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SHORT REPORT

Development of a fast dissolving film of epinephrine hydrochloride as a potential anaphylactic treatment for pediatrics

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Abstract

Objective: To develop a fast dissolving film strip containing epinephrine HCl for the potential treatment of pediatric anaphylaxis.
Methods: Four different films have been prepared by solvent casting technique where the percentages of the polymer (Lycoat RS720) were optimized. The polymