixed, tempered, formed, rope-sized, molded, cooled, and sized.

E. Addition of Liquid Salvage with Color (10% Salvage)

Example 5: Antihistamine Lozenges (10.0 mg/2.5-g lozenge)

Ingredient	Quantity
A. Liquid sugar (67.5% w/w solids)	80.00 lb
B. Corn syrup 43°Baumé (80.5% w/w solids)	44.75 lb
C. Liquid salvage (70% w/w solids)	14.30 lb
D. Ground candy salvage (20—50 mesh)	4.00 lb
E. Diphenhydramine HCl	185.00 g
F. Artificial wild cherry flavor	125.00 g
G. Citric acid USP, fine granular	325.00 g
H. FD&C Red No. 40	8.50 g

The FD&C Red No. 40 is dissolved in the liquid salvage. Liquid sugar, corn syrup, and salvage solution are

Example 5: (Continued)

gear metered into the dissolver and precooked at 125°C. Final cooking is performed at 150°C with a vacuum of 736 mm Hg to produce 100 lb of candy base with a 60:40 sugar/corn syrup ratio and 10% salvage-color mixture. The diphenhydramine HCl is dissolved in the flavor, added to a mixture of citric acid and ground salvage, and mixed until uniformly incorporated. The flavor-drug-ground salvage mixture is added to the color-salvage-candy base mixture on the mixing table. Candy base is mixed, tempered, formed, rope-sized, molded, cooled, and sized.

F. Addition of Liquid Salvage with Color and Medicament (20% Salvage)

Example 6: Anesthetic Lozenges (2.4 mg/3.5-g lozenge)

Ingredient	Quantity
A. Liquid sugar (67.5% w/w solids)	71.1 lb
B. Corn syrup 43°Baumé (80.5% w/w solids)	88.6 lb
C. Liquid salvage (70% w/w solids)	88.6 lb
D. Hexylresorcinol	43.75 g
E. FD&C Yellow No. 5	2.5 g
F. FD&C Green No. 3	2.5 g
G. Natural and artificial spearmint blend	100.0 g
H. Menthol crystals	75.0 g
I. Ground candy salvage (20–50 mesh)	4.0 lb

The FD&C Yellow No. 5, FD&C Green No. 3, and the hexylresorcinol are dissolved in the liquid salvage. Liquid sugar, corn syrup, and salvage solution are gear-metered into the dissolver and precooked at 125°C. Final cooking is performed at 146°C with a vacuum of 710 mm Hg to produce 100 lb of candy base with a 60:40 sugar/corn syrup ratio and 20% salvage-medicament-color mixture. The menthol crystals are dissolved in the flavor, added to a mixture of ground salvage, and mixed until uniformly incorporated. The ground salvage-flavor mixture is added to the medicament-color-salvage-candy base mixture on the mixing table. Candy base is mixed, tempered, formed, rope-sized, molded, cooled, and sized.

IV. CENTER-FILLED HARD CANDY LOZENGES

Incorporation of soft or liquid centers into hard candy lozenges enables the product formulator to modify the presentation of medicament to the patient. The rationale for preparation of a product of this type normally would fall into the same categories as those presented for developing two-layer tablets (elimination of drug incompatibilities). In the case of liquid-center hard candy products, the major criteria cannot be met since preparation of a pharmaceutically acceptable filled lozenge cannot be realized due to unacceptable content uniformity variations which result when centers are placed in lozenges. While most centers will fall within the desired 10% fill, an unacceptable number will fall outside this range and some will be as far off as ±50% from theory.

Eliminating the separation of medicaments in either the shell or the center, the major advantage for formulating medicated center-filled products is aesthetics. A different flavor can be placed in the center than in the shell. High-impact flavors can be incorporated in the center that will contrast with subtle flavorings presented in the shell. Aromatics can give a burst of flavor or perceived efficacy to the user, thus increasing the overall organoleptic presentation of the product. However, medicament must be uniformly distributed between the shell and the center to eliminate the problem of nonuniformity of center fill.

A. Types of Center Fills

Four major categories of center fill are now utilized [84].

Liquid Fill

This type of center is utilized when a high-impact type of filling is desired. The liquid is presented in a very short concentrated burst after the user breaks through the shell. This results in a noticeable sensation of liquid coating the throat. Normal percentage fill (w/w) ranges from 10 to 20%. Due to the low viscosity of the material and the low specific gravity, higher fill percentages result in a thin shell wall which if cracked or ruptured will contaminate surrounding lozenges or the product container. Some of the materials utilized for this type of filling include fruit juice, sugar syrup, hydroalcoholic solutions, and sorbitol solution. Flavor and colors can be incorporated in the center or the center can be left unaltered.

Two major disadvantages of liquid center include (1) the tendency for the product to leak if the shell cracks or the ends of the tablet are not properly sealed, (2) reduced product shelf life due to the liquid center. The liquid center material, being highly aqueous, will cause the lozenge to grain from the inside out. Water in contact with sugar and corn syrup actually melts the product from within. Eventually, the shell wall weakens and the liquid material leaks out of the center. Average shelf life for liquid centers is 6–9 months. Storage in heated environments will shorten this time span.

Another problem with the use of liquid center material is leakage during processing. If the aqueous material should leak onto forming rollers or shell material, the candy base will become sticky thus making processing difficult.

Fruit Centers

Fruit center fillings are prepared when highly confectionary-type products are desired. This type of center is richly flavored, sweet, and full bodied. Jams and jellies, whose viscosity has been adjusted with corn syrup or liquid sucrose, are most frequently utilized in this type of center. While the impact of this material is not as pronounced as with liquid center, the rich flavor and sweetness help differentiate the center from the shell. The average fill weight of fruit centers is 20–25%. The lower moisture content of fruit center along with higher viscosity helps retard the internal graining and melting characteristics, thus increasing the shelf life to 12–15 months. Leakage during processing is a problem since the more viscous fruit will coat rollers and make processing extremely difficult.

Paste Centers

Paste centers are not utilized to a great extent since they are more difficult to fill and afford the poorest differentiation between shell and center. The high specific gravity allows for fill of up to 40% w/w and the high viscosity reduces the tendency for the center material to leak out of the lozenge should cracking occur. The same problems of processing difficulty, if leaking should occur during filling, are applicable here. Paste formulations contain granular or crystal-sized materials such as nuts or fruits. The lower moisture content of the paste center helps retard graining and internal candy base melting, so typical shelf life of paste centers can be as long as 24 months.

Fat Centers

The fill material most applicable to medicated lozenges is the fat-based center fill. Here, the medicament and/or flavor can be suspended or dissolved in hydrogenated vegetable oil and incorporated in the lozenge center. During processing, if leakage should occur, the fat will act as a lubricant that will not impede production or cause the sticking of candy base to the rollers or the faces of candy dies.

Utilization of a high melting point fat (85–100°F) will reduce the tendency for center to leak out of the tablet during packaging or storage since at room temperature the center is a solid or semisolid. When the lozenge is placed in the mouth, body heat melts the center material thus releasing a liquid when the shell is broken. Fats can be incorporated in lozenges at 25–32% w/w fill. The projected shelf life of a fat-filled lozenge is 3–5 years since the candy base is insoluble in the oil and will not grain or melt from the inside. If the lozenge is protected from atmospheric moisture, the shelf life can be extended indefinitely.

A disadvantage of the fat filling is presentation of flavors from the matrix. Vegetable oil retards the impact of flavor to the taste buds so the true impact and goodness of flavors is markedly reduced. Even high aromatic flavors such as menthol and eucalyptus do not retain their usual organoleptic characteristics. This is a problem when different flavors are

incorporated in the shell and center. The lower flavor impact reduces the differentiation of shell from center.

One formulation modification used to circumvent this problem is to form an emulsion of glycerin or propylene glycol with the vegetable oil, flavors, and medicaments. This emulsion is less oily, more hydrophilic, and gives an improved presentation of flavor to the mouth. While the emulsion will make the candy base more sticky if leakage should occur during processing, in most instances this is not severe enough to discontinue production. Fill volumes with the emulsion are about 3–5% lower than with the fat alone.

Since the candy base is also insoluble in glycerin and propylene glycol, the shelf life is not compromised when the emulsion is filled into hard candy. Addition of glycerin or propylene glycol to the vegetable oil will lower the melting point of the fat but in most cases the center will still be a semi-solid that will not readily leak out of the shell. If the center does become fluid after formation of an emulsion center, use of a higher melting point fat should alleviate the problem. Fats with a melting point above 102°F should not be used under any circumstances since they will leave a fatty-oily taste in the mouth.

A summary of type of filling vs. shape and center fill percentage is summarized in Table 4.

B. Processing

Candy base is prepared in the normal manner described for hard candy lozenges. Ideally, candy base at 60:40 or 55:45 sugar–corn syrup ratio should be used since higher sugar ratios tend to crystallize too fast and do not stretch properly when center material is injected. Sugar ratios below 55:45 are too elastic and do not hold their shape.

Candy base is cooked and medicament, flavor, and color are added in the normal manner. The candy is tempered and transferred to the batch former.

In the batch former is a hollow Teflon-coated fill pipe attached to a jacketed pump (Figure 63). The candy base is added to the batch former which converts the mass to a sugar cone. The candy during forming is wrapped around the Teflon-coated pipe in the former (Figure 64).

With the candy in the batch former, but prior to reaching the draw-down rollers, the end of the Teflon pipe is positioned so that the center fill material can be pumped into the candy rope. At the position immediately beyond the pipe, a hollow cavity is formed. The liquid is pumped into this void. The speed of the rope determines the diameter of the hollow space and thus the quantity of center material available for filling. If the rope is pulled or pushed, the cavity diameter changes and the percent center fill is compromised. Immediately after the center fill is deposited into the rope, it is sized through the rollers and formed into tablets, cooled, sized, and collected (Figure 65).

The temperature of the center fill material should be close to that of the candy base at the point of filling (85–95°C) [60]. This will prevent crystallization and premature hardening of the candy should cold center fill come in contact with hot candy. If this occurs, control of tablet weight will be affected and the cooked candy will become brittle when formed thus increasing the number of center fill leakers. If the center material is too hot, cooling is delayed and the number of deformed lozenge rejects increases.

Table 4 Type of Filling vs. Shape and Typical Percentage Center Fill[a]

Type	for machine	for candy	Filling percentage			
			Liquid	Fruit	Fat	Paste
97 A	Superrostoplast 96 A	>14 mm ø	20	25	32	43
67 B	Superrobust 85 A	>14 mm ø	–	–	–	–
67 C	Superrobust 85 A	Ring tablet	–	–	–	–
67 D	Superrobust 85 A	>14 mm ø	–	–	–	–
161 H	Uniplast 160 A B C D	>14 mm ø	18	22	28	43
161 K	Uniplast 160 A B C D	>18 mm ø	20	25	32	–
161 L	Uniplast 160 A B C D	Pillow, waffle	–	25	32	–
161 M	Uniplast 160 A B C D	Humbug	–	–	–	–
161 N	Uniplast 160 C D	Center-ring tablet	–	–	–	–
161 P	Uniplast 160 D	>18 mm ø	20	25	32	–
161 S	Uniplast 160 C D	Chewable candy	20	–	22	–
161 SO	Uniplast 160 C D	Toffee	–	–	22	–
161 T	Uniplast 160 D	>18 mm ø	18	22	28	32

[a]The oval shape lozenge configuration lends itself to the best geometry for center filling.
Source: Robert Bosch, GmBH, Division of Hamac-Höller.

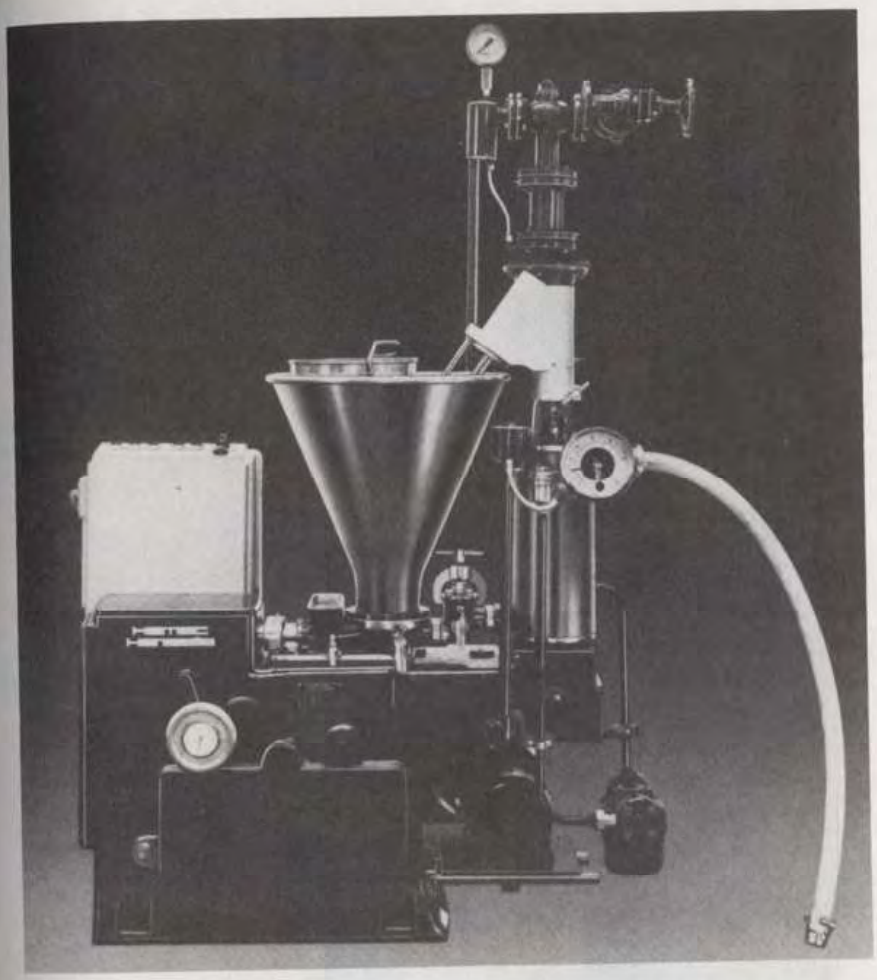


Figure 63 Hansella 148A center fill machine. Hopper is jacketted to maintain center fill temperature. Product is recirculated to maintain uniformity. (Robert Bosch GmBH, Div. Hamac-Höller.)

The diameter of the feed pipe, speed of forming, center fill flow rate, and pressure all must be coordinated to produce finished lozenges with a uniform center fill. The candy rope must not be stretched. This could result in breakage of the rope around the fill pipe resulting in leakage of center fill material onto the batch former rollers, candy base, or around the sizing rollers. If the candy base becomes sticky when coated with center fill material, lozenges will stick to the dies during forming (Figure 66). Cleanup after a center fill leak is laborious.

Adequate crimping pressure must be used to cut the lozenges during forming. This prevents tearing of the candy or incomplete closure of the tablet thus allowing fill material to leak from the center.

Much progress has been made in improving center fill procedures. Utilization of extruders to feed candy base and improved center fill material delivery systems have increased the percentage center fill, but the technology has not progressed to the stage where centers are uniform to the extent that pharmaceutical content uniformity values can be met should segregation of medicaments between shell and center be attempted.

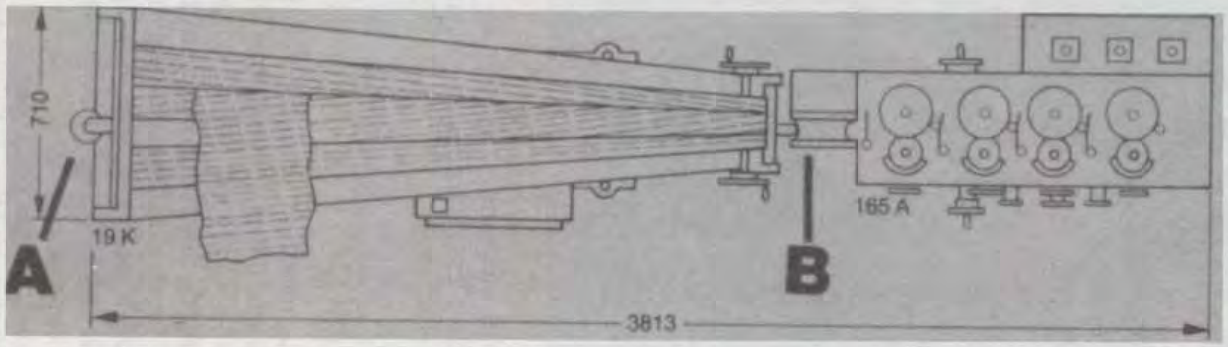


Figure 64 Tempered candy base is added to the batch former as a thin ribbon to assure that a uniform encasement of the teflon coated fill pipe is achieved. Center fill pump is attached at point A. Center fill material fills hollow space in candy rope at point B where the center fill pipe ends. Candy passes through the first draw down roller and then to the rope sizer. (Robert Bosch GmBH, Div. Hamac-Höller.)

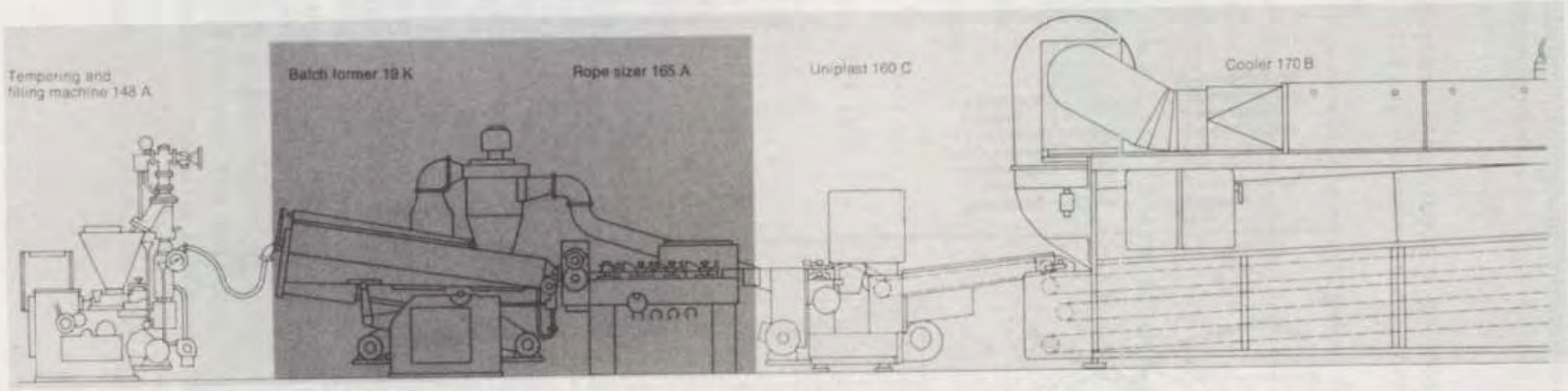
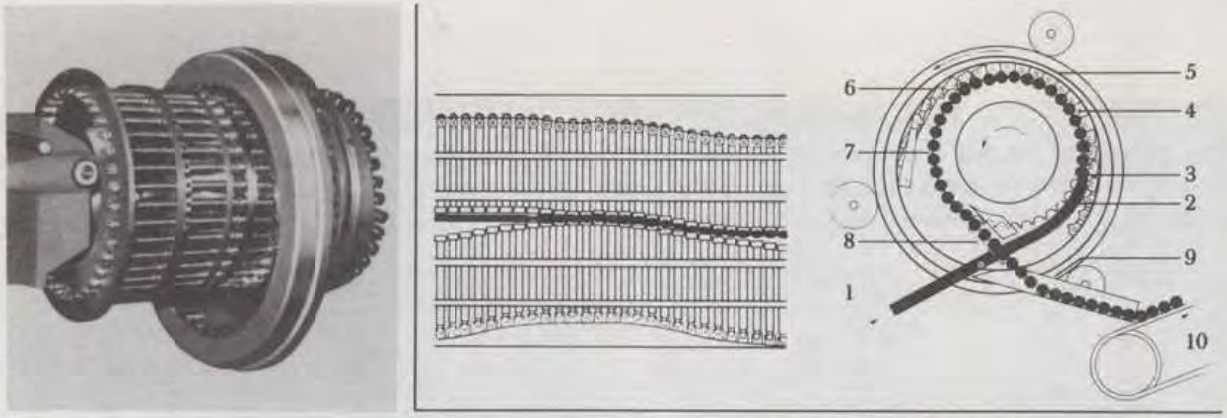


Figure 65 Typical hard candy lozenge center fill production line. The center fill machine stores, maintains temperature, recirculates fill material and pumps the center into the formed candy rope as it exits the batch former. The rope is then sized to the proper diameter, formed into lozenges in the uniplast and cooled prior to final tablet sizing and packaging. (Robert Bosch GmBH, Div. Hamac-Höller.)



Functional diagram
1 rope feed
2 rope infeed
3 pre-forming
4 embossing die-section closed
5 embossing
6 opening of embossing die-sections
7 ejection
8 sliding section
9 feed chute to distributor belt
10 distributor belt

Figure 66 Uniplast tablet dies and a functional diagram showing the lozenge forming operation. Pressure at embossing step 5 must be controlled to assure complete closure of the tablet to avoid, leakage of center fill from the center. (Robert Bosch GmBH, Div. Hamac-Höller.)

V. FORMULATIONS (CENTER-FILLED LOZENGES)

The following formulations represent various methods of manufacturing center-filled medicated confections.

Example 7: Decongestant (15.0 mg/4.5 g) Medicated Lozenges with Liquid Center—Direct Medicament Addition, 15% w/w Center Fill

Ingredient	Quantity
A. *Shell*	
Liquid sugar (67.5% w/w solids)	88.90 lb
Corn syrup 43°Baumé (80.5% w/w solids)	49.70 lb
Ground candy salvage (20—50 mesh)	2.00 lb
Pseudoephedrine HCl USP	155.00 g
Spearmint flavor	50.00 g
Green color cubes	10.00 g
B. *Center*	
Pseudoephedrine HCl USP	152.00 g
Peppermint flavor	75.00 g
Menthol	100.00 g
Liquid sugar (67.5% w/w solids)	74.10 lb
Corn syrup 58—62 DE	62.25 lb

Liquid sugar and corn syrup are gear-metered into the dissolver and precooked at 125°C. Final cooking is performed at 148°C with a vacuum of 736 mm Hg to produce 100 lb of candy base with a 60:40 sugar/corn syrup ratio. The flavor is uniformly mixed into the ground salvage. Color is added to candy base in the collection kettle. The pseudoephedrine HCl is added in the transfer kettle and folded into the mass and the flavor-salvage mixture is added on the mixing table. Candy base is mixed and tempered. The mass is transferred to the batch former containing the center fill pipe where it is formed to a candy rope around the pipe. Center fill sugar and corn syrup are mixed and heated to 105°C. Pseudoephedrine HCl and flavor are dissolved and the mixture added to the reservoir of the pump. Center fill material is cooled to 95°C, then pumped into the rope prior to sizing. The filled rope is sized, molded, cooled, and lozenges are collected for packaging.

Example 8: Anesthetic (10.0 mg/5.0 g) Medicated Lozenges with Fat Emulsion and Direct Medicament Addition—25% Center Fill Weight

Ingredient	Quantity
A. *Shell*	
Liquid sugar (67.5% w/w solids)	81.50 lb
Corn syrup 43°Baumé (80.5% w/w solids)	56.04 lb
Ground candy salvage (20—50 mesh)	2.00 lb
Benzocaine NF	93.00 g
Spearmint flavor	35.00 g
B. *Center*	
Benzocaine NF	93.00 g
Hydrogenated vegetable oil 98°F mp	50.00 lb
Glycerin USP	50.00 lb
Glyceryl monostearate	1.00 lb
Menthol	150.00 g
Eucalyptus oil	75.00 g
Green color paste	20.00 g

Liquid sugar and corn syrup are gear-metered into the dissolver and precooked at 120°C. Final cooking is performed at 148°C with a vacuum of 736 mm Hg to produce 100 lb of candy base with a 55:45 sugar/corn syrup ratio. The flavor is uniformly mixed into the ground salvage. The benzocaine is added in the transfer kettle and folded into the mass and the flavor-salvage mixture is added on the mixing table. Candy base is mixed and tempered. The mass is transferred to the batch former containing the center fill pipe where it is formed to a candy rope around the pipe. The glycerin and vegetable oil are each heated separately to 90°C. Emulsifier is added and dissolved in the oil. Add glycerin to the oil and mix until a smooth emulsion is formed. Add menthol dissolved in flavor and benzocaine. Cool to 90°C. The center fill emulsion is added to the reservoir of the pump, then pumped into the rope prior to sizing. The filled rope is sized, molded, cooled, and the formed lozenges are collected for packaging.

VI. PACKAGING

Hard candies are hygroscopic and prone to absorbing atmospheric moisture. Confections, when exposed to humid conditions, are susceptible to graining and sticking, resulting in a product with reduced consumer appeal. Moisture absorption in medicated lozenges can also result in drug decomposition because of interaction of medicament with the candy base, flavor, or acidulent.

Confectionary products which are marketed for mass appeal and rapid turnover are produced with an expected shelf life of 8–12 months. Medicated lozenges, on the other hand, should be expected to have a shelf life of 3–5 years. The location in the home where the material is stored is another factor that governs the integrity of both medicated and nonmedicated products. Confections are usually stored in the kitchen, whereas medicated lozenges are stored in the medicine cabinet—a location that exposes the product to cycles of extreme temperature and moisture.

The hygroscopic nature of the candy base, the storage conditions to which medicated lozenges are exposed, the length of time they are stored, and the potential for drug interactions (because of the reactivity of candy base components) require that packaging offer the product more than just an aesthetic surrounding that presents product to consumer.

A. Individual Bunch Wrap

The majority of medicated lozenge products are individually bunch-wrapped with either cellophane or aluminum foil laminated with tissue paper impregnated with a wax or FDA food-approved release agent (Figure 67). This covering is provided for aesthetics rather than as a protective moisture barrier, as bunch wrap offers only minimal moisture protection in that open

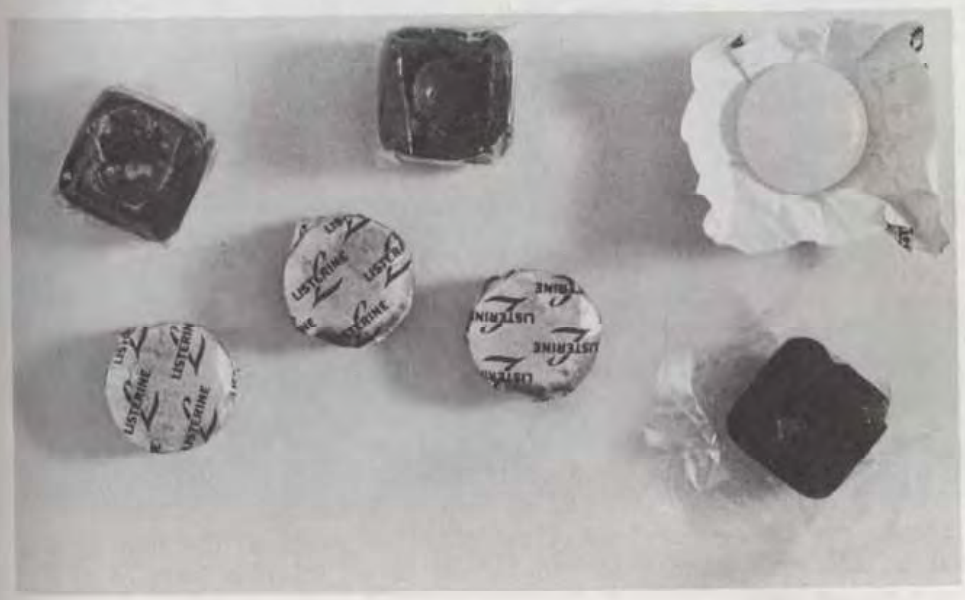


Figure 67 Individually bunch wrapped lozenges. Laminated aluminum foil or cellophane wraps are most commonly used.

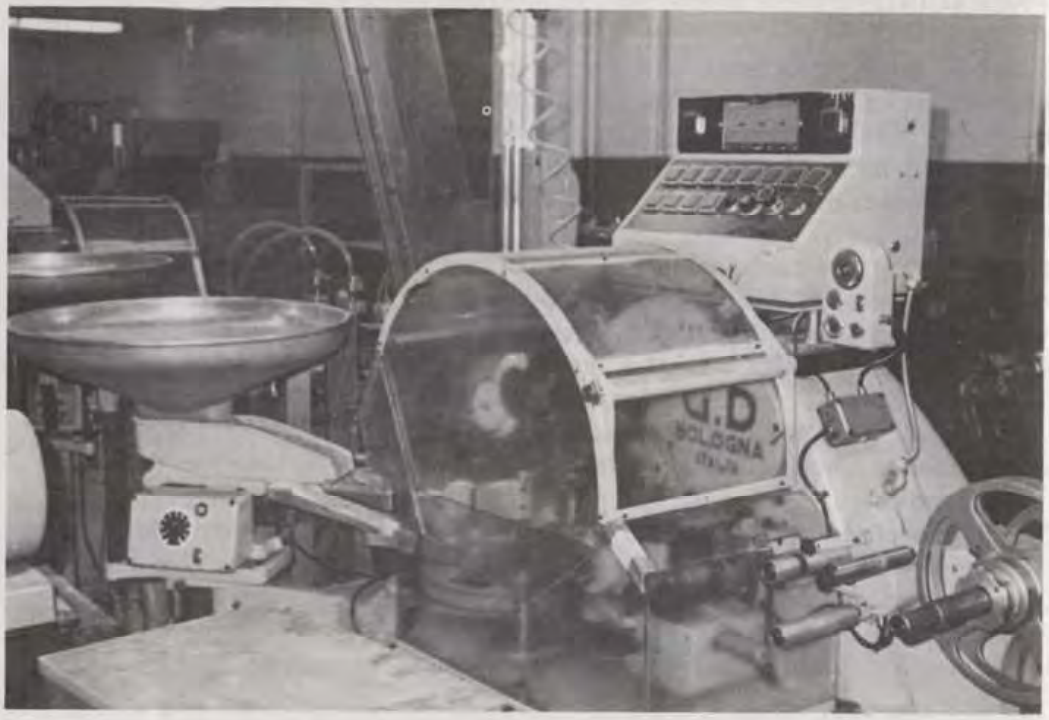


Figure 68 G. D. (Bologna, Italy) lozenge bunch wrapping machine. Unwrapped lozenges are stored in the hopper prior to mechanical aligning and passage into the bunch wrapping machine. (Warner-Lambert Co.)

spaces result when the foil or cellophane is folded around the lozenge. Production of a completely moisture-proof bunch wrap is not practical from the standpoint of cost, machine speed, or efficiency. The major advantage is that bunch wrap prevents lozenges from sticking together and from becoming dusty or breaking during shipping, shelving, or storage. Bunch wrap also aids in keeping the lozenges sanitary before use, expecially if the product is handled or carried individually in the pocket or purse [28].

Two disadvantages associated with the use of bunch wrap are (a) a tendency of the cellophane portion of the foil laminate to stick to the lozenge during prolonged storage at elevated humidity (lozenges that grain more than 40% become increasingly more sticky and prone to adhering to the bunch wrap); (b) the extra time that bunch wrapping adds to the packaging operation. The bunch wrapping process is the slowest of all the packaging procedures because each lozenge must be mechanically aligned and handled individually (Figures 68 and 69). Conversely, the benefits derived from bunch wrapping by increasing consumer appeal and confidence in the product—by professionalizing the mode of presentation, eliminating the sticking together of lozenges, and reducing the dusting or chipping of lozenges during transit and storage, as well as presenting a uniform appearance inside the box regardless of the physical state of the lozenges—indicates that bunch wrap should be considered as an integral part of the medicated lozenge package.

B. Container

The container offers the lozenges protection from breakage during transit (Figure 70) and provides a convenient vehicle for transportation. The more portable the container, the easier it is for the user to maintain a uniform dosage schedule (Figure 71).

The container does not offer complete protection from moisture because the end folds of the package are not airtight. A sealed, waxed paper lining will increase moisture protection, but in general the carton is used only as a means of protecting, displaying, and transporting the lozenges. A plastic tube may offer greater moisture protection than a paper carton depending on the type of plastic resin, thickness, and the seal integrity of cap to body.

C. Carton Overwrap

Overwrapping the container with cellophane, foil, or waxed paper will improve the resistance to moisture penetrating the package. A carboard carton overwrapped with nitrocellulose cellophane or Saran Wrap and stored at 25°C with a relative humidity of 80% will contain lozenges with an average grain of 40% after 90 days, while the same package stored without the cellophane overwrap will contain lozenges grained to an average of 90–95%.



Figure 69 G. D. (Bologna, Italy) bunch wrapping machine. Wrapped lozenges ready for packaging. (Warner-Lambert Co.)



Figure 70 Outer cardboard box offers the trade containers protection during warehouse storage and shipping.



Figure 71 Production trade packages. Cardboard box, foil pouch, styrene tube, metal box, strip-pack, and roll are the most common in use.



Figure 72 Carton overwrap. Moisture protection afforded the contents depends on the quality of seal and the moisture-transmission values of the wrap.

Sticking to the bunch wrap dramatically increases after the lozenge has grained 40% or more. The sticking is so intense after 80% graining occurs that the laminate will separate from the foil and stick to the lozenge surface. Lozenges that have maintained drug potency and flavor integrity become so physically unattractive when this condition does occur that they are unusable to the patient (Figure 72).

D. Bundle Wrap

A portion of any product's shelf life is spent in a warehouse. A medicated lozenge may at times experience 12–24 months of warehouse storage before reaching the consumer. Warehouse conditions vary from location to location, but in many instances warehouses are not climate-controlled. Prolonged storage in the ambient environment may cause product graining and decomposition even before the product is placed on store shelves. A means of mitigating this condition is to wrap a moisture-resistant covering around groups of boxes. This bundle wrap acts as a primary barrier to prevent moisture damage or premature graining before the product is placed on the retail shelves. The bundle wrap is removed before displaying the product since its only function is to protect the product during warehouse storage. Typical bundle wrap materials include waxed aluminum foil, Saran Wrap, polypropylene, waxed paper, or other materials with low-water-vapor transmission values. Routine checking of the seal integrity throughout the bundle-wrapping operation is carried out by either water submersion or vacuum-testing procedures. Incomplete sealing, folds, creases, or holes can negate much of the protection offered by the bundle wrap. An efficient bundle wrap (Figure 73) should offer medicated lozenges adequate



Figure 73 Bundle wrap. Vital for moisture protection during warehouse storage.

ambient shelf life storage, free from graining, for a minimum of 24 to as many as 36 months.

E. Foil Pouches

Perhaps the best protection that can be afforded a medicated lozenge product is packaging in a sealed aluminum foil, heat-sealable pouch [29]. This package employs aluminum foil as thin as 0.0009 in. laminated with polyethylene and tissue paper, and impregnated with wax to aid in sealing the pouch. As few as one and as many as four pieces can be packaged in one pouch, depending on the pouch and lozenge sizes. The product is guaranteed an indefinite shelf life free from the disadvantages associated with moisture permeation, as this type of package has a moisture transmission value approaching zero.

A quality control check of seal integrity is performed on a routine basis during the foil-pouching operation. A method both rapid and efficient for determining seal integrity is to place a group of five pouches in a container (a desiccator is suitable) under vacuum (380 mm Hg) in water for 60–120 sec; break the vacuum; open the pouches; and observe whether moisture has entered the pouch. Use of a colored water solution highlights moisture permeation, rendering pinhole imperfections more visible. The vacuum test, while efficient, is destructive to the pouches. Testing via a destructive procedure results in waste of a significant number of pouches, expecially when extended packaging runs or frequent interval testing is involved.

A second test, classified as nondestructive, is the carbon dioxide permeation test. Here the pouches are placed in a carbon dioxide atmosphere

for a predetermined time, then checked with a carbon dioxide-sensing device for the presence of the gas in the packet. The packages that pass this test are suitable for inclusion as salable production material. Testing of foil integrity is more fully described in Chapter 5.

Packaging lozenges in foil pouches eliminates the need for individually bunch-wrapping the product. The lack of moisture penetration through the foil laminate removes the tendency for lozenges to stick together. Lozenges will not break or cause excessive dusting in the pouch during transit since excessive movement with resulting attrition is limited by the tight fit of the lozenge in the packet (Figure 74).

A drawback of not bunch-wrapping foil pouched lozenges is the dusting that occurs during the packaging operation. The attrition in the storage hopper and delivery chutes as lozenges are fed into the pouches results in increased dusting of the lozenge surface. This does not affect product efficacy, stability, or surface texture; but from the standpoint of aesthetics, the quality of the product's appearance has been reduced. Lozenges in pouches can be sold as individual units of two to four lozenges per pouch or boxed in groups of pouches and sold in cartons.

Examples of some typical carton wrap and bundle wrap materials with their physical characteristics are contained in Table 5 [30]. Examples of graining characteristics of lozenges stored in various containers with different overwraps are present in Table 6 and Figure 75.



Figure 74 Foil pouches. Best protection afforded hard candy lozenges.

Table 5 Physical Properties of Selected Packaging Films

Product/opacity	Water vapor transmission rate in $g/m^2/100°F$, 95% RH/24 hr	Sealing properties	Machine performance	Printability	Heat shrinkability	Grease/oil resistance
Waxed glassine paper/opaque	4	Heat	Excellent	No	No	Excellent
Polymer-coated cellophane (1 mil)/transparent	6–14	Heat or adhesive	Excellent	Excellent	No	Excellent
Unoriented polypropylene (1 mil)/transparent	8–10	Heat	Fair to good	Good if treated	No	Excellent
Vinyl (1 mil)/transparent to translucent	8 and higher	Heat or adhesive	Fair to good	Special inks	Some types	Excellent
Propylene medium density (0.926–0.940 mil)/transparent to translucent	8–15	Heat	Fair to good	Good if treated	Some types	Good

Table 6 Effect of Wrap on Graining of Stored Lozenges

Container	Percent of lozenge exhibiting graining						
	Months at 25°C/80% RH				Months at 37°C/80% RH		
	1	2	3	6	1	2	6
Unprotected lozenges	70	90	100	100 (Liquefied)	82	100	100 (Liquefied)
Cardboard box without overwrap	52	78	93	100	72	93	100 (Liquefied)
Cardboard box with nitrocellulose cellophane overwrap	14	22	36	50	28	47	72
Cardboard box with polyethylene film overwrap	7	16	29	45	14	38	69
Cardboard box with nitrocellulose cellophane overwrap and waxed aluminum foil bundle wrap	0	0	0	<5	0	0	<10
Cardboard box with nitrocellulose cellophane overwrap and polypropylene shrink film (1.0 mil) bundle wrap	0	0	5	17	0	<10	25
Foil lozenge pouch—pouch paper/ polyethylene (1 mil)/foil (0.0008")	0	0	0	0	0	0	0

Note: Lozenge studied was medicated hard candy.



Figure 75 Grained lozenges. Top left: ungrained lozenge; top right: 25% grained lozenge; bottom left: 50% grained lozenge; bottom right: 75% grained lozenge.

VII. CHEWY OR CARAMEL BASE MEDICATED TABLETS

An alternative to the conventional "suck-type" hard candy lozenge is incorporation of medicament into a caramel base which can be chewed instead of dissolved in the mouth. Caramel is the general term for all chewy candies [78]. There are two main types: caramels and toffees. Toffees are not prepared by pulling (mechanical air incorporation) and are considered high-quality confectionary items. The term *toffee* came from the word *toughy* and in the United States it is called taffy [23]. This dosage form is more suitable for systemic vs. mucous membrane-active drugs since the dwell time of the active ingredient in the oral cavity is significantly less than is experienced with throat lozenges.

Many of the raw materials utilized in the preparation of chewy candies parallel those found in high-boiled sweets, but the method of preparation and the final product composition result in a dosage form that can be chewed or, if desired, slowly dissolved in the mouth. By changing the ratios of certain ingredients, the consistency of the product and the type of chew obtained can be significantly altered.

A. Raw Materials

Candy Base

Typical confectionary-based chewy tablets contain from 40 to 80% candy base. This is a mixture of sugar and corn syrup, with a ratio of 50:50 to 75:25 sugar to corn syrup. As this ratio approaches 50:50 the resultant product becomes more chewy and taffy-like while at 70:30 sugar–corn syrup, a grained, soft, and dry chew results. In between lies a large variety of alternative chew possibilities that can suit the overall desire of the product formulator.

The size of the tablet vs. the concentration of medicament will also help dictate the ratio of sugar to corn syrup. As the concentration of drug

present in the matrix increases, the softer will be the chew and the faster the time for graining. If a firmer chew is desired, more corn syrup is added, but if more structure (body) is needed, the sugar concentration must be increased. The candy base is the frame around which the product is built.

Sugar-Corn Syrup Ratio

As mentioned above, the ratio of sugar to corn syrup is critical in determining the type of product chew. Higher corn syrup-to-sugar ratios form a hard, sticky, taffey-like chew, while increasing sugar concentrations favor a dry, grainy chew associated with after-dinner mints.

Candy base is cooked in a manner similar to that described for hard candy lozenges. The major differences occur in the cook temperature and level of vacuum applied during processing. Whereas hard candy base has an average moisture content of 0.5–1.5%, chewy confections are prepared in the range of 3–5% moisture. This increased moisture lowers the viscosity of the corn syrup vehicle thus allowing for the softer consistency. The lower viscosity also allows for more sugar crystal movement in the base, thus explaining the increase in graining tendencies and the formation of a softer and drier chew when the product is prepared with higher sugar contents.

As the candy base content of the product increases, so does its effect on the overall processability of the tablet. Chewy candies with a high candy base content (greater than 65%), high moisture (above 3.5%), and high corn syrup-to-sugar ratio (50–55% corn syrup) will tend to "cold-flow" (stick, droop, and flatten out even at room temperature) and have a taffy-like chew. Products with a high sugar-to-corn syrup ratio (60–70% sugar) and high moisture (above 3.5%) will grain rapidly (sugar crystallization), have a dry, soft chew and be difficult to process. This is because the product will lack the elasticity for acceptable forming and shaping. Graining gives the product structure but also a brittleness that reduces stretch and causes the candy rope to break and tear instead of stretching. Reduction of moisture in this situation will result in a harder, more brittle chew. Increased moisture will cause cold flow and increase stickiness.

The sugar, corn syrup, and moisture contents of the chewy product must be well controlled if a tablet with optimum chew characteristics, processability, and shelf life is to be formulated.

The use of high-maltose corn syrup tends to produce a tablet with a somewhat harder chew. This raw material, at equivalent moisture, will produce candy base with a higher viscosity which will be harder and less grained than candy prepared under identical conditions utilizing regular 42- to 43-DE corn syrup. The dextrose equivalent of the corn syrup will also affect the chew characteristics of the final tablet. Reduction of dextrose content below 36 DE will result in product with a tougher, taffy-like chew, while use of corn syrup with a DE above 46 increases the incidence of cold flow, product browning, and atmospheric moisture intolerance. Except for the browning problem, the use of 42- to 43-DE regular grade corn syrup is indicated when preparing medicated chewy confections.

Aeration

Air must be incorporated in toffee-based confections in order to attain the desired, distinctive type of soft chew. Since a pulling machine is not used [67,81], aeration must be accomplished by using a whipping agent that will entrap air and lower the density of the final product. This aeration, with

resultant reduction in density, makes the product more chewy and gives the impression of a more meltaway type of chew. Utilization of a pulling machine reduces the efficiency of product manufacture, especially when high-speed forming equipment is employed.

Raw materials such as milk protein, egg albumin, gelatin, xanthan gum, starch, pectin, algin, carageenin as well as combinations of these materials have all been used successfully to lower the density of the candy. The whipping agent is prepared as a separate mixture before incorporation in the product.

One or more of the whipping agents are suspended in hot water and rapidly mixed with cooling until a highly aerated, foamlike mixture is produced. Gums are often mixed with the whipping agent in order to give body to the mass and allow for the entrapment of more air. The gum will impart extended stability to the whip thus enabling longer storage of this component and more efficient reduction of the final tablet density. This stabilized mass will also hold the air better when incorporated in the candy base.

Addition of the whipping agent must be accomplished at a temperature low enough to prevent the destruction of the whip but high enough to allow incorporation of cold materials in the hot mass without causing crystallization. The whip should be added at a temperature somewhere between 90 and 120°F. During the addition procedure, a gentle kneading action is indicated. This will assure a uniform incorporation of the whip in the candy base without destroying its air retention characteristics.

Humectants

Addition of humectants to the chewy base enables the product to meet two criteria. First, the addition of humectant lowers the equilibrium relative humidity (ERH) [61] of the formulation, while at the same time improving the chew and mouth-feel characteristics of the product.

Many toffee-based formulations have an equilibrium moisture level of 45–55%. Products with higher corn syrup levels may even test at 55–70%. The significance of equilibrium relative humidity value means that at times, when the ambient relative humidity is below the ERH of the formulation it will surrender moisture to the atmosphere. On the other hand, when stored in environments above the ERH, the product will pick up ambient moisture and become sticky. Ideally, when the product is formulated, it should be targeted at a 35–40% equilibrium level. Achieving this concentration means that if the ambient conditions are maintained at 35–40% RH, the product will maintain its integrity. Should the product be exposed to higher humidity conditions, it will pick up some moisture but rapidly lose it when the conditions are again favorable. In the winter, when the relative humidity is low, the product may lose water at the surface but will regain its integrity when exposed to favorable humidity conditions. Formulation of a product with this type of equilibrium moisture tolerance results in one that is much less apt to harden in the package, since it is easier to protect a product from moisture pickup than it is to protect it from drying out and hardening. If the product is hard, the customer will consider the chew totally unacceptable, but a tablet that softens and becomes slightly sticky in most cases is still consumer-acceptable. Chewy-based confections that are formulated at a high ERH are most always subject to hardening.

Glycerin is the best of the food-acceptable, humectant materials. It has a bland taste, good mouth-feel, and is completely inert. Propylene glycol

is bitter and sorbitol tends to crystallize and make the tablet harder to chew. The humectant can be added to the product after incorporation of the whip. If desired, any colorants can be suspended or dissolved in the humectant and added at the same time. Normal concentrations of humectant run between 1.5 and 5% of the batch weight.

Lubricants

Addition of a lubricant to a chewy product helps prevent the candy from sticking to the teeth during chewing. Since most lubricants are oils and do not incorporate well in candy base, care must be taken to use the lowest concentration that will give the desired effect. In most instances 3–7% will properly lubricate the candy. If higher concentrations are needed, emulsions may be required to prevent oil separation.

Vegetable oils and fats are used as lubricants in chewy candies. When selecting a proper lubricant, the melting point of the fat and the concentration must be evaluated. Incorporation of the oil in the chewy candy base is most easily accomplished as a simple mixture and not by preparing an emulsion. In either case, the oil tends to express out of the candy when the product is placed under stress. Heat or mixing may cause the oil to separate from the product. When this occurs, the candy loses some of its elasticity and becomes more difficult to process. Another problem of oil separation is product flavor change since the oil occludes the flavor. The tablet chew may become grainy and nonhomogeneous.

Reduction of oil content below 5% or the use of a higher melting point fat or oil can remedy this problem. Oils with a melting point of 98–105°F are well suited for this type of product. Below 95°F the oil is still a solid or a semisolid, which reduces the chances of migration. When chewed, the oil rapidly softens and melts in the mouth thus allowing it to perform its function of lubricating the product to prevent sticking on the teeth. Fats above 105°F are not recommended because they do not melt in the mouth. This will produce a confection that, when chewed, will have a fatty sensation in the mouth, since the candy will dissolve and the unmelted fat remains on the teeth.

Any of the bland hydrogenated vegetable oils (cottonseed, palm, soy, etc.) that fall in the desired melting point range are acceptable lubricants for this type of product.

Addition of the hydrogenated vegetable oil should take place below 90°C and after the whipping agent has been thoroughly incorporated. If the oil is added too soon after addition of the whipping agent it will cause the whip to deaerate and lose its density reduction characteristics.

Medicaments

Whereas hard candy lozenges can accommodate only 2–4% medicament, the chewy tablet can take up to 35–40% material. The soft tablets are not difficult to chew; therefore preparation of 4.0- to 5.0-g tablets is not unreasonable. This means that as much as 1.5–2.0 g of certain medicaments can be delivered per dosage unit.

Addition of medicament to chewy base poses a unique problem to the formulator. As the patient chews the tablet and releases the drug, it is solubilized or suspended in the saliva. Therefore, any off-taste, bitterness, or anesthetic characteristics are accentuated both during and after chewing. Medicated syrups are quickly swallowed, and hard candy lozenges

release the medicament slowly and it is quickly swallowed. Chewable compressed tablets keep some of the medicament entrapped in the granules where it is partially masked, but the chewy dosage brings out the worst flavor and bitterness characteristics of all active ingredients. Even flavor oils appear bitter when used at concentrations that would normally help mask an unacceptable taste, since the flavor oils are picked up by the saliva and retained in the mouth.

Utilization of adsorbate technology [70–75] helps to mitigate this problem. Preparation of 5–20% medicament adsorbates on carriers such as magnesium trisilicate or Veegum [63,70] renders many bitter principles palatable in the mouth. Once swallowed, the adsorbate readily releases the drug at the low pH of the stomach. Use of powder coating and microencapsulation techniques are also procedures that will make many drugs palatable when incorporated in the confectionary mass.

Based on the heat stability of the medicament, the drug addition can take place anywhere between 105°C and 65°C with 95–105°C being optimum addition temperatures. This allows for adequate mixing time and sufficient candy base fluidity to assure a uniform incorporation of drug throughout the product.

Seeding Crystals

Under normal circumstances, after cooling, the chewy base will crystallize [62,82] into a pliable mass that can be processed into individual dosage units. Depending on the ratio of sugar to corn syrup, this crystallization may take from 24 to 72 hr and may be variable depending on atmospheric conditions. A method utilized to speed up this crystallization and allow the base to be formed into tablets in a much shorter time is a process called *seeding* [82]. Here fine sugar crystals are added to the warm candy mass. These crystals become a seed which stimulates crystallization of other sugar crystals and thus the formation of product with sufficient strength to withstand final tablet processing. Ideally, sufficient seed should be added to the product to produce a rapid and coarse graining. A coarse grain when broken down by extrusion will result in formation of tablets with a very fine grain. The fine-grained tablets are softer, have more resistance to cold flow, and have a more acceptable chew characteristic.

Fine-powdered sugar at 3–10% is used as seed material. If the sugar is too course, the resultant tablets tend to be gritty. If the sugar is too fine, the seeding characteristics are diminished. If properly seeded, the product should be fully grained within 3–6 hr after addition. Seed material should be added to the base at a temperature not exceeding 85°C. Above this temperature the sugar will melt into the product and lose its crystalizing characteristics. The seeding material should not be mixed for more than 5–10 min since excessive mixing will also tend to melt the seed into the product.

Flavors

Flavors may be added to the chewy base at the same time as the seed material. Temperatures should be below 90°C to prevent excessive flavor flash-off. Rapid incorporation of the flavor in the base will also reduce flavor loss. Liquid or powdered flavors are suitable for use in this type of product.

The concentration of flavor used in chewy products should be kept to a minimum. The flavor itself can impart bitterness to the base when chewed

out of the tablet since it will be rapidly solubilized and mixed with saliva. In most cases flavor concentration should not exceed 0.5%. When developing the product flavor, the formulator should taste flavored and unflavored candy base to determine how much of the product bitterness is contributed by the flavor oils.

B. Processing

Many of the procedures utilized in the manufacture hard candy lozenges are incorporated into the preparation of the chewy dosage form.

Hard Candy Base

Candy base is prepared in the same manner as described for medicated lozenges. Cooking temperatures and vacuum parameters are lower in order to prepare base with a higher moisture content (3–5%). This increased water lowers the viscosity of the corn syrup phase, which helps avoid the brittle glassy candy that results when base is manufactured at 0.5–2.0% moisture [77].

The candy base, after cooking, is transferred to a suitable mixer (Figure 76). Planetary or sigma blade configuration is acceptable. The vessel must be heated to a temperature of 95–125°C in order to avoid rapid cooling and crystallization of the candy when it contacts a cool surface. If the vessel surface is too cool and the candy crystallizes, lumps of hard candy will be dispersed throughout the product. If the mixer temperature is set too high (above 130°C), the extra mixing time required to cool the batch will result in a condition whereby candy base is cooled with extended mixing. The friction generated onto the candy base along with cooling causes a seeding of the batch that results in a rapid fine crystallization of the sugar from the base. This is nonreversible and, if allowed to continue, will form a solid mass of grained candy in the vessel. Ideally, the container temperature must be high enough to prevent candy base sticking to the walls and blades but low enough to minimize the mixing time required to cool the base to the initial desired processing temperature (Figure 77).

Once the candy base has been cooled to a temperature below 120°C, the whipping agents may be added. These ingredients include milk solids, egg albumin, gelatin, starches, gums, or a combination of these materials all whipped and hydrated before addition. This is critical because the foaming and air-holding qualities of the whip are diminished when added to hot candy base. For optimum effect, maximum air must be entrapped into the whipping agents during the hydration procedure. The thicker whipped mass will entrap more air into the candy. A negative is that too much gum or protein will result in a hard, taffy-like chew.

The whipping agent should be added to candy base that is below 105°C. This allows for optimum retention of air in the product and formation of a good protein matrix. If the candy base is too hot (above 120°C), aeration is lost and the protein matrix collapses. Addition of this material at too low a candy base temperature (below 90°C) results in product sticking and candy base crystallization.

Colors and Humectants

Any colorants may be added by dispersing them in the humectant. Color addition to the humectant must be accompanied by efficient mixing to assure



Figure 76 Candy base cooked to proper temperature is transferred to preheated mixer. Mixer temperature should be no more than 20°C below that of the candy base to avoid rapid cooling and crystallization. (Warner-Lambert Co.)



Figure 77 Candy base is mixed to a temperature below 120°C. At this point the whipping agents may be added. (Warner-Lambert Co.)

uniform particle distribution and prevention of dye lumps which results in mottled tablets. Dyes suspended in glycerin, dextrose, or propylene glycol may be used and added directly to the product. Color addition (Figure 78) can take place at any time during the process and is limited only to the stability of the dye component in the presence of hot candy base.

Humectants should be added at a temperature above 90°C to avoid rapid and uncontrolled cooling of the product in the mixing kettle.

Medicaments

Medicament addition (Figure 79) to the product is governed by the heat stability of the drug in the presence of candy base. The earlier in the process the medicament can be added, the longer the mixing time and the

better the distribution. Conversely, heat-sensitive drugs may be added at the lowest workable product temperature and mixed for a time period sufficient to achieve content uniformity.

Drugs such as dextromethorphan HBr, chlorpheniramine maleate, calcium carbonate [76], acetaminophen, carbetapentane citrate, aluminum, or magnesium hydroxide and diphenhydramine HCl are heat-stable. They can be added at any time in the process (after aeration) and mixed until the product is cooled. Other medicaments such as benzocaine, pseudoephedrine HCl, phenylpropanolamine HCl, dyclonine, aspirin, and dimenhydrinate are subject to rapid heat degradation. These ingredients are added at temperatures ranging from 65 to 75°C and are mixed for as little as 5 min to achieve proper distribution. Medicaments should be added after the addition of aeration ingredients to avoid interference with the air entrapment



Figure 78 Color addition. Dyes are suspended in propylene glycol or glycerin to aid distribution. (Warner-Lambert Co.)



Figure 79 Medicament addition. Heat stability of the drugs determines at what temperature they may be added. (Warner-Lambert Co.)

procedure but added before addition of flavors to avoid interaction of medicament and flavor. Optimum medicament addition temperature is 95–105°C. Addition temperatures below 70°C increase distribution problems due to the high viscosity of the product.

Lubricants

Lubricants (vegetable oils) should be added away from the whipping agent. The oil acts as a defoaming agent, which lessens the aeration characteristics of the whip and results in a product with a hard chew. Lubricant, if added after the medicament, causes the lowest degree of product deaeration. Addition of lubricant below 80°C is not recommended since the candy base will not completely incorporate the oil when it gets too thick. Addition at temperatures below 80°C may result in a phase separation of the lubricant causing the final tablet to lose elasticity and have an oily texture with a fatty taste.

Flavor and Seeding Crystal Addition

Incorporation of the flavor into the seeding crystals prevents excessive flash-off from the hot product and aids incorporation of the oil or powder in the batch. Seeding crystals should be added to the product at a temperature not exceeding 85°C (Figure 80). This will prevent the melting of the seed crystals, thus lessening the product's crystallizing characteristics. The seed should not be mixed for more than 10 min after addition to prevent crystal melting. If the batch temperature is too low (less than 60°C), premature crystallization will make removal of the product from the mixing vessel difficult.

Product is removed from the mixing kettle after seed addition (Figure 81). Ideally, the product should have a viscosity low enough to allow the material to slowly flow out of the mixer without operator assistance. The higher the viscosity, the more difficult and time consuming is this step. Product that is too fluid at this stage, even if in the desired temperature range (60–85°C), may have been overmixed thus allowing the seed to melt back into the base. When the seed is lost, the time for the candy to grain is markedly increased. Properly seeded base can be processed 3–4 hr after cooling while unseeded or improperly seeded candy may take 1–3 days at controlled temperature and humidity conditions to reach an acceptable level of product grain.

Graining gives the tablet structure and body. Incomplete grain results in cold flow, or drooping and flattening of the product. The inability to hold the desired shape occurs when the incomplete candy base structure allows movement of the corn syrup in the vehicle. Proper graining will allow for a solid structure so that tablets are formed with a soft chew and a resistance to cold flow even under elevated temperature or humidity conditions.

Tablet Forming

As the candy base cools to room temperature (Figure 82), the combination of high (3–5%) moisture content, seed, and falling temperature results in the formation of a rapid, coarse-grained product. The coarse-grained material is hard to chew and very brittle. Coarse graining gives the product extreme strength and resistance to cold flow.



Figure 80 Flavor and seeding crystal addition. Seed should not be mixed for more than 10 minutes to avoid melting of the seed crystals into the batch. (Warner-Lambert Co.)

In as little as 3–4 hr after cooling, the product has grained to an extent that individual tablets may be formed. Depending on the type of equipment available, product may be cut and wrapped or formed in a manner similar to that utilized for hard-boiled candy lozenges.

Since the product is now hard, brittle, and cooled to room temperature, it must be worked into a pliable state that will allow the formation of individual dosage units. This must be done regardless of the type of tablet-forming operation. The method of choice is extrusion [79]. Here the mass is broken down to a more flexible state by passing the product through an extruder (Figure 83). The course-grained mass is broken down so that a more elastic and workable base is produced. This is accomplished by reducing the coarse-grained matrix into a fine-grained state (Figure 84). This fine grain has more elasticity, a softer chew, but sufficient structure to restrict the tendency toward cold flow.

The work of extrusion adds heat to the product. To control sticking and prevent expression of the vegetable oil lubricant, the candy base temperature should be kept between 30 and 45°C during the extrusion and



Figure 81 Removal of the medicated candy mass from the mixer. Ideally the product should have a viscosity low enough to allow the material to flow out of the mixer without operator assistance. Some manual cleaning around the blades may be required. (Warner-Lambert Co.)



Figure 82 Medicated caramel base is deposited onto a cooling table. During this rapid cooling period a product with a coarse grain is formed. At least 3 to 4 hours cooling is required to enable the product to properly grain before extrusion. (Warner-Lambert Co.)

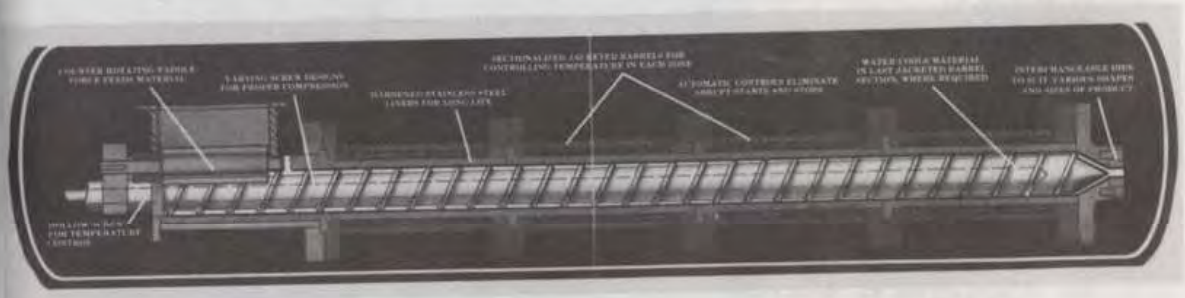


Figure 83 Schematic of jacketted extruder. The screw design of the extruder can be varied to obtain the desired compression and mixing force. (The Bonnot Company, Kent, Ohio.)



Figure 84 Grained caramel mass is extruded into a flexible candy rope. Diameter and shape of the rope can be adjusted by changing the exit die configuration. (Warner-Lambert Co.)

forming operations (Figures 85 and 86). Should the base exceed this temperature, oil separation is noted, sticking of tablets to the punch faces occurs, and the formed tablets are soft, thus increasing the incidence of tablets sticking together or deforming. If the product temperature falls below 30°C, the candy mass is brittle and nonelastic. This results in a nonuniform candy rope and difficulty in maintaining an acceptable tablet weight variation. Tablets prepared from a cold rope are also difficult to form thus increasing the tendency for fissures and imperfections on the tablet surface.

The candy base is extruded into a 1- to 2-in. round rope (diameter depends on final tablet weight) (Figure 87). The candy rope temperature is maintained at a level that allows for adequate elasticity to assure uniform weight tablets. The temperature must not reach the point that sticking to the punch faces or sticking of tablets together after forming or deformation of product while cooling results. After extrusion, the rope, tablet-forming, cooling, and collection operations are the same as described for hard candy lozenges (Figures 88 and 89).

An alternative to forming tablets utilizing hard candy lozenge procedures is passing extruded rope through a cutting and wrapping machine (Figure 90). Here the extruded candy rope (square instead of round) is cut into chunks using a knife, then wrapped in the desired bunch wrap. The

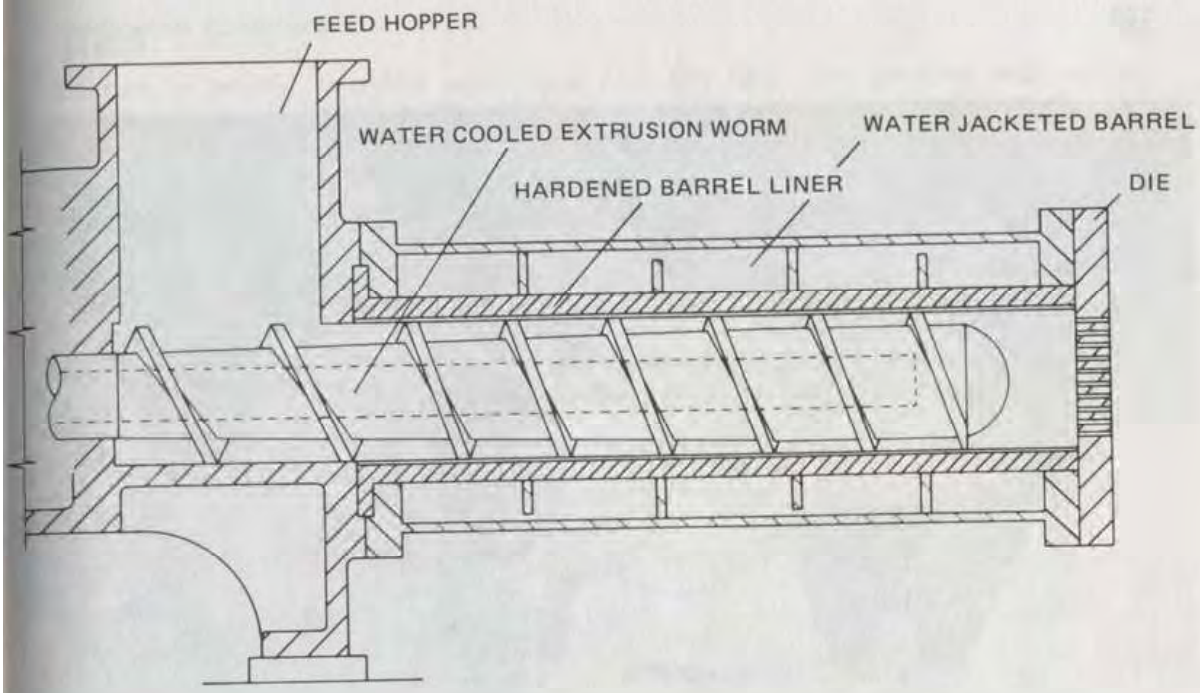


Figure 85 Schematic of jacketted extruder. More than one pass or a series of extruders may be required to obtain a product rope with the proper consistency. (The Bonnot Company, Kent, Ohio.)

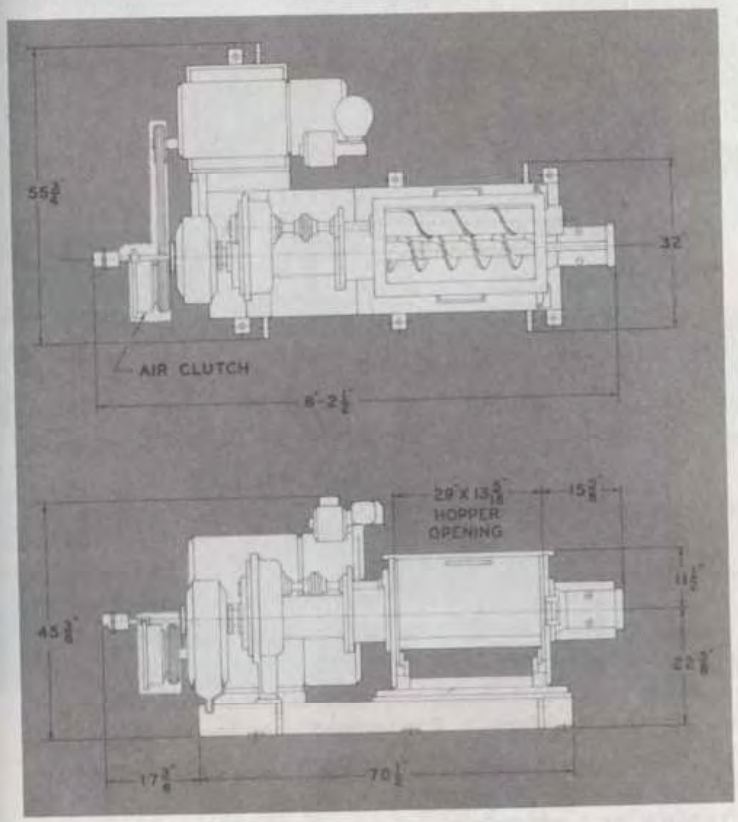


Figure 86 Schematic of extruder hopper and screws. (The Bonnot Company, Kent, Ohio.)

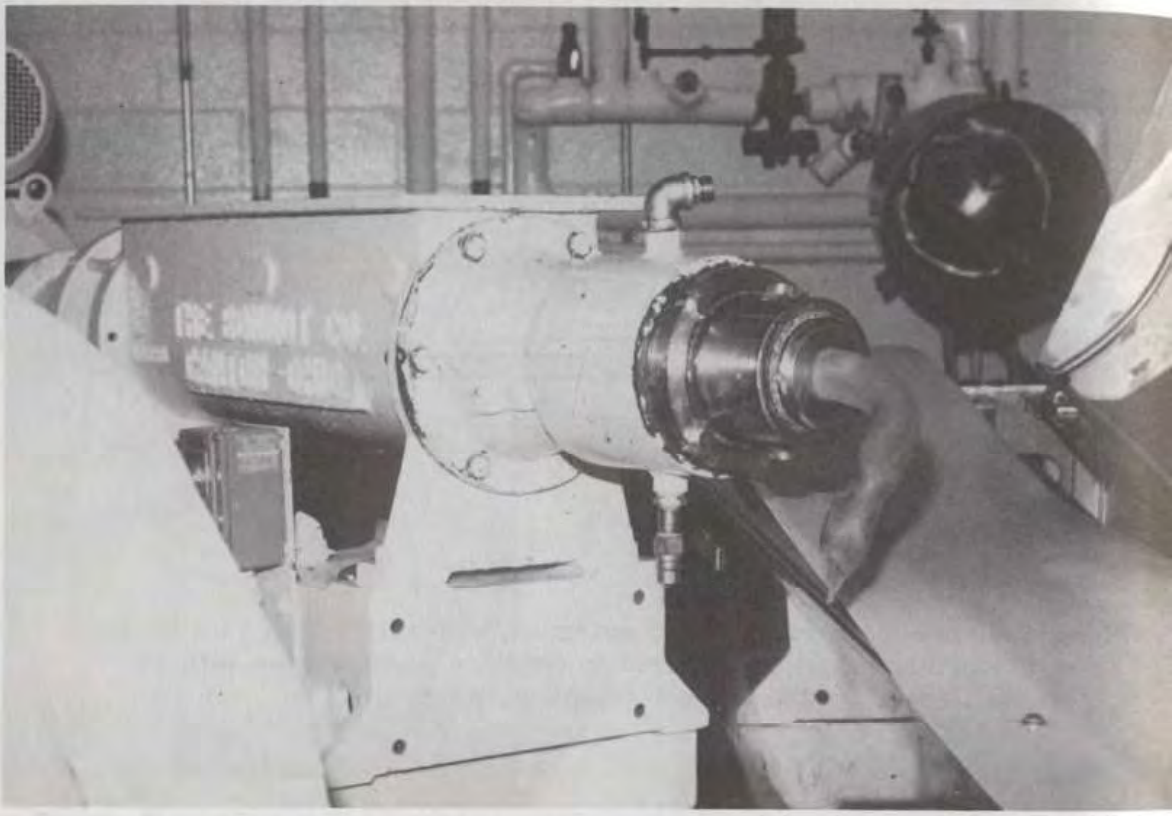


Figure 87 The diameter and shape of the candy rope is governed by the die configuration placed on the end of the extruder. Tablets weighing 4 to 5 grams require a 1-1/2 to 2 inch rope. This rope must then be sized to the proper diameter prior to the tablet forming operation. (Warner-Lambert Co.)

advantage of cut and wrap is that it is a single-step operation. Disadvantages include speed of tablet preparation and the limited shapes available.

C. Packaging

Control of moisture both in and out of the package is a major consideration when choosing a primary package for chewy tablets.

If the final product is prepared at an equilibrium moisture content of 35%, transmission of water into the product in summer months is more of a problem than release of moisture from the tablets in the winter. If properly formulated, unprotected tablets in low-humidity conditions will case-harden forming a tough crust at the surface. Prolonged exposure to a low-humidity environment will result in a gradual hardening of the tablet. Conversely, at elevated humidity conditions, moisture will be drawn into the product resulting in softening and sticking. Once the tablets are re-

turned to normal humidity conditions (30–50% RH), the product will return to its original condition. To circumvent these moisture-related phenomena the product may be packaged in glass, high-density polyethylene bottles, fin-sealed pouches, or fin-sealed sticks (Figure 91).

Summary

Chewy type confectionary-base tablets can be prepared using many of the raw materials and processes utilized for hard candy. Regulation of candy base moisture and addition of aerating ingredients, humectants, lubricants, and seed control the product texture and give the desired chew characteristics.

Higher quantities of medicament can be delivered in this dosage form that can be incorporated into hard candy lozenges, but flavor masking of bitter principles is more of a problem.

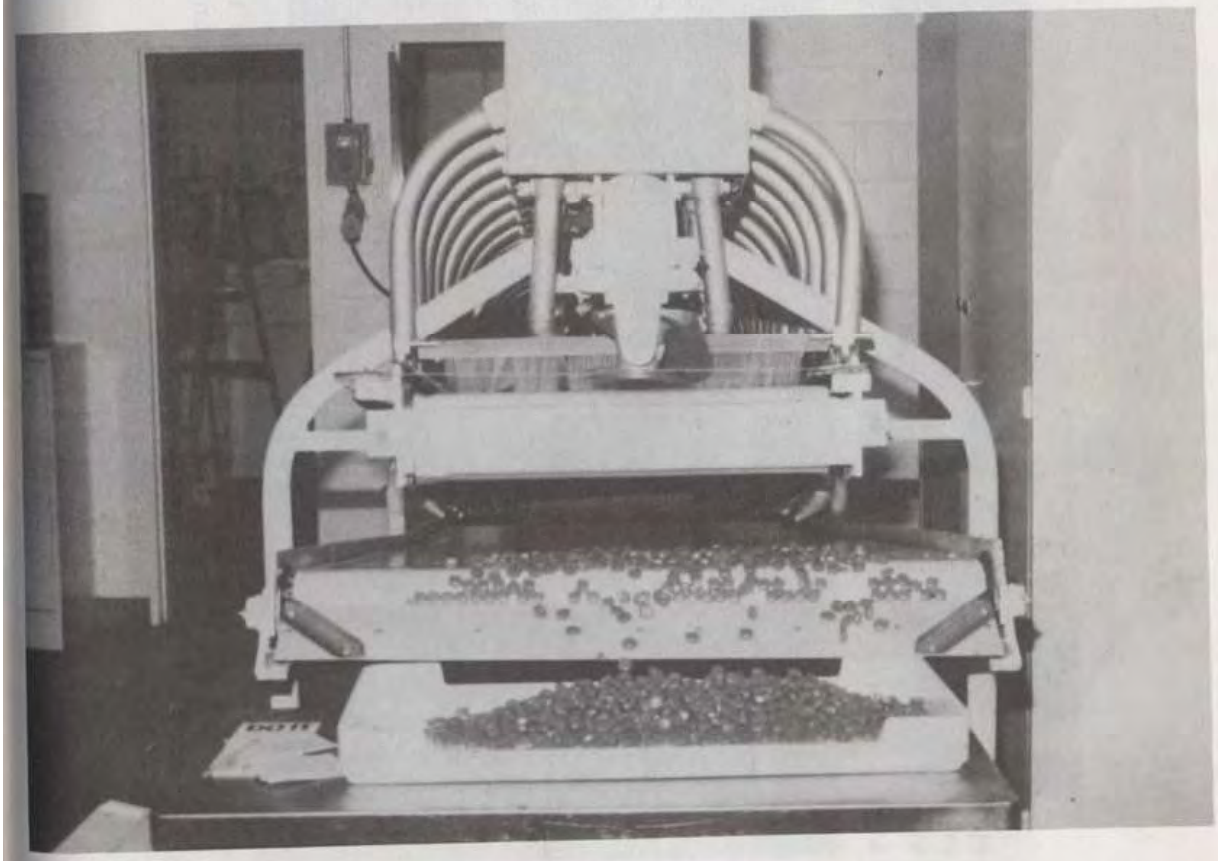


Figure 88 Formed tablets are passed through a cooling tunnel similar to that used for hard candy lozenges. This prevents sticking or deforming of the tablets. (Warner-Lambert Co.)

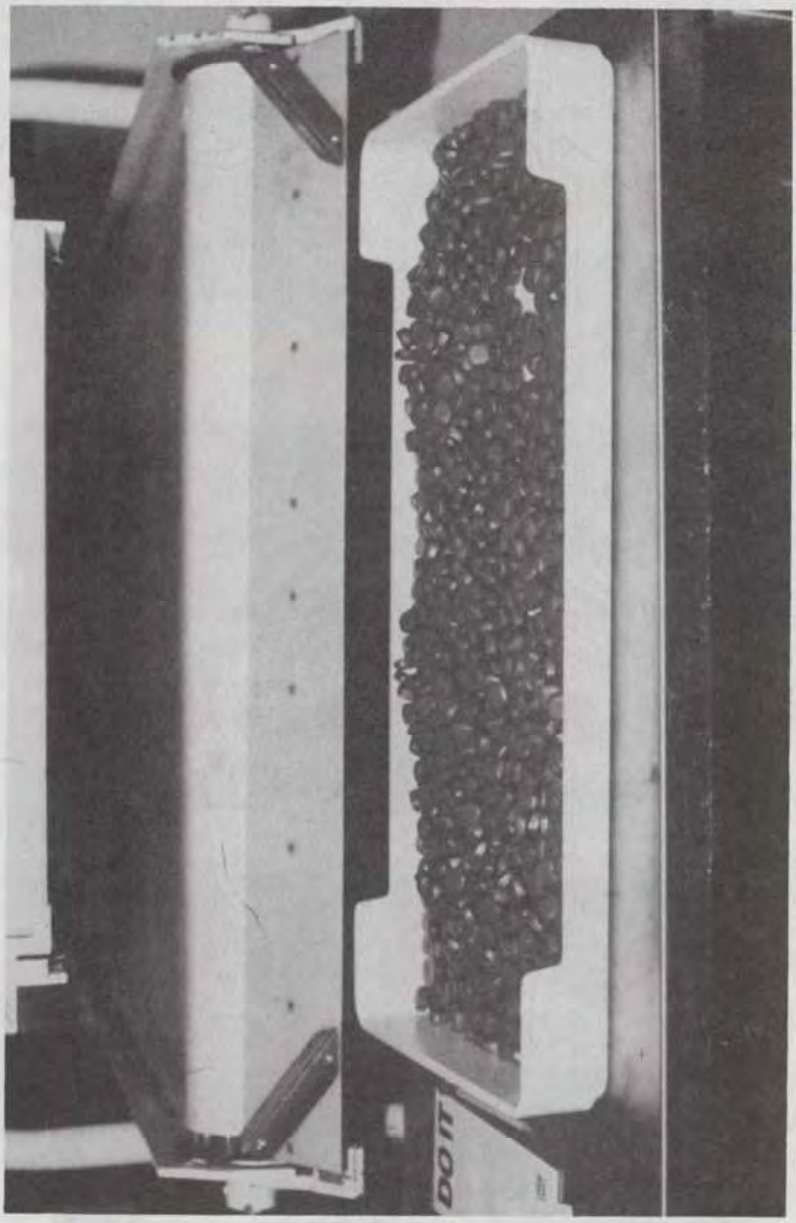


Figure 89 Cooled tablets are collected in trays. The tablets should not be stored more than one deep to prevent sticking of flattening of the product. (Warner-Lambert Co.)

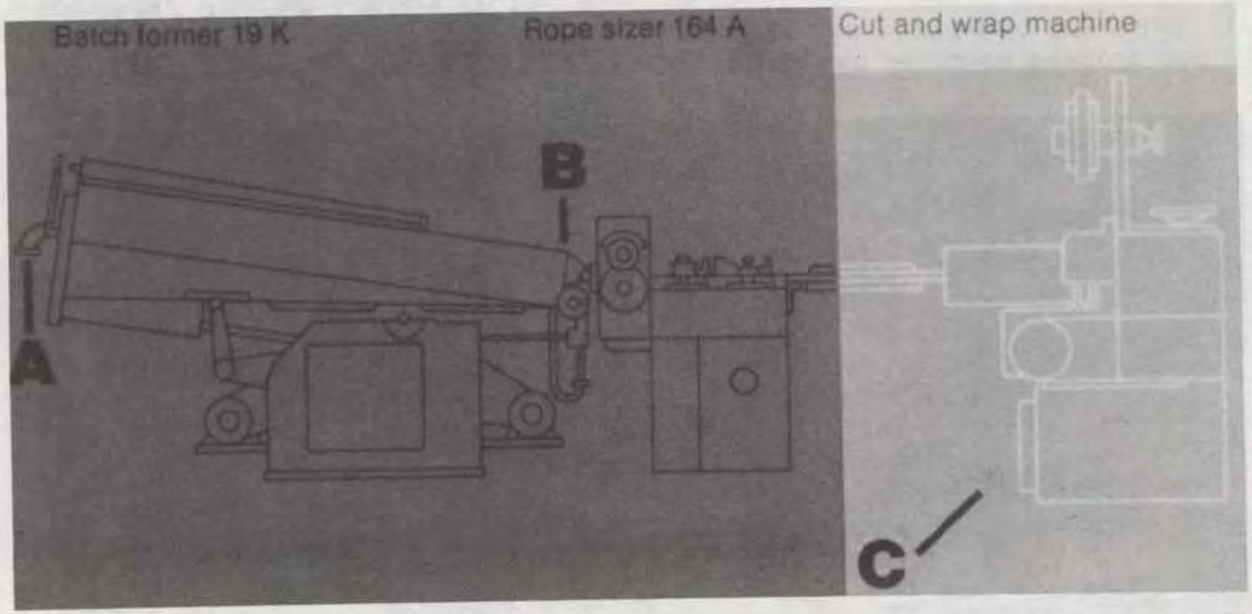


Figure 90 Cut and wrap machine. The candy mass is formed and rope sized in the same manner as Uniplast formed lozenges. Instead of tablet forming, the candy rope is passed through a cut and wrap machine that cuts the rope with a knife and wraps the product as a continuous operation. (Robert Bosch GmBH, Div. Hamac-Holler.)



Figure 91 Chewy or caramel base medicated tablets can be bunch wrapped and packaged in glass or plastic bottles or foil wrapped and placed into fin-sealed pouches. (Warner-Lambert Co.)

VIII. FORMULATIONS (CHEWY-BASED CONFECTIONS)

The following formulations represent various methods of manufacturing medicated chewy-based confections.

Medicament—Egg Albumin—Cut-and-Wrap Process

Example 9: Decongestant Tablets (30.0 mg/4.0 g)

Ingredient	Quantities
Liquid sugar (67.5% w/w solids)	88.9 lb
Corn syrup 43°Baumé (80.5% w/w solids)	47.9 lb
Pseudoephedrine HCl 15% adsorbate	4280.0 g
Egg albumin	250.0 g
Gelatin USP	100.0 g
Water	450.0 g
Sorbitol solution	450.0 g
Hydrogenated vegetable oil 98°F MP	3000.0 g
FD&C Yellow No. 6	10.0 g
Glycerin USP	1500.0 g
Citric acid USP anhydrous	65.0 g
Imitation orange flavor	50.0 g
Fine-granulated sugar	1000.0 g

Liquid sugar and corn syrup are gear-metered into the dissolver and precooked to 125°C. Final cooking is performed at 143°C with a vacuum of 15 in. Hg. to produce 100 lb of candy base with a 60:40 sugar/corn syrup ratio.

The egg albumin and gelatin are dissolved in a mixture of water and sorbitol solution and heated with mixing to 65°C. Heat is removed and rapid mixing continued until an aerated mass is formed.

Candy base is transferred to a jacketed mixer that has been prewarmed to 125°C. Add egg albumin mixture and mix until temperature is 110°C. Add glycerin and dye mixture and mix until temperature falls to about 90°C. With mixing add pseudoephedrine adsorbate. Cool to 80°C and add hydrogenated vegetable oil. Mix until temperature falls to 70°C and add flavor, sugar, and citric acid. Mix for 5 min and remove from the mixer.

The mass is cooled for 4 hr, extruded into a 2-in. square rope, and passed through a cut-and wrap-machine to form 4.0-g square pieces.

Medicament—Milk Solids—Lozenge-Forming Equipment

Example 10: Antitussive Tablets (15.0 mg/4.0 g)

Ingredient	Quantity
Liquid sugar (67.5% w/w solids)	96.30 lb
Corn syrup 43° Baumé (80.5% w/w solids)	43.57 lb
Nonfat dry milk solids high heat	400.00 g
Xanthan gum	200.00 g
Water	500.00 g
Dextromethorphan HBr 10%, adsorbate	2075.00 g
Sorbitol solution	350.00 g
Hydrogenated vegetable oil 98°F MP	2500.00 g
FD&C Red No 40	25.00 g
Glycerin USP	2000.00 g
Menthol USP	50.00 g
Wild cherry flavor	60.00 g
Fine-granulated sugar	1500.00 g
Citric acid USP anhydrous	75.00 g

Liquid sugar and corn syrup are gear-metered into the dissolver and precooked to 125°C. Final cooking is performed at 140°C with a vacuum of 12 in. Hg to produce 100 lb of candy base with a 65:35 sugar/corn syrup ratio.

The milk solids and xanthan gum are dissolved in a mixture of water and sorbitol solution and heated with mixing to 60°C. Heat is removed and rapid mixing continued until an aerated mass is formed.

Candy base is transferred to a jacketed mixer prewarmed to 125°C. Add milk solids and mix until temperature is 115°C. Add glycerin and dye mixture and mix until temperature falls to about 100°C. Add dextromethorphan 10% adsorbate. Cool to 85°C and add hydrogenated vegetable oil. Mix until temperature falls to 70°C and add flavor, sugar, and citric acid. Mix for 5 min and remove from the mixer.

The mass is cooled for 3 hr, extruded into a 2-in. round rope, and passed through an extruder to a series of sizing rollers, molded, and cooled. Formed pieces are individually bunch-wrapped before packaging.

IX. COMPRESSED-TABLET LOZENGES

This section, devoted to describing the preparation of compressed-tablet lozenges, includes many facets covered in other chapters of this text. The general guidelines to be set forth—for wet and dry granulations, milling, and drying, as well as for tablet compression—are analogous to those for regular compressed tablets. The major deviations occur in the specific types of raw materials most applicable to this type of dosage form, the non-routine lozenge disintegration requirements, tablet press and granulation considerations associated with preparing a tablet of the diameter and guage of a compressed lozenge—as well as certain specific organoleptic peculiarities unique to this specialized route of drug administration.

Whereas the typical tablet is designed for rapid disintegration and dissolution characteristics, compressed-tablet lozenges, with the desired area of activity on the mucous membrane of the mouth and pharynx, are usually large-diameter tablets (5/8 to 3/4 in.), compressed in a weight range of 1.5–4.0 g and formulated with a goal of slow, uniform, and smooth disintegration or erosion over an extended time period (5–10 min). The formulator performing product development should remain cognizant of any deviations from normally occurring medicament bioavailability profiles that may result from the addition of binders or excipients to the formulation.

As previously discussed, the emphasis in the case of the lozenge is on the slow, uniform release of medicament directly onto the affected mucous membrane. This increased dwell time in the oral cavity places an added burden on the formulator to develop flavor blends that will effectively mask unpleasant principals contributed by the medicaments, while at the same time maintaining a smooth lozenge surface texture as the tablet slowly disintegrates. This attribute enhances the patient acceptance and desire to hold the tablet in the mouth until it is completely dissolved. The tablet should erode (not disintegrate) while in the oral cavity, as the presence of particulate matter can be extremely disconcerting to the patient. For maximum drug efficacy, the product must not be chewed; thus a tablet with hardness approximating that of the boiled candy lozenge (30–50 kg in.^{2}) should be compressed.

A. Rationale for Preparation of Compressed-Tablet Lozenges

Hard candy base is the most widely used vehicle for administration of medicaments that act by direct contact on mucous membrane of the oral cavity or are ingested by first dissolving the dose slowly in the mouth. Along with its sweet taste and pleasing appearance, the candy base imparts a demulcent effect of its own, increasing the efficacy of anesthetics or other materials added to relieve the discomfort of inflamed or abraded tissue. From an aesthetic aspect, adults and children find the hard candy base a pleasant and palatable vehicle for medicament administration, expecially when multiple dose or prolonged administration is indicated.

Four primary characteristics associated with preparation and storage of hard candy preclude the universal incorporation of medicaments in this type of vehicle. These factors include (a) the high temperature (135–150°C)

necessary to drive off water and prepare hard candy. (b) The reactivity of candy base with medicaments—from the base itself as well as from flavors and acidulents that may be added to the formulation. (The intimate combination of ingredients may lead to drug instability problems since hard candy base, with its 0.5–1.5% moisture content and hygroscopic characteristics, more closely follows the kinetics of liquid rather than solid dose.) (c) The required therapeutic dose of medicament or combination of medicaments may be at a level sufficiently high as to preclude the incorporation of adequate material into either a single or two-lozenge dose. (The larger the number of doses the patient is required to take to achieve a therapeutic response, the greater the chance of noncompliance with a proper dosage schedule. Also, because of its physical nature, the drug may produce a lozenge with a rough surface texture when combined with candy base, thus reducing the organoleptic appeal of the product.) (d) Suitable candy base and lozenge-forming equipment may not be available, or the volume of sales does not warrant the capital expenditures required to set up a candy line. (A company that is already manufacturing tablets may feel that the production of a compressed lozenge is a more logical extension of its technology than entrance into the boiled candy lozenge area).

A suitable formulation alternative may be the compressed-tablet lozenge if one or more of the above situations apply, and the category of medicament and mode of drug administration require contact with the mucous membrane of the oral cavity, thus indicating a lozenge type of vehicle. This type of dosage form can fulfill all the parameters of the hard candy version, but can be manufactured in the conventional mode of pharmaceutically acceptable dosage forms.

The incorporation of medicaments into a compressed tablet lozenge may pose fewer problems than are associated with hard candy base. Whereas the type of medicament, quantity, reactivity, particle size, heat sensitivity, moisture sensitivity, and melting point are critical to the ultimate success of producing a hard candy lozenge with medicament, many of these same aspects are of minor concern when preparing the compressed tablet version. Much of the appeal that the medicated hard candy lozenge offers to the patient comes from the organoleptic presentation of the drug in a pleasing and somewhat demulcent vehicle. Incorporation of medicament into tablet base makes the drug no more or less efficacious. From a vehicle presentation aspect, with proper blending of ingredients a base with the same pleasing and demulcent characteristics can be formulated.

The compressed lozenge can be prepared by the historical wet granulation technique or by direct compression. For maximum efficacy and prolonged dwell time in the mouth, the tablet should be of sufficient size (1.5–4.0 g) and hardness (30–50 kg in.^{2}) to dissolve slowly and posses the organoleptic appeal of the hard candy version.

Raw Materials

Use of tablet compression techniques open up a myriad of raw materials that may be suitable for incorporation in this type of base. Previous discussions centered around the proper ratios of sugar and corn syrup that would produce a controlled crystallization rate and a resultant product with maximum clarity, smoothness, and resistance to graining or sticking. Addition of raw materials to compressed lozenges is determined by the effects of the raw materials on tablet compression, disintegration, erosion, mouthfeel, and powder or granulation flow characteristics.

The following materials are essential to the preparation of a pharmaceutically elegant product when formulating a compressed-tablet lozenge [31]:

1. Tablet base or vehicle
2. Binder
3. Flavor
4. Colors
5. Lubricants
6. Medicaments

A working knowledge of the principles of tablet base preparation and compression are essential if the formulator is to produce any compressed lozenge product. The art and science of tablet manufacture is complicated and beset with many pitfalls and potential problem areas, mainly in the selection of raw materials, granulation preparation, comminution, mixing, and compression. Chances of preparing an acceptable product—unless the formulator has had previous tableting experience—are as remote as the chances of the uninitiated successfully manufacturing the hard candy lozenge version.

Tablet Base or Vehicle

This is the basis of any tablet formulation. The materials chosen for incorporation in the tablet base will determine the overall method of tablet preparation (wet granulation or direct compression) [66] as well as the final physicochemical characteristics that may be associated with the product.

Sugar

Perhaps the simplest tablet formulation would involve the use of sugar as the base. Sugar, in this case, is pulverized by mechanical comminution to a fine powder (40–80 mesh), blended with medicament, granulated with either a sugar syrup or corn syrup binding solution in order to prepare medium- to large-size (2–8 mesh) granules, dried, milled to smaller and more uniform particle size (20–30 mesh), flavored, lubricated, and compressed into tablets of desired shape and size.

Sugar is inexpensive and lends itself to the formation of tablets with acceptable compression and mouth-feel characteristics. The resultant mouth-feel will be creamy in texture with an unabrasive and smooth surface if the final particle size of the sugar granulation is controlled at 20 mesh or finer.

Dextrose- and Sucrose-Modified Vehicles

The use of dextrose by itself, as well as dextrose- and sucrose-modified materials in combination with or in place of sucrose, can produce tablets as acceptable as those prepared with sucrose—in terms of compression characteristics, mouth-feel, and appearance, and in some cases at a cost lower than is possible with sucrose alone. Some examples of modified tablet vehicles now available are included here.

Dextrose is produced by a number of different manufacturers under a variety of trade names and is supplied as a white crystalline sugar (a pure monosaccharide) that is 100% fermentable and available in either a hydrated or anhydrous form [32]. Dextrose possesses a negative heat of dissolution, which imparts a more cooling mouth-feel characteristic to tablets than does sucrose.

Dextrose exhibits good flow and compression characteristics but is more suited to wet granulation procedures as opposed to direct compaction,

expecially where high-weight tablets or tablets with a high percentage of active ingredient are involved. Dextrose tablets tend to exhibit browning at elevated temperatures (37°C and above) as well as in direct sunlight.

Emdex is a highly refined, total-sugar product composed of free-flowing crystallized maltose-dextrose porous spheres of 92% dextrose, 2–5% maltose, and a portion of higher glucose saccharides [33]. Emdex has good flow and compression characteristics, and while it does contain 8–10% moisture, it is not hygroscopic. Emdex is not as reactive as dextrose, but some evidence of reactivity with primary amino groups does exist.

Mor-Rex is a white, bland-tasting, low-density maltodextrin with lower hygroscopicity than corn syrup and a moisture content of about 5%. The composition of Mor-Rex includes 82% hexasaccharide, 4% disaccharide, and 1% monosaccharide. The total reducing sugar content is 10–13% [34].

Mor-Rex, while not suitable as a primary compression vehicle because of its bland taste and marginal flow properties, possesses good binding character, inertness, and resistance to moisture pickup, all of which make it an acceptable filler, expecially where hygroscopic, deliquiscent, or sticky materials must be added to the vehicle. Because of its binding qualitites, Mor-Rex cannot be used in large quantities in wet-granulated formulations, as the resultant tabet will either be too hard or possess a gummy consistency. Mor-Rex is a valuable ingredient for slowing disintegration time and for binding tablets that tend to exhibit unacceptable compression quality.

Royal-T Dextrose with Malto-dextrin is a specially compounded agglomerated dextrose containing maltodextrin [35]. This material is supplied as white agglomerated crystals with a moisture content of 8.5% and a dextrose equivalent of 96. Royal-T is suitable for both direct compression and wet granulation procedures. The resultant tablets have the organoleptic advantages associated with dextrose (cooling mouth-feel), but improved compression characteristics due to the presence of the maltodextrin.

Nu-Tab is a directly compressible tablet vehicle composed of processed sucrose, invert sugar (equimolecular mixture of levulose and dextrose), starch, and a small quantity of magnesium stearate. Nu-Tab can be supplied in a range of controlled particle sizes [36]. It possesses better flow, compression, and mouth-feel characteristics than sucrose alone. Nu-Tab is primarily used in direct-compression tableting and can accept up to 30% medicament and still produce tablets of acceptable quality. Nu-Tab is resistant to moisture pickup, thus making it an acceptable vehicle for moisture-sensitive medicaments. This vehicle is resistant to elevated temperature darkening.

Di-Pac represents a cocrystallization of 3% highly modified dextrins with sucrose to produce a tablet vehicle with improved flow, compression, and a mouth-feel similar to that of sucrose. Di-Pac contains less than 1% moisture, less than 1% reducing sugar, and is resistant to moisture pickup [37]. This vehicle is intended for directly compressible tablets where low to medium concentrations of active ingredients (less than 20%) are to be incorporated. Di-Pac is resistant to discoloration and its low moisture content makes it ideal for reactive or moisture-sensitive medicaments.

Sugartab is a white, free-flowing agglomerated sugar product recommended for direct compression of tablets. Sugartab contains approximately 90–93% sucrose, with the balance being invert sugar. The moisture content is less than 1% [38]. Sugartab is composed almost entirely of coarse particles—offering a typical distribution of 30% retained on 20-mesh screen

and 3% passing through an 80-mesh screen. The coarse mesh size makes it a good carrier for certain materials that may have inherent compression problems of a type that may be alleviated by combining with a controlled particle size excipient milled to the optimum size range for the formulation.

Care must be taken when evaluating this material to ascertain if medicament distribution or segregation problems will occur after milling of the large Sugartab particles to a finer mesh size. Browning has occurred upon storage at elevated temperature (37–45°C).

Sweetrex is a directly compressible tablet base containing a special blend of natural sugars possessing a sweetness factor greater than that of sucrose. Sweetrex contains dextrose, levulose (fructose), maltose, isomaltose, and other higher polysaccharides in a blend with a binding capacity of up to 50% active ingredients [39]. This material will pick up moisture to a certain extent, but its major drawback is a tendency toward darkening at elevated temperature (37–45°C) and upon exposure to sunlight when combined with certain medicaments.

Mola-Tab is a directly compressible tablet vehicle containing 60% molases solids, 30% whole wheat flour, and 10% wheat bran. Mola-Tab contains about 4% moisture. This material is a deep-brown-colored, free-flowing granule with good compressibility. Tablet products containing this material have a good mouth-feel and a noticeable molasses flavor which helps mask some of the medicament bitterness. Because of the high quantity of reducing sugar and 4% moisture, a noticeable increase in product darkening is noted at elevated temperature storage conditions. Tablets compressed with this material exhibit slow erosion and a smooth surface texture. Tablets will pick up moisture but are not hygroscopic. Mola-Tab is a source of natural molasses and dietary fiber [86–87].

Hony-Tab is a directly compressible tablet vehicle containing 60% honey solids, 30% whole wheat flour, and 10% wheat bran. Hony-Tab contains about 4% moisture. This material is a straw-colored, free-flowing granule with good compressibility. Compressed tablets containing this material have a good mouth-feel with a noticeable sweetness and honey flavor which helps mask medicament bitterness. Because of the high quantity of reducing sugar and 4% moisture, a noticeable increase in product darkening is noted at elevated temperature storage conditions. Tablets compressed with this material exhibit slow erosion and a smooth surface texture. Tablets will pick up moisture but are not hygroscopic. Hony-Tab is a source of natural honey and dietary fiber [86,88].

Sugar-Free Vehicles

Manufacture of a sugar-free compressed tablet lozenge is more readily achievable than the counterpart hard candy lozenge. Sugar-free candy lozenges of sorbitol or sorbitol-mannitol combinations cannot be prepared on high-speed lozenge-manufacturing equipment due to the length of time it takes for crystallization to occur (0.5–14 hr). The long crystallization time relegates the preparation of sugar-free lozenges to that of a molding operation; thus manufacturing plants geared for conventional lozenge production cannot be readily adapted to the molding procedures unless a change of equipment is instituted. This is one reason medicated sugar-free lozenges have not gained wide acceptance in products containing medicaments.

Conversely, compressed sugar-free lozenges do not require any special handling, manufacturing procedures, or equipment, thus lending themselves

to this type of manufacturing process. The most commonly used sugar-free tablet base vehicles include the three described below:

Mannitol is a naturally occurring sugar alcohol, an isomer of sorbitol but with a different chemical configuration and a different set of physical properties [40]. Mannitol is available as a fine powder, primarily for use in wet granulations, and in granular form for use in direct-compression tablets where the need for improved flow and compression characteristics exists. Mannitol contains less than 0.3% moisture and is nonhygroscopic. Its flow and compression characteristics are good, as are its chemical inertness and resistance to discoloration. Mannitol is only 50% as sweet as sugar, but its negative heat of solution enables it to impart a pleasant, cooling sensation in the mouth as the lozenge dissolves. Mannitol is noncariogenic.

Sorbitol is a chemical isomer of mannitol that is 50% as sweet as sugar, noncariogenic, nonreactive with most medicaments, but extremely hygroscopic [41]. Its flow, compression, and mouth-feel characteristics are similar to those of mannitol, and its negative heat of solution helps it impart a pleasant, sweet, cooling sensation in the mouth. Sorbitol is better able to carry high quantities of active ingredients than most excipients, especially in a wet-granulated tablet base, since formulations containing greater than 20% sorbitol tend to be tacky and adhesive with good compression characteristics; but its hygroscopic nature makes it undersirable where extended shelf life is required or when moisture-sensitive medicaments are incorporated in the granulation. Moisture-resistant packaging is essential with sorbitol-containing compressed lozenges. Sorbitol is available as a crystalline powder or as free-flowing granules [65]. Tablets prepared with sorbitol are less resistant to discoloration because of the presence of higher quantities of moisture picked up from the atmosphere during storage in containers that are resistant to moisture [68]. The incidence of formulation discoloration is minimal when sorbitol formulations are protected from moisture.

Polyethylene Glycol 6000 and 8000 are polymers of ethylene oxide with the generalized formula $HOCH_2(CH_2OCH_2)_nCH_2OH$, with n representing the average number of oxyethylene groups. Polyethylene glycols (PEGs) are designated by a number roughly representing their average molecular weight. Most polyethylene glycols in the molecular range of 1000–8000 are white, waxy solids, soluble in water and in many organic solvents, and resistant to hydrolysis [42]. PEG 6000 has a melting range of 53–56°C, while PEG 8000 has a melting range of 60–63°C. PEGs 6000 and 8000 are best suited for use in tablet formulations since lower molecular weight polyethylene glycols, with their reduced melting points (less than 50°C), increase the incidence of tablet binding and picking during compression. The punch faces, die walls, and table become heated during the manufacture of tablets because of friction. This increase in temperature is sufficient to soften a granulation and increase its tackiness, expecially if low-melting-point materials are present in the formulation. The higher the percentage of low-melting-point materials in the product, the greater the propensity for sticking and picking. Conversely, higher molecular weight polyethylene glycols exhibit no advantage over PEG 6000 or 8000 in improving compression characteristics of the granulations to which they are added, or in reducing picking or sticking. Addition of the high molecular weight material (PEG 20,000) may produce brittle tablets or tablets with unpleasant mouth-feel characteristics.

Polyethylene glycols are not intended to be incorporated in tablet granulations as the primary excipient or vehicle but are added in quantities

ranging from 5 to 35% of the final tablet weight. The major benefits derived from addition of PEG to tablet granulations include prolonging disintegration time and improving the tablet surface texture in instances where the addition of certain medicaments to the formulation might result in a tablet with a rough or pitted surface. The inclusion of varying percentages of PEG 6000 or 8000 to a formulation aids in increasing the attainable hardness of many directly compressible tablet vehicles as well as improving the compressibility of some marginally acceptable granulations. Also, the PEG 6000 or 8000 does not have any discernible flavor or mouth-feel characteristics of its own. Polyethylene glycol, being inert, is compatible with most medicaments that may be incorporated in the tablet formulation. This material can be added to a powder mixture before wet-granulating, added with flavors and lubricants after the granulation is dried, or added to a direct-compression vehicle prior to mixing.

The quantity of PEG added to direct-compression tablet bases is determined by the physical characteristics of each individual vehicle. Some formulations possess a slow disintegration profile of their own and compress to a hardness sufficient to give the desired 5- to 10-min dwell time in the oral cavity. This desired, slow, in vivo disintegration is not possible with some bases because of the rapid disintegration characteristics of the tablet components. Addition of PEG (20–30%) will, in many instances, slow disintegration (erosion) to the desired time interval [43]. Incorporation of PEG in tablets containing medicament in the 30+ percentage range may improve particle cohesive forces, compression characteristics, and tablet hardness values in those instances where addition of the medicament results in a poor or marginally acceptable product.

Addition of polyethylene glycol to a wet-granulated tablet base will also aid binding and improve the organoleptic quality of the product, but its use in this type of granulation is mostly relegated to the latter function, as tablet disintegration can be controlled by the incorporation of different binders or binder concentrations. The resulting tablet will have a soft, wet, and spongy consistency, difficult to compress, susceptible to picking and binding, as well as possessing an exceptionally long (20–30 min) in vivo disintegration time if the quantity of PEG added to a wet-granulated vehicle is excessive. Polyethylene glycol is best added externally with flavor and lubricants when incorporated in a wet granulation tablet base.

Other Fillers

Other fillers suitable for inclusion into compressed lozenge tablet base include *dicalcium phosphate* (*Emcompress* [89]), *calcium sulfate* (*powder* or *Compactrol* [90]), *calcium carbonate*, and *lactose* [44]. These materials, when added in varying percentages, aid in the densification of the granulation to improve flow and die fill characteristics. Dicalcium phosphate, Compactrol, and lactose can be used in either wet granulations or direct-compression vehicles, while powdered calcium sulfate and calcium carbonate are most suitable for wet-granulated tablet bases.

Microcrystalline cellulose (*Avicel*) is another filler suitable for incorporation into both wet and direct-compression granulations, as an aid in improving marginal compression characteristics of a formulation. Avicel is available in a variety of particle sizes as well as in anhydrous form, and is suitable for moisture-sensitive medicaments or for materials that are sticky or hygroscopic [45]. Some disadvantages of microcrystalline cellulose

in lozenge tablet base include (a) diminution of granulation flow characteristics when this material is incorporated in concentrations above 20%; (b) decrease in lozenge disintegration time due to the exceptional disintegration properties of Avicel; (c) production of a particulate disintegration instead of a smooth erosion of the lozenge; (d) reduction in organoleptic appeal due to the starchy, fibrous, and drying mouth-feel imparted to the lozenge as it dissolves in the oral cavity. Avicel added in concentrations of less than 20% can improve the compression of marginally compressible tablet granulations without imparting many of the above-mentioned negative characteristics to the product. A summary of tablet vehicle components is presented in Table 7.

Binders

The function of a binder in a wet-granulated tablet base is to hold together as discrete granules the particulate matter that forms as a result of the granulating procedure. The binder is also the major contributor to final tablet hardness, since the type and concentration of binder present will enhance the *intragranular* forces in each individual granule as well as the *intergranular* forces, which are the bonding forces between granules [31].

When preparing a tablet granulation, if the intragranular force is greater than the intergranular force, the tablet will break, leaving an irregular and rough surface on the fracture line; but if the intergranular force or forces are greater, the fracture will be smooth. When compressing quantities of active ingredients into direct-compression vehicles, the intergranular forces must be maintained at a level sufficient to produce tablets with acceptable hardness and compression characteristics of their own. As these materials are added to a direct-compression tablet base, the level and efficiency of the intergranular forces of the tablet base are reduced, resulting in a lessening of tablet hardness, compression, and, in some instances, flow characteristics. At a certain critical concentration (different for each medicament in each individual tablet vehicle), the compression quality or attainable hardness values fall out of the acceptable range. Additional binder is required when this situation occurs, to form particles possessing sufficient intergranular force to produce a tablet within the required hardness and compression parameters.

Remedial actions required to improve direct-compression granulations may include (a) the addition of more tablet base to lower medicament concentration; (b) the incorporation of adjunct materials designed to improve the compression quality (e.g., PEG 6000 or 8000). A major disadvantage of adding more tablet vehicle is an increase in final tablet size and weight. The alternative, if neither of the above approaches proves acceptable, may be conversion to the preparation of a wet-granulated tablet base.

Since the compressed-tablet lozenge weight is in the range of 1.5–4.0 g, medicament concentration usually will not exceed 20%, a level that is suitable for compression into most directly compressible granulations. Use of wet granulation is reserved for improvement of organoleptic quality of the tablet, prolonging disintegration time, or the preference of the formulator for the wet granulation method of tablet base preparation.

Binders that are most effective in the wet granulation of compressed-tablet lozenges include acacia, corn syrup, sugar syrup, gelatin, polyvinylpyrrolidone, tragacanth, and methylcellulose. These ingredients are effective in increasing the intergranular forces while at the same time helping to improve the demulcent and surface texture characteristics of the lozenge when it is dissolving in the oral cavity.

The effects of binders on the resultant tablets can only be determined by a series of compression trials. The preparation of tablets with optimum compression and organoleptic characteristics is greatly influenced by the selection of the proper binder at an optimum concentration. Therefore, the formulator is required to screen a number of different granulations and binder combinations at various levels to determine which binder is best for any particular medicament or medicament combination. Other factors, such as particle size and distribution, moisture content, and granulation milling conditions, must be evaluated as they are also an integral part in optimizing final tablet compression and mouth-feel qualities.

Flavors

The selection of flavors is a vital aspect in the development of compressed-tablet lozenges. When formulating chewable tablets, as opposed to lozenges, the formulator must consider the critical aspect of mouth-feel after a tablet has been chewed. In contrast, the long dwell time of lozenges in the oral cavity requires that the formulator develop not only a pleasantly flavored product, but also a product whose flavor masks bitter principles that may be present in the formulation. The chemistry of the flavors incorporated in medicated lozenge tablet base must be evaluated by the formulator to minimize the possibility that interactions will occur between flavor components and the medicaments present in the lozenge.

Unlike the problems encountered in the hard candy lozenge base, where surface grittiness and possible nonuniform distribution result if flavors are not added in the liquid state, flavors are best added to compressed-tablet lozenges almost exclusively in spray-dried or liquid forms adsorbed onto a suitable diluent (Cab-O-Sil or Microcel). Spray-dried flavors cause fewer problems than liquid flavors because addition of liquid flavors to a wet granulation along with the granulating solution results in potentially high and nonuniform flavor losses occurring during the drying operation. If liquid flavors are added subsequent to the comminution of a granulation, or if they are added to a direct-compression granulation, the result is the formation of sticky and wet powders with a tendency to nonuniform distribution of flavor through the product. A secondary result of the addition of liquid flavors to the completed tablet granulation is a reduction in the cohesive characteristics of the granules because of the presence of the oily flavor adsorbed onto the surface of the granules. The net result is a lessening of tablet hardness and a reduction in compression quality characteristics.

The probability of medicament–flavor interactions is lessened with the addition of spray-dried flavors to the medicated granulation. This allows for the use of a greater variety of flavors than can be incorporated into the hard candy lozenge version.

Colors

Water-soluble and Lakolene dyes* can be used to color compressed tablet lozenges. Water-soluble dyes can be added to the powder mixture during

---

*An FD&C Lakolene dye is any *lake* made by extending on a substrate of alumina, a salt prepared from a certified FD&C water-soluble straight color by combining such a certified color with the basic aluminum or calcium ions.

Table 7 *Physical Characteristics of Components Utilized as Base Filler*

Material	Composition	Form	Tablet base	Accepts >20% medicament into base	Granulation flow characteristics
Sucrose	Derived from sugar cane or beet root	Coarse crystals to fine powder	Wet granulated	Excellent	Very good
Dextrose	Complete hydrolysis of cornstarch	Coarse crystals to fine powder	Wet granulated	Excellent	Good
Emdex	92% Dextrose 2–5% Maltose	Crystals	Direct compression	Fair	Decrease with tablet weight >3.5 g
Mor-Rex	82% Hexasaccharide 4% Disaccharide 1% Monosaccharide	Fine powder	Direct compression; Wet granulation (not a primary component)	–	–
Royal-T dextrose	Agglomerated dextrose with maltodextrin	Fine crystals	Direct compression	Very good	Good
Di-Pac	97% Sucrose 3% Modified dextrins	Fine to coarse crystals	Direct compression	Fair	Decrease with tablet weight > 3.5 g
Sugartab	90–97% Sucrose Invert sugar	Coarse particles	Direct compression	Very good	Very good
Sweetrex	Dextrose Levulose Maltose	Fine crystals	Direct compression	Fair	Good
Mannitol	Sugar alcohol	Fine powder to coarse granules	Direct compression; wet granulation	Fair; very good	Fair; very good
Sorbitol	Chemical isomer of mannitol	Fine crystals	Direct compression; wet granulation	Very good; excellent	Good
Polyethylene glycols	Polymer of ethylene oxides	Coarse crystals to fine powder	Direct compression; wet granulation (not a primary component)	–	–

Disintegration characteristics	Mouth-feel	Surface texture	Compression quality	Stability under moist conditions	Resistance to discoloration
Controlled with selected binders	Good; fine particle size produces creamy feel	Smooth	Excellent	Fair	Good
Rapid, but can be controlled with binders/other fillers	Very good; cooling mouth-feel	Smooth	Very good	Fair	Poor
Rapid but can be controlled with binders/other fillers	Very good; slight cooling mouth-feel	Good	Good	Excellent	Fair
Slows disintegration of rapidly soluble medicaments and exipients	–	–	–	Excellent	Good
Maltodextrin content slows disintegration	Very good; slight cooling mouth-feel	Smooth	Very good	Fair	Poor
Hard tablets slow disintegration	Good	Smooth	Very good	Excellent	Good
Hard tablets with slow disintegration	Good	Good	Very good	Fair	Fair
Rapid, but can be controlled with binders/other fillers	Very good; slight cooling mouth-feel	Good	Very good	Fair	Poor
Rapid, but can be controlled with binders/other fillers	Very good; slight cooling mouth-feel	Smooth	Very good	Excellent	Good
Hard tablets slow disintegration	Very good; cooling mouth-feel	Smooth	Excellent	Poor	Good
Slows disintegration of rapidly soluble medicaments and excipients	–	–	–	Very good	Good

Table 7 (Continued)

Material	Composition	Form	Tablet base	Accepts >20% medicament into base	Granulation flow characteristics
Dicalcium phosphate	Produced by various chemical means	Fine powder to coarse granules	Direct compression; wet granulation	Good; good	Improves granulation flow qualities
Calcium sulfate	Natural form	Fine powder to coarse granules	Wet granulation Direct compression	Fair	Improves granulation flow qualities
Calcium carbonate	Various chemical means	Fine powder	Wet granulation	Fair	improves granulation flow qualities
Lactose	Milk sugar	Fine powder to coarse granules	Direct compression; wet granulation	Good; excellent	Improves granulation flow qualities
Avicel	Microcrystalline cellulose	Fine powder	Direct compression; wet granulation	Good; very good	Fair Very good
Mola-Tab	60% Molasses 30% Wheat flour 10% Wheat bran	Fine to coarse crystals	Direct compression	Very good	Very good
Hony-Tab	60% Honey 30% Wheat flour 10% Wheat bran	Fine to coarse crystals	Direct compression	Very good	Very good

Disintegration characteristics	Mouth-feel	Surface texture	Compression quality	Stability under moist conditions	Resistance to discoloration
Slows disintegration of rapidly soluble medicaments and excipients	Poor	Chalky	Good	Very good	Good
Slows disintegration of rapidly soluble medicaments and excipients	Poor	Chalky	Fair	Excellent	Good
Slows disintegration of rapidly soluble medicaments and excipients	Poor	Chalky	Fair	Excellent	Good
Hard tablets with slow disintegration	Good	Good	Very good	Fair	Fair
Rapid—difficult to control with binders/other fillers	Poor	Chalky	Very good	Very good	Good
Slow disintegration	Very good	Smooth	Very good	Fair	Fair
Slow disintegration	Very good	Smooth	Very good	Fair	Fair

the preparation of wet-granulated vehicles prior to granulation in combination with the excipients and medicaments, or they can be dissolved in the granulating solution and added with the binder. Either soluble or Lakolene dye may be used if color is added to the powder mixture prior to granulation, although the appearance of the final tablet (mottled rather than uniform color distribution) will determine which type of dye is best suited for a particular granulation. Replacement with a soluble dye is indicated should incorporation of a Lakolene dye cause the final tablet to appear mottled. If a situation occurs where a dye (soluble or Lakolene) is added internally (with excipients and medicaments) to the granulation before adding binder, and the resulting tablets have a mottled appearance after compression, addition of small quantities (0.01–0.05%) of Lakolene dye with the external portion of the granulation (lubricant, flavor, or glidant) may alleviate the problem.

Incorporation of Lakolene dyes is indicated in the manufacture of direct-compression granulations since no logical step exists in the process where water-soluble dyes can be added [31]. Before its addition to the powder mixture, the Lakolene dye is mixed with an equal portion of one of the granulation components to prevent dye particle agglomeration—a situation that occurs if the dye is added to the powder mixture as a single portion. Mixing with another powder separates dye particles and prevents agglomeration. The powder-dye mixture can be passed through a 60-, 80-, or 100-mesh screen to further distribute the dye.

A method that can be used to add water-soluble dyes to direct-compression granulations in situations where the use of Lakolene dyes is contraindicated (chemical incompatibility with the substrate) involves the preparation of a wet granulation of the soluble dye on cornstarch. The mixture is dried (moisture content less than 0.5%), milled, and incorporated in the direct-compression granulation in the same manner as the Lakolene dyes.

Lubricants

The function of a lubricant as a component of the tablet granulation is divided into three specific areas: (a) lubrication of the individual particles to aid in the release of the tablet from the die wall; (b) antiadhesive properties which facilitate the release of the tablet material from the faces of the lower and upper punches; (c) glidant properties to improve material flow from the powder hopper onto the machine table and into the dies [31].

While many ingredients employed as lubricants fulfill one, two, or (in a few instances) even three of the required functions of a tablet lubricant, some materials function specifically to alleviate problems only in certain areas. Addition of magnesium stearate, zinc stearate, calcium stearate, stearic acid, Sterotex (a mixture of selected triglycerides), PEG, or combinations of these materials will usually alleviate most of the granulation deficiencies associated with die face and sidewall sticking or release problems. When the situation of die wall sticking or incomplete release from punch faces does occur, and addition of excessive quantities of lubricant (concentrations greater than 5%) does not improve the condition, an examination of the granulation binder concentration, particle size distribution, or moisture content (levels greater than 2.5% increase granulation tackiness) should be initiated.

An addition of specialized materials (glidants) that will improve powder or granule flow properties is indicated when a level of lubricant is reached that imparts effective lubricantion characteristics to the granulation but

unacceptable flow or nonuniform die fill problems still remain. Ingredients such as fire-dried fumed silica (Cab-O-Sil) or talc when added at levels up to 0.25% should improve granulation flow and die fill efficacy. Densification of the granulation should be evaluated if glidant addition does not alleviate the situation. The formulator, when selecting the types of lubricants most suitable for inclusion in the formulation, should be aware of the specific lubrication problem involved and choose the materials best suited to remedy the situation. An addition of Cab-O-Sil or talc will not alleviate the problem if the lubrication difficulty is with sidewall adhesion, whereas a slight increase (or addition) of as little as 0.01% alkaline stearate (e.g., magnesium stearate) may improve the condition.

One aspect associated with ingredients added to relieve granulation lubrication difficulties is that more is not always better. Addition of lubricats above certain critical concentrations (different concentrations for each individual granulation) reduces cohesive forces among granules, thus lessening granulation compression characteristics and, in some instances, medicament bioavailability. Incorporation of glidant at levels above 0.5% may form a granulation with reduced bulk density and die fill properties. When lubricant concentrations need be added at levels that begin to adversely affect granulation efficacy, the formulator should examine the base granulation for the reasons why the base does not possess acceptable lubricant or flow characteristics.

Medicaments

The compressed-tablet lozenge granulation, because of its bulk and compression characteristics, will accept from 20 to 60% active ingredient as part of the vehicle. Incorporation of almost any desired dosage of medicament or combinations of medicaments into a single tablet does not pose the difficulties encountered with the hard candy lozenge version. For maximum benefits from the flavor and for best mouth-feel and organoleptic characteristics, no more than 25–30% of the final tablet weight (1.5–4.0 g) should be medicament (0.45–1.2 g). Higher quantities of drugs can be compressed into the base but may adversely affect lozenge flavor, aftertaste, and disintegration (erosion) characteristics.

Anesthetics such as benzocaine (5–10 mg), hexylresorcinol (2.4–4.0 mg); decongestants such as phenylpropanolamine HCl (15–25 mg), pseudoephedrine HCl (15–30 mg); antihistamines such as chlorpheniramine maleate (1–4 mg) and phenyltoloxamine citrate (18–22 mg); antitussives such as dextromethorphan HBr, 10% adsorbate (50–150 mg) and diphenhydramine HCl (10–25 mg); and analgesics such as aspirin and acetaminophen (130–325 mg) are well tolerated in compressed-lozenge base.

Many of the active ingredient incompatibilities, in terms of both medicament (e.g., aspirin-antihistamine, benzocaine-decongestant) and flavor or lozenge base components, are either reduced or eliminated by controlling lozenge base moisture content at low levels (less than 0.5%), by diluting reactants in a nonreactive vehicle, and, in extremely reactive situations, by manufacturing a two-layer tablet to effect maximum separation of reactive components. Other methods utilized by the formulator to minimize drug interactions—in order to present to the patient combinations of drugs with flavors that heretofore were not feasible in candy or lozenge base—include altering the method of granulation preparation (wet method instead of direct-compression base), use of spray-dried flavors, and proper dilution of medicaments.

X. MANUFACTURING: COMPRESSION SEQUENCE

Manufacture of a compressed-tablet lozenge follows all the basic guidelines of tablet compression on a rotary tablet press [46]. When compressing a granulation of any type, the formulator should become familiar with the potential and actual problem areas and be able to take remedial action at any point in the manufacturing sequence of the dosage form. The basic steps of tablet compression include the following steps (Figure 92).

A. Die Filling

Die filling is the step in the compression operation where the granulation leaves the storage hopper and is transferred by gravity or forced-flow feed to the feed frame. At this point the granulation is made available to fill the die cavity as it passes under the feed frame. Except for the final compression step, this is probably the most critical operation in the compression cycle, since an incomplete or nonuniform die fill affects tablet hardness, friability, weight, drug delivery, and uniformity.

Unlike the manufacture of a regular compressed tablet (0.2–0.75 g) or chewable tablet (0.5–1.5 g), the required higher weight (1.5–4.0 g) of the compressed-tablet lozenge requires more material to fill a die cavity

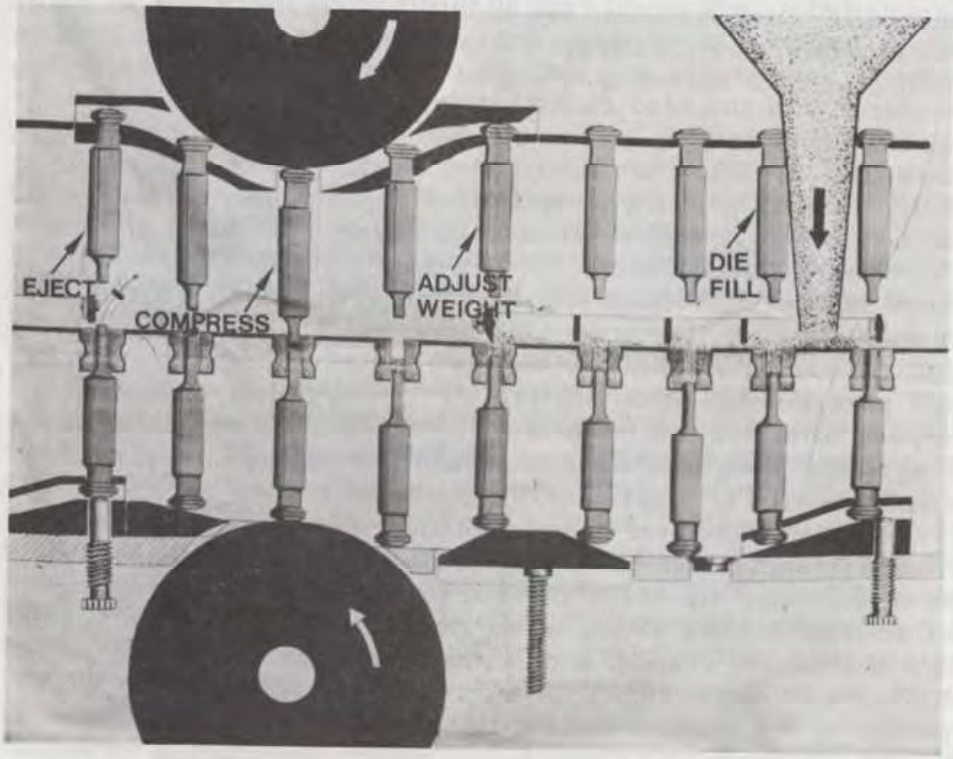


Figure 92 The basic steps of tablet compression. (Sharples-Stokes Div., Pennwalt Corp.)

that has the same dwell time under the granulation in the feed frame. The formulator should take appropriate measures to control particle size distribution and density in order to ensure that the granulation will possess a uniform and complete die cavity fill characteristic. Each individual formulation will require different adjustments to optimize the die fill conditions, some of which include the following: (a) Addition of lactose, dicalcium phosphate, calcium sulfate, or sucrose to a direct-compression granulation; addition of extra binder or use of a coarser milling cycle in the case of a wet granulation, to improve die fill quality in cases where the aforementioned problems of nonuniform tablet hardness, friability, or weight adjustments are die fill-related. (b) The bulk density of the various ingredients added to the granulation should be maintained as closely as possible, expecially when formulating direct-compression products. This prevents powder segregation during the blending operation or during the dwell time in the hopper or in the feed frame. Powder segregation results in nonuniform drug distribution, impairment of flow and die fill characteristics, as well as nonuniformity of tablet lubrication or medicament bioavailability. (c) The quantity of fine powder present in a granulation (fines are those granulation particles that pass through an 80-mesh sieve) should be controlled (less than 15%) to minimize segregation or sifting of excessive powder around the bottom punch and onto the barrel. This accumulation of powder may cause binding of the lower punch in the punch guide. The result is that the punch may not drop to its lowest depth to receive sufficient granulation for a complete die fill. The required weight of granulation will not enter the die and without a complete die fill the desired tablet weight cannot be attained. A granulation that exhibits acceptable flow, density, and die fill characteristics will lend itself to compression on high-speed tablet presses.

B. Weight Adjustment

The depth at which the lower punch is set to produce a specified volume of die cavity is the weight adjustment of the tablet press. The bottom punch is set at maximum depth as it passes under the granulation in the feed frame to allow for the greatest die fill. The lower punch, just before leaving the feed frame area, rides along an adjustable weight adjustment cam track. The height at which this cam is adjusted determines the volume of die cavity and the weight of granulation contained in the die cavity. Excess granulation that was contained in the die cavity before the weight adjustment is scraped off and remains in the feed frame.

The tablet machine weight adjustment is determined by the desired product weight, the quality of granulation flow, and the formulation density. A lower volume is needed to contain the desired weight of granulation if the granulation is dense or the flow is good. The parameters discussed under die fill pertain to weight adjustment, since the better the granulation flow and die fill, the lower the volume necessary to achieve a desired weight. Additionally, the lower the required volume of fill, the more uniform will be the die fill and the lower the tablet weight variation. This aspect is especially critical where large-diameter and high-weight tablets are compressed on a high-speed tablet press. The lower the volume of die cavity that must be filled, the lower the resultant variation in tablet weight.

C. Compression Hardness

The prerequisite for any tablet granulation, whether prepared by wet granulation or by the direct-compression method, is that the granulation should bond together under pressure [47]. The ideal granulation is one that will bond with a minimum of pressure applied for the shortest time. The greater the bonding forces of the particles, the closer to optimum is the hardness achieved. Tablet granulations possessing bonding forces that produce hard tablets with a minimum of pressure applied for a short period of time are most suitable for production on high-speed tablet presses (Figure 93–95) [48–51]. Low-compression forces reduce wear on tablet tooling and on the tablet press (Figure 96).

The phenomenon referred to as *capping* or *lamination* results when particles fail to bond under compression. Capping, a less severe condition than laminating, refers to the tablet when its top is cracked at the edge or is loose—as a cap. Laminating is associated with capping but refers to the tablets that are split or cracked on the sides by expansion when the pressure is released [52]. The three major reasons for the occurrence of capping or lamination are the following.



Figure 93 Stokes Model 551 rotary tableting press. (Sharples-Stokes Div., Pennwalt Corp.)

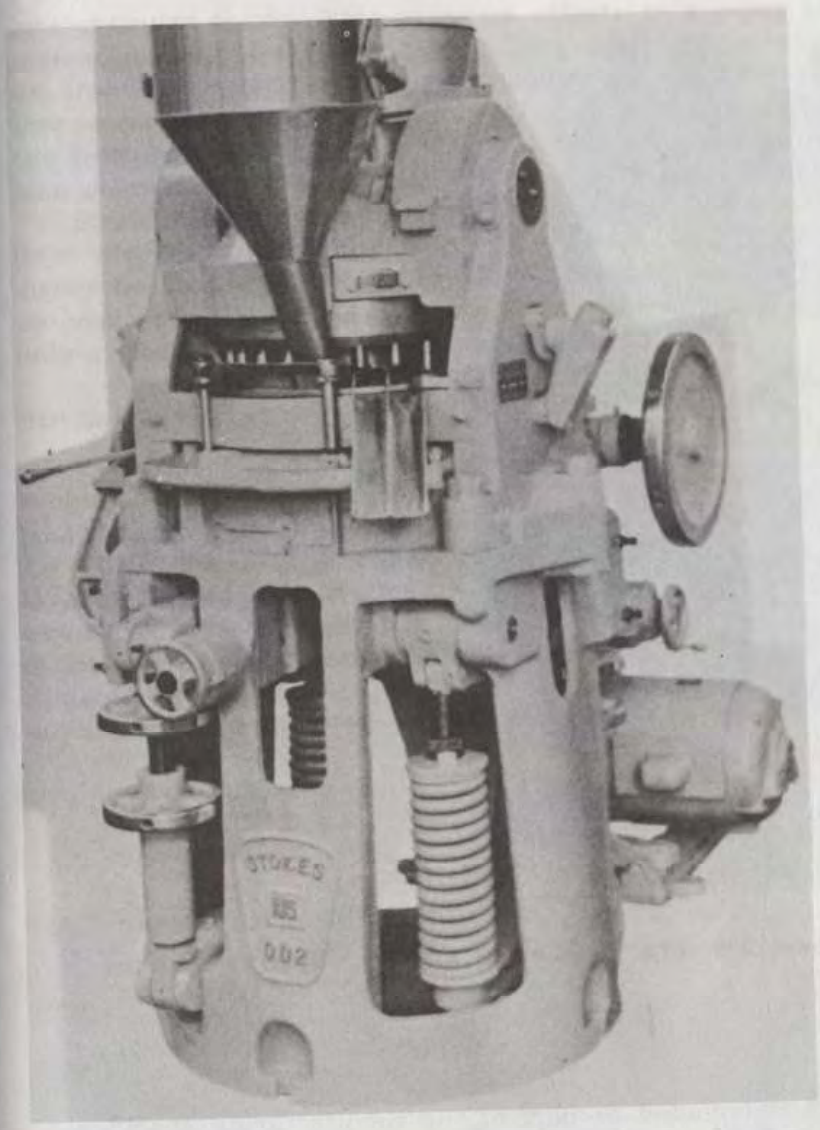


Figure 94 Stokes Model DD-2 double-sided rotary tableting press. (Sharples-Stokes Div., Pennwalt Corp.)

Insufficient Binder, Moisture, or Cohesive Forces Among Granules

Binder

When preparing wet-granulated formulations, addition of insufficient quantities of binder will result in production of granules lacking proper intragranular or intergranular forces which, upon compression, produce tablets with granules that do not bond in areas of high stress.

Moisture

Each indicidual tablet granulation possesses a certain critical moisture-content range which aids in producing granules with optimum cohesive forces. Most granulations perform well when the moisture content falls in the 0.75–2.0% range, but the exact range (both upper and lower limits)

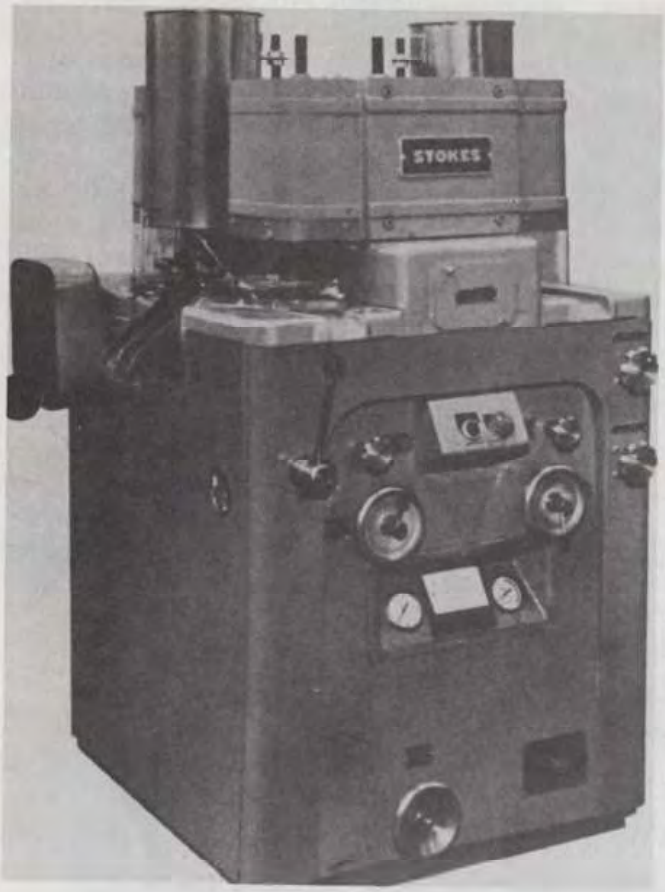


Figure 95 Stokes Model 328 rotary tableting press. (Sharples-Stokes Div., Pennwalt Corp.)

should be determined and included as part of the manufacturing specifications. Moisture content below the critical range cause particles to rapidly lose cohesiveness and the tablets to lose their sheen. However, moisture content above the critical range cause granulations to become sticky and tablets to harden with age. The incidence of medicament reactivity with flavors or tablet base ingredients is increased with the addition of excessive moisture to medicated granulations.

Cohesive Forces

The addition of quantities of medicaments or fillers possessing minimal cohesive forces of their own into direct-compression granulations can reduce overall granulation cohesive forces to the extent that the tablet compression quality is no longer acceptable. Milling a granulation in such a manner as to produce an excessive quantity of fine or coarse particles can affect the compression quality of a granulation to the extent that capping or lamination results.

Excessive Pressure During Compression

Application of forces during compression of the granulation in excess of the optimum particle bonding pressure results in destruction of the

intergranular bond. This pressure effect, as a cause of capping and lamination, can be determined by reducing the pressure of compression in gradual increments until an acceptable tablet is formed or until one that is too soft is compressed. Should a soft tablet result before capping is alleviated, the formulator can eliminate this as a cause of unacceptable tablet compression characteristics.

Since compression of lozenges requires high-compression forces to produce a product with extended disintegration time, the granulation must either be able to withstand the high forces of compression (30–50 kg in.^{2}) or possess sufficient particle bonding forces to produce a hard tablet with only a moderate degree of compression pressure.

Air Entrapment

Air entrapment is a common source of capping problems with high-weight tablets. Should the nature of the granulation (flocculent or containing many coarse particles) result in entrapment among granules of excessive air which is unable to escape during compression, the air will collect in layers and cause separation. This cause of tablet lamination is usually remedied by *densifiying* the granulation—which is accomplished by the addition of more binder in a wet-granulated product or the incorporation of diluents such as lactose, calcium carbonate, or dicalcium phosphate (where applicable) in a direct-compression tablet.

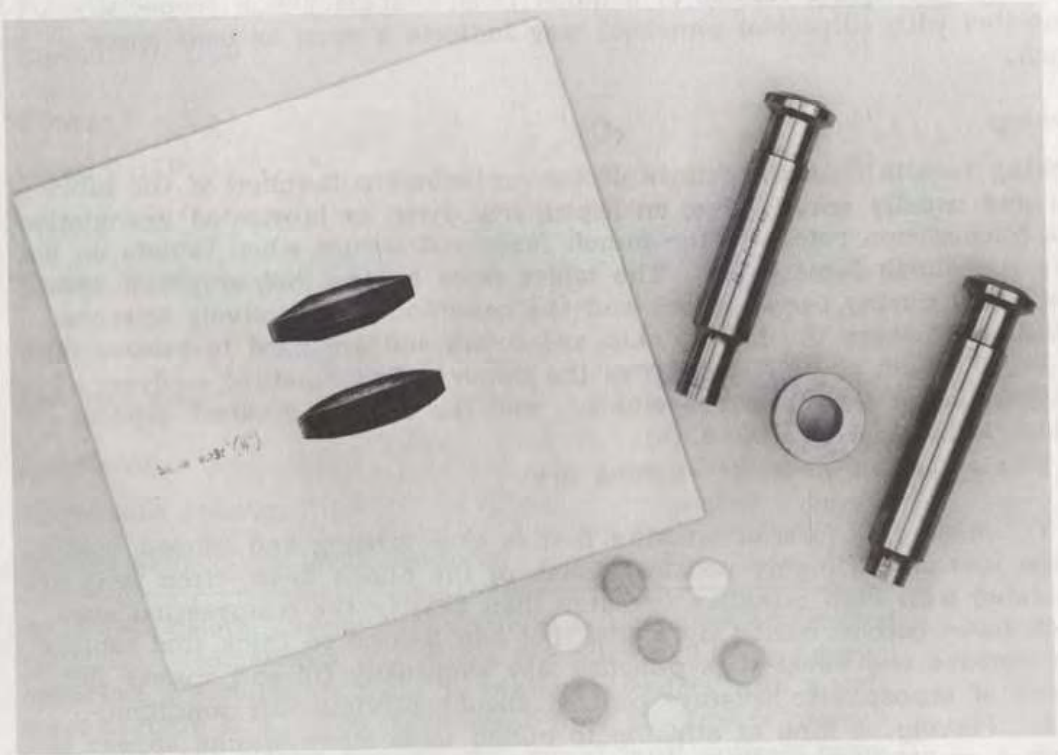


Figure 96 Compressed tablet lozenges. Left: schematic of lozenge punch shape; right: lozenge punches and dies; center: compressed tablet lozenges.

D. Tablet Ejection

The pressure goes outward toward the die wall while the granulation is under compression, making it necessary to use a lubricant to reduce the friction between the tablet and the die wall to permit effective release of the tablet from the upper and lower punch faces and the die walls. The tablet must then be forcibly removed from the die cavity upon completion of the compression operation.

Many of the problems associated with tablet ejection are lubricant-related and fall into two major categories: (a) lubricant failure because of incorporation of insufficient or improper type of lubricant, and (b) sticking.

Lubricant Failure

The tablet ejection difficulties resulting from lubricant failure are usually indicated by the presence of irregular lines on the side band of the tablet. Continued compression under conditions of lubricant failure results in a squeaking or popping sound during tablet ejection, as the die becomes heated by the friction caused by pressure against the die sidewalls. Sidewall pressure will increase if compression is continued and results in a condition where the tablet will not be completely ejected from the die wall at the point of tablet scrape-off. This results in broken tablets and, in extreme conditions, a scoring of the die sidewalls, or even a release of the die from the die lock (a condition that will result in damage to the tablet press or feed frames). Conversely, the presence of regular lines on successive tablets from the same punch and die set may indicate a worn die. The incomplete release of a tablet from a single punch (especially associated with ellipsoidal punches) may indicate a worn or bent lower punch.

Sticking

Sticking results from the failure of the antiadhesive function of the lubricant and usually results from an improperly dried or lubricated granulation. This phenomenon refers to the punch faces and occurs when tablets do not leave the punch faces clean. The tablet faces become dull or pitted (perhaps both) during compression, and the condition progressively worsens to the point where the tablets chip and break and are hard to remove form the lower punch or pull apart from the upper. The moisture analysis of the granulation should be reevaluated, and the alkaline stearate content should be increased (0.05–0.1%).

Two additional forms of sticking are:

1. *Filming*, a form of sticking that is slow forming and caused mostly by the loss of the highly polished finish of the punch faces—from moisture associated with high humidity (greater than 50%) in the compression area. Punch faces become coated by a film that can become so thick that tablets from concave and bevel-edge punches may eventually fill and appear flat. Control of atmospheric moisture content should alleviate this condition.
2. *Picking*, a form of sticking to punch faces when specks appear to be lifted or "picked up" from the tablet faces. This condition is usually caused by moist granules in the granulation or increased tackiness because of the presence of excessive binder. Picking also may be caused by the

incorporation of excessive quantities of lubricant or tablet components with low melting points. The punches become heated during extended compression runs, causing the low-melting-point components to soften and adhere to punch faces. A modification of the lubricating system or a slight (0.01–0.1%) increase in lubricant concentration may eliminate this situation.

XI. TYPICAL FORMULATIONS (COMPRESSED-TABLET LOZENGES)

The following formulations represent various methods of manufacturing compressed-tablet lozenges.

A. Wet Granulation Techniques

Example 11: Antitussive-Anesthetic Lozenges (2.5-g Tablet)

Ingredient	Quantity
Dextromethorphan HBr 10% adsorbate	4.0%
Benzocaine	2.0%
Filler	
Confectioners sugar 6x (3% corn starch)	58.0%
Polyethylene glycol 8000 (powdered)	15.0%
Cornstarch USP	12.0%
Binder	
Gelatin USP	3.0%
Flavor	
Spray-dried powder	As desired
Color	
Lakolene color	As desired
Lubricant	
Magnesium stearate USP	0.5%
Polyethylene glycol 8000 powdered	1.0%

A 15–20% gelatin granulating solution is prepared and cooled to 25°C. Medicaments and fillers are blended. Any lumpy materials are milled in order to prepare powders with a uniform particle size. The medicament-filler mixture is granulated with the binder solution and mixed until uniform granules are formed. The granulation is oven-dried to a moisture content of 1.0–1.5%. The lubricant, color, and flavor are mixed into the dried granulation, which is then mechanically

Example 11: (Continued)

comminuted to a mesh size of 40–80. The granulation is blended to uniformly mix all components. Tablets of 2.5 g each are compressed on a suitable rotary press.

B. Direct-Compression Techniques (Analgesic-Antihistamine Lozenge 3.0 g)

Example 12: First Layer (1.0 g) of Two-Layer Analgesic-Antihistamine Lozenge (3.0 g)

Ingredient	Quantity
Medicament	
Aspirin (100-mesh crystals)	16.25%
Filler	
Polyethylene glycol 8000 powdered	16.25%
Microcrystalline cellulose	15.00%
Mannitol (granular)	50.00%
Flavor	
Spray-dried powder	As desired
Color	
Lakolene color	As desired
Lubricant	
Polyethylene glycol 8000 (powdered)	1.50%
Stearic acid powder	0.50%

Example 13: Second Layer (2.0 g) of Two-Layer Analgesic-Antihistamine Lozenge (3.0 g)

Ingredient	Quantity
Medicament	
Chlorpheniramine maleate	0.25%
Phenylpropanolamine HCl	0.93%

Example 13: (Continued)

Ingredient	Quantity
Filler	
Confectioners sugar 6x (3% cornstarch)	15.0%
Polyethylene glycol 8000 (powdered)	20.0%
Mannitol (granular)	45.0%
Microcrystalline cellulose	10.0%
Flavor	
Spray-dried powder	As desired
Color	
Lakolene color	As desired
Lubricant	
Magnesium stearate USP	0.5%
Polyethylene glycol 8000 (powdered)	3.0%
Stearic acid (powdered)	0.25%
Cab-O-Sil M-5	0.1%

The medicament, filler, flavor, color, and lubricant are mixed and milled to a uniform mesh size. The powder mixture is blended and compressed on a two-layer tablet press.

XII. QUALITY CONTROL PROCEDURES

Since the basis of the lozenge dosage form is sugar and corn syrup, quality control testing begins with the analysis of candy base raw materials and continues through to the final packaging operation [53,64].

A. General Checks: Candy Base Manufacturing

As the manufacture of the candy base is initiated, a final check of the corn syrup and sugar delivery gears, as well as any third ingredient delivery systems, is made to assure the proper ratios of candy base ingredients are delivered to the precooker. Continual checks are also made on the temperature, steam presure, and cooking speed of the precooker as well as the steam pressure, temperature, vacuum, and cooking speed of the candy base cooker. The cooker speed is adjusted according to the speed of the lozenge-forming machine.

Moisture Analysis

Determination of candy base moisture content, regardless of the method used, is a critical procedure in quality control testing to verify that the

metering devices and vacuum settings on the candy cookers are performing correctly. Production of candy base with moisture content exceeding 1.0–1.5% increases candy lozenge-manufacturing difficulties, incidence and rate of graining, as well as medicament–flavor and medicament–candy base interactions, all of which tend to shorten product shelf life. For optimum shelf life, moisture content should range from 0.75 to 1.25% with 1.0% generally the normal manufacturing parameter. A number of different testing procedures are available to determine the percentage of moisture in candy base [54]. Chewy or caramel candy bar-moisture content should range between 3.0–5.0%.

Gravimetric Method (Vacuum Oven)

The sample (usually about 1.0 g) is weighed accurately into a tared weighing container and placed in a vacuum oven at 60–70°C for 12–16 hr. The sample is removed from the oven, weighed, and the difference in moisture calculated.

Titrimetric Method

The titrimetric determination of water depends on the fact that a solution of sulfur dioxide and iodine in pyridine and alcohol (Karl Fischer reagent) reacts with water stoichiometrically. The entire operation requires the rigid exclusion of atmospheric moisture. This method permits the determination of candy base moisture content in a very short period of time (less than 5 min). With this procedure, a sample calculated to contain 10–250 mg of water is added to the titration flask and titrated with Karl Fischer reagent. The end point can be determined visually in colorless solutions; in colored solutions an electronic method is used.

Azeotropic Distillation Method (Toluene or Xylene)

A measured quantity of pulverized candy (10–12 g) is placed into a 500-ml glass flask. Between 150 and 200 ml of toluene is added to the flask, which is connected to a trap with connecting tube and a reflux condenser fitted with a granuated 5-ml-capacity receiving tube. The flask is heated for 1–2 hr, refluxing until all water has come over to the receiving tube—where the percentage that was present in the candy can be calculated from the volume of water present in the receiving tube (Figure 97). During the distillation procedure, care must be taken not to allow the solvent and the residue candy to become discolored (brown or even yellow) because this is certain indication that caramelizing has occurred. Caramelizing of sugar, with the loss of water from the sugar, would give a high reading.

Determination of Sugar and Corn Syrup Ratios

In order to ascertain if pump settings are correct for delivering the desired ratios of sugar and corn syrup to the formulation, or if the candy cooking and delivery systems are functioning properly, a determination of the percentage of sugar, corn syrup, and other ingredients is carried out on a routine basis.

Dextrose Equivalent Method: Lane Eynon Titration Method

The use of dextrose equivalent methods of analysis before and after inversion will determine the percentage of sugar and corn syrup as well as the percentage of inversion due to cooking or due to the types of materials

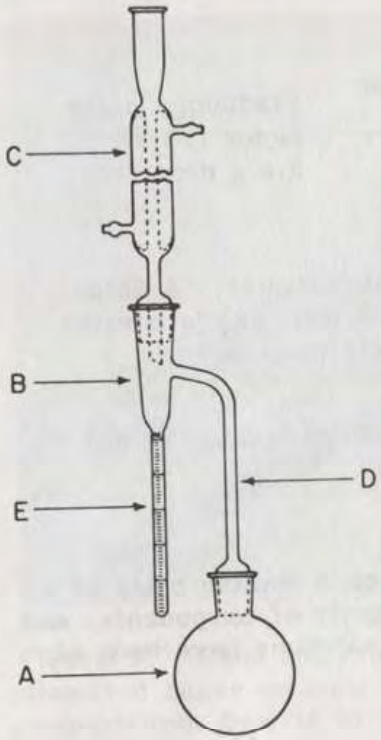


Figure 97 Toluene moisture apparatus. A = 500-ml glass flask; B = trap; C = reflux condenser; D = connecting tube; E = receiving tube of 5-ml capacity. (U.S. Pharmacopeia XXI.)

used in the manufacture of hard candy. One dextrose equivalent is derived from the candy while another portion of candy is inverted so that all sugars will read as dextrose equivalents. The difference will be the noninverted sugars or regular sugar. A correction factor is also used. The first dextrose equivalent will be the portion of sugar inverted by cooking along with the dextrose equivalent from the corn syrup [4].

Calculation of the candy base, corn syrup dextrose equivalent, on a dry basis before cooking, the cooked candy base moisture content, and the dextrose equivalent before and after inversion will determine the percent invert formed during cooking as well as the composition of the original candy-base. A *cook invert* (inversion during cooking) above 2.5% will increase candy base moisture pickup tendencies, whereas a cook invert below 2.0% will increase sugar crystallization.

Percentage Reducing Sugars

Standard

A 3-g portion of anhydrous dextrose is dissolved in 500 ml water. A 25-ml volume of alkaline cupric tartrate solution (Fehling's solution) is titrated with the dextrose solution to within 1–2 ml of the expected end point. The solution is boiled for 2 min and then two drops of methylene blue indicator is added and titrated to a yellowish red end point. Controlling boiling and titrating times is important for reproducible results.

The calculation is as follows:

$$\frac{(3.0\text{ g}) \times [\text{volume of standard dextrose solution consumed by Fehling's solution}]}{500} = [\text{Reducing sugar factor (F) for 3.0 g dextrose}]$$

Sample

A 10-g sample of candy base is dissolved in 250 ml water. A 25-ml volume of alkaline curpic tartrate solution (Fehling's Solution) is titrated in the same manner as the standard. The calculation is as follows:

$$\frac{\text{Reducing sugar factor} \times 100}{\frac{\text{Sample weight}}{250} \times [\text{Volume of sample solution consumed by Fehling's solution}]} = [\text{Percent reducing sugars}]$$

Reducing sugar analysis should be carried out on a routine basis as a check for proper cooking times, temperatures, integrity of components, and corn syrup content, and to check whether salvage solutions have been adusted to the proper pH.

Salvage Solutions

Salvage solutions manufactured with and without medicaments must undergo a series of quality control procedures before incorporation in the candy base cooking cycle. Immediately upon dissolution of the lozenge salvage, the solution pH is adjusted within the range of 4.5–7.5 by addition of either citric acid or sodium carbonate monohydrate to prevent excessive sugar inversion when the solution is cooked with the other candy base components. When the salvage solution has been adjusted into the desired pH range, the solids content is determined. The optimum solids content for salvage solutions is in the 65–74% range, with 70 ± 2% the most suitable concentration. Salvage solutions that exceed the upper limit of the solids content range become progressively thicker and more difficult to pump. This will result in nonuniform delivery of product to the cooker. Solutions that are prepared below the desired lower limit of solids content contain quantities of water that will lengthen cooking times, thus resulting in the formation of higher invert sugar levels and increased yellowing of the candy.

Solids content of salvage solution is determiend by using a refractometer calibrated in Brix (a saccharometer scale of measurement used to designate the concentration of sugar in water solution, with the weight of the solids being expressed as a percentage of the total weight). A hand-held refractometer (Figure 98) can be used to determine the approximate solids content, but for quality control purposes an Abbé refractometer (Figure 99) with a temperature-controlled bath (20 or 25°C) should be employed.

Once the salvage solution pH and solids content have been determined and adjusted to the required range, colors and medicaments (if desired) are added, mixed, and assayed for concentration levels in the salvage. (An assay is performed at this time to assure that the proper quantity of color and medicament will be delivered to the candy base. Improper drug or color content in the salvage solution will produce finished lozenges out of specification for medicament or out of the acceptable color range. Failure



Figure 98 Hand refractometer. Designed for rapid field-determination of dissolved sugar content. The instrument automatically compensates for temperatures from 16 to 38°C. (American Optical Co.)

to determine the drug or color content in salvage may result in 60–200 batches of lozenges being rejected.)

In instances where drug or colors present in salvage cannot be passed through the cooker after solution pH and solids content have been adjusted (Sec. I.A), activated charcoal or diatomaceous earth is suspended in the solution and filtered in order to remove color and/or medicament as required [20,69]. When no medicament or color need be added to the salvage solution or removed due to incompatibility, the material is ready for use after pH and solids content have been adjusted to the desired ranges.

Forming Checks

While lozenges are being formed, a continuous weight check progresses in order to ascertain whether the candy rope is of the proper diameter. Adjustments to the rope diameter are made by adjusting the clearance between the sizing rollers. The operator checks the weights of groups of 10 or 20 lozenges as well as the weight of individual lozenges. At the same time, the operator checks the guage (thickness) of the lozenges being formed, using a micrometer guage. Adjustments to the forming machine molding pressure can be made in order to increase or decrease the lozenge guage as required.

The finished lozenge weight check reduces the quantity of rejects formed as oversized or undersized, as well as detecting any inconsistencies in lozenge weight (rope diameter) resulting from improper candy base manufacture, incomplete mixing of raw materials into the base, nontempering or overcooling, improper adjustment of the batch former height, or lozenge-forming machine molding difficulties. Lozenge weight checks must conform to the USP XXI test for tablet weight variation:

Weigh individually 20 whole tablets and calculate the average weight: the weights of not more than 2 of the tablets differ from the average weight by more than the percentage listed and no tablet differs by more than double that percentage.

The average lozenge weight usually exceeds 1.0 g. In this weight range, if two tablets fall outside the weight range, a resample of 80 lozenges is taken. If the resample has five or fewer lozenges outside the acceptable limits, the batch is considered satisfactory.

Cooling Checks

Lozenges are visually examined during and after the cooling operation [55] in order to determine whether (a) any stress cracking is occurring because of too rapid cooling; (b) excess air bubble formation has resulted because of prolonged mixing; (c) surface cracking is occurring due to excessive cooling of the candy base before forming or due to low temperatures of

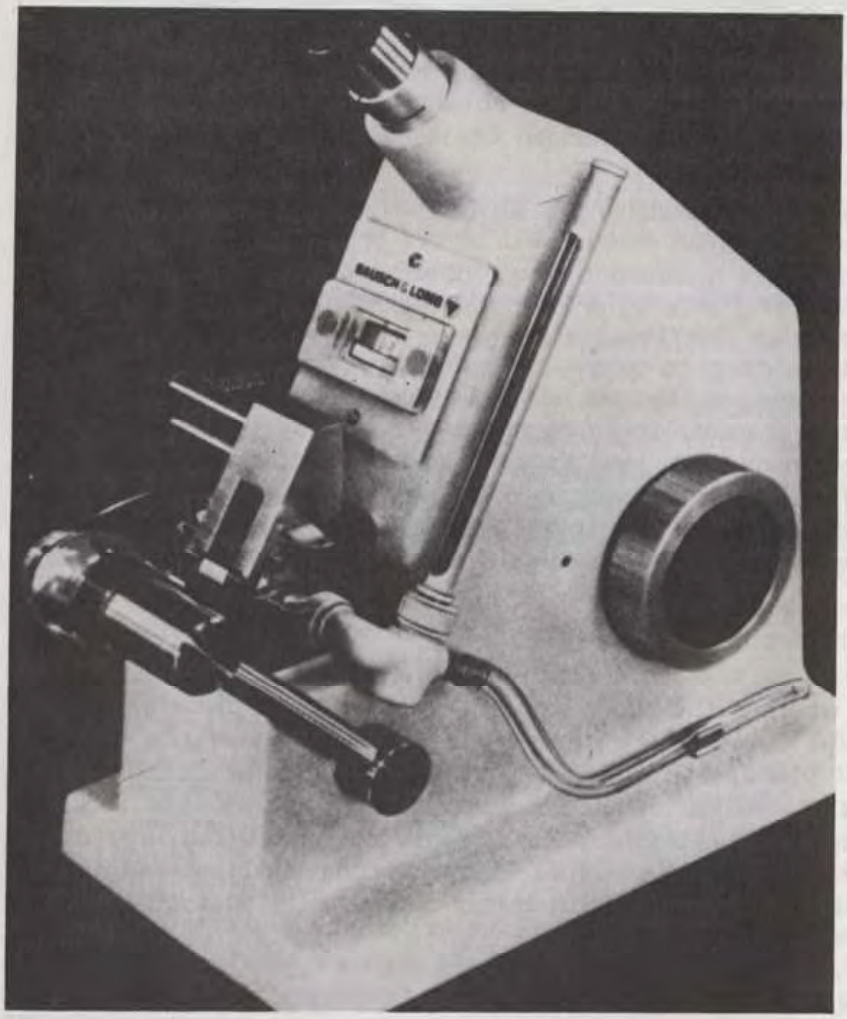


Figure 99 Abbé-3L refractometer. This instrument is accurate to ±0.05% for Brix measurements (0 to 85% sucrose). For precision temperature control, an external water bath can be connected into the refractometer case. (Bausch and Lomb, Analytical Systems Div.)

forming rollers, tempering table, or die faces; (d) lozenges are broken, chipped, or brittle because of low reducing sugar content or premature graining of the lozenge base; (e) black specks and air bubbles have resulted because of dieseling resulting from terpene-containing flavor oils; (f) color is correct; (g) organoleptic presentation is satisfactory.

Lozenges that fail the visual test are rejected and remedial actions initiated to remedy the situation. Twenty lozenge samples are taken at random from various portions of each batch. If more than one defect is found, a second sample of 125 lozenges is taken. The resample is considered satisfactory if seven or fewer major defects are found.

Sizing Checks

Oversized and undersized lozenges are routinely checked for diesels, excessive sugar dust formation, or breaking. On a regular basis, the oversized or undersized salvage is resized in order to determine if the sizing operation speed is correct. If the operation is proceeding too rapidly, undersized lozenges will appear in the production material and properly sized lozenges will appear in the oversized salvage.

Sampling

Lozenges are sampled from different sections of each batch. At least one sample is taken for each 30–35 lb of lozenges sized. After lozenges are manufactured, they are stored on a batch basis in temperature- and humidity-controlled areas (15–20°C at 25–30% relative humidity) until quality control testing of physical and chemical (flavor and medicament) parameters is complete. Such testing would include:

Description: Physical examination
Taste: Organoleptic comparison to type sample
Hardness for compressed or chewy caramel tablets: Meets specifications for compression or chew
Color: Comparison to type sample
Thickness: Meets specifications for packaging and appearance
Weight variation: Described above
Drug content and content uniformity

Groups of 10 lozenges are assayed for drug content. Analytical procedures used should be stability-indicating in nature (gas-liquid chromatography or liquid chromatography) [56,57]. ...the content of each of 10 tablets is within the limits of 85.0 percent and 115.0 percent of the average of the limits specified in the potency definition. If not more than one result falls outside the limits of 85.0 to 115.0 percent and if none of the tablets falls outside the limits of 75.0 percent to 125.0 percent of the average, assay each of the remaining tablets. The requirements are met if the content of each of the additional 20 tablets falls within the limits of 85.0 percent and 115.0 percent of the average of the limits specified. . . .

B. Microbiological Testing

While a continual check is made on the physical and chemical properties of the hard candy lozenges both during and after processing, another problem

area that must be considered is microbiological contamination [58,59]. During the candy base cooking cycle, temperatures are high enough to sterilize the raw materials, but addition of contaminated raw materials on the mixing table, contaminated cooling air, contaminated utensils, or improper hygiene by the production workers can cause bacteria, mold, or spore contamination of the candy. The high solids content will not in itself support bacterial growth, but as the lozenge picks up surface moisture, conditions may be suitable for an increase in bacterial or mold counts. A strain of *Salmonella typhosa* can persist in hard candy under proper conditions for more than 12 months. The presence of any bacterial, mold, or spore contamination is indicative of a lack of adequate housekeeping or hygiene among the production workers. If microbiological contamination becomes evident, a complete evaluation of all possible problem areas must be carried out until the source is located and eliminated.

Routine microbiological testing is as critical as routine analytical evaluation. The quality control department must develop a microbiological sampling plan to effectively determine areas of possible contamination. Raw materials, finished products, machinery, cooling tunnels, environmental conditions, and storage drums are all sources of microbiological contamination. Production workers should be educated toward proper hygiene, and sufficient washing facilities must be provided.

Laboratory microbiological testing should include the following counts: (a) total plate; (b) total coliform; (c) yeast and mold; (d) *Escherichia coli*; (e) *Staphylococcus*; (f) *Salmonella*.

C. Product Release

Once the finished lozenge is determined to be within the physical, chemical, and microbiological specifications set for the product, it is approved for packaging and distribution.

D. Stability Testing

The previous section described the routine quality control tests necessary to determine if the product is being manufactured according to a series of predetermined formulation guidelines. If these guidelines are followed and the product is within specifications, then an acceptable product will result. Stability testing is not a *routine* quality control test, but rather an analytical tool to determine the effective product shelf life.

Shelf life determination, or product storage stability testing, is initiated upon completion of the first laboratory prototypes when production begins and at periodic intervals during routine production, and continues for a minimum of 5 years. The purpose of this series of tests is to determine the physical and chemical stabilities of medicament, flavor, candy base, and color—both under accelerated temperature and humidity conditions and at ambient storage conditions. This testing will enable the formulator to predict the acceptable shelf life of the product in a relatively short period of time and make changes as required to eliminate any incompatibilities that may influence product stability.

E. Arrhenius Relationship

The chemical kinetics of medicament, flavor, and color in hard candy base is directly applicable to the Arrhenius relationship [24]. This relationship is valid only as long as it is possible to linearize a property of the degradation (drug concentration, flavor content, color loss) with time. By plotting the property vs. time on arithemetic or semilog graph paper, it is possible to determine whether the degradation is proceeding according to zeroth-order, first-order, or pseudo-first-order reaction. Most materials in candy base degrade by first-order or pseudo-first-order reactions, permitting a measure of the degradation rate from a plot of the logarithm of residual drug concentration vs. time. The slope of the resultant straight line represents the rate of degradation. Plots that do not result in a straight line indicate that the drug is degrading through a more complex reaction.

Once the rates of degradation are determined for the medicament in candy base at three or more elevated temperature storage conditions, it is possible to estimate the rate of degradation at room temperature through the use of the Arrhenius relationship. If, by plotting the logarithm of the rates of degradation vs. the reciprocal of the absolute temperature, a linear relationship results, it is possible to determine degradation at room temperature. This makes it possible to calculate the shelf life of the product which, for medicinals, is generally the time it will take for the dosage form to retain 90% of its labeled drug content [24].

F. Elevated Temperature and Elevated Humidity Testing

Elevated temperature and elevated humidity testing is initiated as soon as product is manufactured. While the choice of time and temperature storage conditions is left to the discretion of the formulator, an effective stability program should include product storage for 1–2 months at 60°C, 3–6 months at 45°C, 9–12 months at 37°C, and 36–60 months at 25 and 4°C. These conditions are suitable for determining the initial Arrhenius plot relationship and the follow-up confirmatory medicament stability values.

As soon as possible, product should be tested in the proposed trade package both at elevated temperature and elevated humidity conditions. Testing conditions generally utilized by the product development laboratory include 25°C at 80% relative humidity for 6–12 months, 37°C at 80% relative humidity for 3 months, and 25°C at 70% relative humidity for 6–12 months. The elevated humidity studies are carried out both at constant humidity and in humidity cabinets with day and night cycling. Elevated humidity tests are vital for ascertaining medicament stability, candy stickiness, surface-graining characteristics, clouding, and development of cold flow. At the same time the moisture protection characteristics that different packaging materials offer to the lozenge are evaluated. Bunch wrap, cartons, carton overwrap, shipping boxes, and bundle wrap are tested. Materials that offer the product maximum protection from moisture are chosen so that optimum warehouse, store, and in-home protection from moisture penetration are afforded the product.

G. Flavor Stability

Volatile oils in medicated candies are not only responsible for taste but may also contribute to the antiseptic action of the lozenge. The quantity of volatile oils in the medication can be determined quantitatively or by subjective taste response. The method of choice for determining the loss of flavor oils with time is gas-liquid chromatography [57]. Using the data in accordance with the Arrhenius relationship will enable an estimation of the loss rate of the oils under normal shelf storage conditions [24].

H. Physical Stability

Concurrent with the chemical stability evaluation, a physical stability study is carried out on the product in order to determine what factors will detract from the organoleptic appeal of the product and how long these changes will take to occur. A routine physical stability evaluation includes the following:

Color. Lozenges are placed in direct sunlight, in a fadeometer, and at elevated temperature to determine if the colors are light-fast. Lozenges are also tested for color changes occurring due to the presence of medicaments, flavors, or acidulents in the formulation.

Odor. Changes in the odor of flavors stored at elevated temperature conditions are evaluated by sealing the lozenges in glass bottles and determining if any off-odors result.

Taste. The product is tasted and compared to production controls in order to determine if any flavor changes have occurred. Many small flavor changes that cannot be detected via gas-liquid chromatography can be ascertained when the lozenge is tasted. Any changes in the surface texture are also evaluated during the taste evaluation.

Hardness. Compressed tablet lozenges are tested for proper hardness using an instron or schleuniger hardness tester. Chewy caramel products are tested for hardness using an instron or a penetrometer. The force required to penetrate the tablet is used as a measure of chewiness, surface hardness, and stability.

Grain. Lozenge sticking is noted. When graining occurs, the degree is recorded. The lozenge is broken in half and the grain is measured with an eyepiece fitted with a micrometer guage. The degree of lozenge graining is usually reported as *percentage of lozenge grained*.

Bunch wrap appearance. Color changes that may occur on the paper surface due to medicament or color reaction with the bunch wrap material, sticking of bunch wrap to the surface of the lozenge, or splitting of the laminate from the foil are evaluated.

REFERENCES

1. Lozenges, Mouthwashes, and Gargles. *Drug Ther. Bull.* *10*:33 (1972).
2. A. H. Kutscher and E. V. Zegarelli, A New Long Lasting Lozenge: Properties and Uses. *J. Oral Ther. Pharmacol.*, *4*:6 (1968).
3. E. W. Martin and J. E. Hoover, *Husa's Pharmaceutical Dispensing*, 5th Edition. Mack Publishing, Easton, PA, 1959.
4. Simon Schnitzer, *Hard Candy*. NCESF Short Course in Candy Technology. University of Wisconsin, 1970.

5. E. W. Martin, E. F. Cook, et al., *Remington's Practice of Pharmacy*, 16th edition. Mack Publishing, Easton, PA, 1980.
6. J. M. Newton, *Properties and Functional Uses of Corn Syrup*. From Symposium Proceedings, Products of the Wet Milling Industry in Food, 1970.
7. *A Formulary for Better Candies*. Technical Information sheet, A. E. Staley Manufacturing Company, Decatur, IL.
8. W. J. Hoover, *Corn Sweeteners*. NCESF Short Course in Candy Technology. University of Wisconsin, 1970.
9. E. E. Fauser, J. E. Cleveland, et al., Baumé–Dextrose Equivalent–Dry Substance Tables for Corn Syrup and Corn Sugar. *Industrial and Engineering Chemistry, 15*:3 (March 15, 1943.)
10. S. E. Allured, A Most Unique Hard Candy. *The Manufacturing Confectioner, 51*:6 (1971).
11. R. Lees, High Boiled Sweets; Simple in Composition But Physical Structure Is Complex; *Confectionary Production, 38*:9 (1972).
12. Fred Janssen, *Invert Sugar as a Doctor in Candy Making*. Presented at a Northern California Section of American Association of Candy Technologists, November 1968.
13. R. E. Henry, Versatility of Corn Syrups Expands with Wider Research. *Candy and Snack Industry, 141*:6 (1976), pp. 748–752.
14. M. E. Schwartz, *Confectionary and Candy Technology*. Noyes Data Corporation, 1974, pp. 9–15, 298–299.
15. R. Lees, High Boiled Sweets; Products Should Not Grain Nor Become Sticky. *Confectionary Production, 38*:10 (1972).
16. B. R. Suri, Stabilization of pH of Corn Syrup for Hard Candy. *The Manufacturing Confectioner, 47*:7 (1967).
17. G. Richardson, Coloring Matters: Their Addition to Different Types of Confectionary. *The Manufacturing Confectioner, 53*:10 (1973).
18. R. R. Frey, et al., Process of Incorporating Volatile Aromatics in Hard Candy. South African Patent Application 112,856, May 1971.
19. G. Fellows, Confectionary Flavors. *The Manufacturing Confectioner, 52*:4 (1972).
20. W. T. Clarke, The Re-use of Chocolate and Confectionary Rejects. *The Manufacturing Confectioner, 55*:6 (1975).
21. M. A. Cherkas, et al., Medicated Hard Candy, U.S. Patent 3,439,089 (1969).
22. P. Kabasakalian, et al., Fractional Experimental Design. Study of the Incompatibility of Benzocaine in Throat Lozenges, *Journal of Pharmaceutical Sciences, 58*:1 (1969).
23. Eberhard Berten, *Hard Candy and Caramels*, 3rd Revised Edition. Hamac-Hansella Machinery Corporation, Piscataway, NJ, 1965.
24. L. Lachman, H. A. Lieberman, and G. Richardson, Medicated Candies, *Drug and Cosmetic Industry, 99*, Nos. 1, 2, and 3 (July, August, and Sept. 1966).
25. C. D. Pratt, et al., *Twenty Years of Confectionary and Chocolate Progress*, AVI, Westport, CT, 1970.
26. A. B. Cramer, Hard Candy and Continuous Cooking—8 Years Later—A Reappraisal, *The Manufacturing Confectioner, 51*:5 (1971).
27. A. Meiners, Incorporating Flavor and Acid in Continuous Manufacturing Systems, *The Manufacturing Confectioner, 53*:10 (1973).
28. Anonymous: Hard Candy Packaging: Moisture Content, Humidity are Factors in Selection of Wrapping Materials and Styles, *Candy and Snack Industry, 141*:11 (1976).

29. Anonymous: Chocolate Packaging Roundup: Product Composition Affects Material Selection, *Candy and Snack Industry*, *141*:10 (1976).
30. *Modern Packaging 1976—77 Encyclopedia and Buyer's Guide*, *49*:12 (1976).
31. W. Vink, Tabletting: Manufacture of Compressed Candies, *The Manufacturing Confectioner*, *56*:1 (1976).
32. Cerelose Dextrose, *Technical Bulletin*, CPC International, Englewood Cliffs, NJ.
33. A Series of Unique Chemicals for the Pharmaceutical Manufacturer, *Technical Bulletin*, Edward Mendell Co., Carmel, NY.
34. Mor-Rex Hydrolyzed Cereal Solids, *Technical Bulletin*, CPC International, Englewood Cliffs, NJ.
35. Royal-T Dextrose with Malto-Dextrin 2031, *Technical Bulletin*, CPC International, Englewood Cliffs, NJ.
36. NuTab—A direct Compression Binder, *Technical Bulletin* Sucrest Pharmaceutical Division, Pennsauken, NJ.
37. Di-Pac, *Technical Bulletin*, American Sugar Company, NY.
38. SugarTab, *Technical Bulletin*, Edward Mendell Co., NY.
39. Sweetrex, *Technical Bulletin*, Edward Mendell Co., NY.
40. Mannitol, USP, Tablet Excipient, *Technical Bulletin*, ICI America. Wilmington, DE.
41. Crystalline Sorbitol Tablet Type, *Technical Bulletin 615*, Pfizer Chemical Division, NY.
42. Carbowax Polyethylene Glycols, *Technical Bulletin*, Union Carbide Corporation, NY.
43. H. N. Wolkoff and G. Pinchuk, Throat Lozenge Vehicle, U.S. Patent 3,511,914 (1970).
44. Lactose, USP Fast-Flo: The Perfect Excipient, *Technical Bulletin*, Formost Foods Company, San Francisco, CA.
45. Avicel in Direct Compression Tabletting, *Technical Bulletin PH-9*, FMC Corporation, Marcus Hook, PA.
46. Tablet Making, *Technical Bulletin 14-100.500A*, Pennwalt-Stokes, Warminister, PA.
47. Factors Determining the Hardness of Tablets, *Technical Bulletin 11-100.621B*, Pennwalt-Stokes, Warminister, PA.
48. J. P. Malle, Compacted Candy Concepts, *The Manufacturing Confectioner* *56*:5 (1976).
49. Model 541 Rotary Tableting Press, *Technical Bulletin 551-A*, Pennwalt-Stokes, Warminister, PA.
50. Model 328 Rotary Tableting Press, *Technical Bulletin 374*, Pennwalt-Stokes, Warminister, PA.
51. Model DD-2 Double-Sided Rotary Tableting Press, *Technical Bulletin* 358, Pennwalt-Stokes, Warminster, PA.
52. Binding, Capping, Laminating and Sticking of Tablets: Cause and Remedy Charts, *Technical Bulletin 8-100.652A*, Pennwalt-Stokes, Warminster, PA.
53. E. J. Abeling, Finished Goods Quality Assurance, *The Manufacturing Confectioner*, *52*:7 (1972).
54. *The United States Pharmacopeia, Twenty-First Revision*, United States Pharmacopeial Convention, January 1, 1985.
55. R. Lees, High Boiled Sweets: Suggested Data Sheet for Remedying Faults, *Confectionary Production*, *38*:11 (1972).
56. Derek McManua, Candy Laboratory Use of Gas-Liquid Chromatography, *The Manufacturing Confectioner*, *50*:2 (1970).

57. M. M. Hussein, Gas Chromatography: Superior Method for Determining Flavor Content in Finished Candy, *Candy and Snack Industry, 141*:8 (1976).
58. B. Ostergren, Practical Biological Testing in Confectionary Plants, *The Manufacturing Confectioner, 54*:6 (1974).
59. I. I. Kazi, "Plant Sanitation," *The Manufacturing Confectioner, 56*:4 (1976).
60. H. Becker, Filled Hard Candy Production Requires Precise Control of Unit Quality, Uniformity and Temperature, *Candy and Snack Industry, 142*:3 (1977).
61. S. H. Cakebread, The Shelf Life of High Boilings. V. Calculating the E.R.H., *The Manufacturing Confectioner, 50*:1 (1970).
62. H. E. Horn, Crystallization Guidelines Provide Criteria and Control for Panning Process, *Candy and Snack Industry, 142*:11 (1977).
63. Veegum, *Technical Bulletin*, R. T. Vanderbilt Company, NY.
64. A. J. Chalmers, Hard Candy Processing: Problems and Solutions, *The Manufacturing Confectioner, 63*:10 (1983).
65. J. DuRoss, Modified Crystalline Sorbitol, *The Manufacturing Confectioner, 62*:11 (1982).
66. D. Caton, Direct Compression, *The Manufacturing Confectioner, 62*:11 (1982).
67. J. Schleuter, Aeration of Hard Candies, *The Manufacturing Confectioner, 62*:6 (1982).
68. R. Calliari, Sorbitol for Confections, *The Manufacturing Confectioner, 63*:11 (1983).
69. A. J. Chalmers, Reclaiming Hard Candy Reworks, *The Manufacturing Confectioner, 65*:10 (1985).
70. J. Denick, D. Peters, and A. K. Talwar, Medicament Adsorbates of Decongestants with Complex Aluminum Silicate and Their Preparation, U.S. Patent 4,758,424 (1988).
71. J. Denick, D. Peters, and A. K. Talwar, Magnesium Trisilicate Suitable for Preparation of Medicament Adsorbates of Decongestants, U.S. Patent 4,632,821 (1986).
72. D. Peters, J. Denick, and A. K. Talwar, Magnesium Trisilicate Suitable for Preparation of Medicament Adsorbates. U.S. Patent 4,581,232 (1986).
73. D. Peters, J. Denick, and A. K. Talwar, Magnesium Trisilicate Suitable for Preparation of Medicament Adsorbates of Antihistamines, U.S. Patent 4,642,231 (1987).
74. D. Peters, J. Denick, and A. K. Talwar, Confectionary Compositions Containing Magnesium Trisilicate Adsorbates, U.S. Patent 4,647,459 (1987).
75. D. Peters, J. Denick, and A. K. Talwar, Magnesium Trisilicate Suitable for Preparation of Medicament Adsorbates of Analgesics, U.S. Patent 4,643,892 (1987).
76. D. Peters and J. Denick, Chewable Mineral Supplement, U.S. Patent 4,582,709 (1986).
77. J. Hume, Notebook of a Practical Confectioner. I. Preparing, Cooking and Making Toffees and Caramels, *Confectionary Products*, 43:385–386 (Sept. 1977).
78. E. Pyrz, Caramel: A Review, *The Manufacturing Confectioner, 56*:6 (1976).

79. B. W. Minifie, Extrusion: Caramel, Fudge and Chewing Sweets, *The Manufacturing Confectioner*, *55*:11 (1975).
80. B. Vospalek, Sugar in the Confectionary Industry, *The Manufacturing Confectioner*, *66*:5 (1986).
81. P. W. Jung, Aeration of Hard Candy, *The Manufacturing Confectioner*, *67*:5 (1985).
82. R. W. Hartel, Sugar Crystallization in Confectionary Products, *The Manufacturing Confectioner*, *67*:10 (1987).
83. T. Long, Forming Hard Candy, Pennsylvania Manufacturing Confectioners Association, April 1980.
84. H. R. Riedel, Hard Candy Fillings, *The Manufacturing Confectioner*, *56*:9 (1976).
85. C. J. DeBlaez, Buccal Residence Time of Lozenges, *Pharm. Acta Helv.* *52*:5 (1977).
86. S. D. Uko-nne and R. W. Mendes, Directly Compressible Molasses and Honey, *Pharmaceut. Technol.* *6*:11 (1982).
87. Mola-Tab, *Technical Bulletin*, Ingredient Technology Corporation, Woodbridge, NJ.
88. Hony-Tab, *Technical Bulletin*, Ingredient Technology Corporation, Woodbridge, NJ.
89. Encompress, *Technical Bulletin*, Edward Mendell Co., Carmel, NY.
90. Compactrol, *Technical Bulletin*, Edward Mendell Co., Carmel, NY.
91. P. A. Lane and B. A. Brown, Anesthetic lozenges, U.S. Patent 4,139,627 (1979).
92. J. E. F. Reynolds and A. B. Prasad, *Martindale: The Extra Pharmacopoeia*, 28th Edition. The Pharmaceutical Press, London, England, 1982.

SUGGESTED READING*

Ahrens, G. W.: Sugar-free Compounded Tablet or Lozenge Base Material for use in the Preparation of Suckable, Structurally Sound and Hard at Room Temperature Nonhygroscopic Noncaries Forming Tablets or Lozenges, U.S. Patent 3,525,795 (1970).

Barnett, C. D.: *Candy Making as a Science and Art*, Don Gussow Publications, NY.

Barry, R. H., Weiss, M.: Dextromethorphan and Benzyl Alcohol Hard Candy Lozenges Free From Opaqueness and/or Tiny Entrapped Air Bubbles, U.S. Patent 3,427,379 (1969).

Bornberg, John D.: Practical Quality Control in the Confectionery Industry, *The Manufacturing Confectioner*, *51*:6 (1971).

Burlinson, H.: The Evolution of the Compressed Tablet, *Aust. J. Pharm.*, *49*:738–752 (October 1968).

Bush, J. W. and Pyrz, E. Z.: Lower Calorie Candies, U.S. Patent 3,809,756 (1974).

Cakebread, S. H.: Chemistry of Candy I, *The Manufacturing Confectioner*, *49*:2 (1969).

*References included in this list are intended as general sources of information regarding the various aspects of confectionary manufacture.

Cakebread, S. H.: The Shelf-Life of High Boilings, *The Manufacturing Confectioner*, *49*:9–12 (1969).
Cakebread, S. H.: Deriving Recipes From Analytical Figures—Complex High Boilings II, *The Manufacturing Confectioner*, *50*:3–4 (1970).
Cakebread, S. H.: The Chemistry of Candy Part V: Mainly Arithmetic, *The Manufacturing Confectioner*, *51*:6 (1971).
Cakebread, S. H.: Requirements for Production of Grained Confections, *The Manufacturing Confectioner*, *52*:3 (1972).
Candy Industry Catolog and Formula Book, 23rd Annual Edition (1969–1970), Magazines for Industry, New York.
Candy and Snack Industry Buying Guide 1975, Magazines for Industry, NY.
Carle and Montanari Spa., Lanzillo, A., Candy Mass Production, U.S. Patent 4,054,271.
Chalmers, A. J.: Hard Candy Processing and Quality Observations, *The Manufacturing Confectioner*, *63*:5 (1983).
Christenson, G. L. et al: Long Lasting Troche, U.S. Patent 3,594,467 (1971).
Confectionary Production *37*:12, 1981, pp. 528–529, 546.
DuRoss, J. W.: Sugar Free Hard Candy, German Patent 2,409,107 (1974).
Frey, R. R.: Additives for use in the Preparation of Cooked Candies, U.S. Patent 3,738,843 (1973).
Gillies, Martha T.: *Candies and Other Confections*, Noyes Data, Park Ridge, NJ, 1979.
Gobba, A. H. et al: In Vitro Effects of Separate Ingredients and Combinations Proposed to be used as Oropharyngeal Lozenges on Different Bacterial Flora and Yeasts, *Drug Res. J.*, *1*:111–128, No. 1 (1968).
Gotsch, G.: Hard Caramels II, *Dragoco Report*, *1* (1979).
Gott, P. P. et al: *All About Candy and Chocolate*, National Confectioners Association, Chicago, 1978.
Griffenhagen, G. B. and Hawkins, L. L., ed., *Handbook of Non-Prescription Drugs*, American Pharmaceutical Association, Washington, D.C., 1973.
Gutterson, M.: *Confectionary Products Manufacturing Processes 1969*, Noyes Development, Park Ridge, NJ.
Hohberger, N.: Continuous Cooking with a Batch System, *The Manufacturing Confectioner*, *63*:11 (1983).
Horn, H. E.: Crystallization Guidelines Provide Criteria and Control for Panning Process, *Candy and Snack Industry*, *142*:12 (1977).
IPT Standard Specifications for Tableting Tools, *Tableting Specification Manual*, American Pharmaceutical Association Academy of Pharmaceutical Sciences, 1971.
Kuzio, W.: Flavor Enhancers Broaden Product Appeal, *Candy and Snack Industry*, *141*:8 (1976).
Laino, J. M.: Quality Control—or Quality Assurance? *The Manufacturing Confectioner*, *53*:5 (1973).
Leighton, A. E.: A Text Book on Candy Making, *The Manufacturing Confectioner* (1952).
Liebrand, J. T.: Process for the Manufacture of Sugarless Confections, U.S. Patent 3,738,845 (1973).
Minifie, B. W.: Pectin: Its Use in Candy Technology, *The Manufacturing Confectioner*, *51*:11 (1971).
Norrish, R. S.: Selected Tables of Physical Properties of Sugar Solutions, *Scientific and Technical Surveys*, *51* (July 1967).

Pariser, E. R.: How Physical Properties of Candy Affect Taste, *The Manufacturing Confectioner*, *41*:5 (1961).
Products of the Wet Milling Industry in Food, *Symposium Proceedings*, Washington, D.C., Corn Refiners Association, (1970).
Richmond, W.: *Choice Confections*, Manufacturing Confectioner Publishing Company, Glen Rock, NJ (1976).
Ross, J. W.: Sugarless Confection, U.S. Patent 3,438,781 (1969).
Slawatycki, A.: Producing Lozenges Automatically, *The Manufacturing Confectioner*, *50*:11 (1970).
Toscano, V.: The Use of Fructose in Confections, *The Manufacturing Confectioner*, *55*:5 (1975).
Vink, W.: Continuous Processing of Hard Candy: A Different Approach, *The Manufacturing Confectioner*, *66*:10 (1988).
Vrana, P.: New Machinery for Confectionary Cooking and Processing, *The Manufacturing Confectioner*, *64*:12 (1984).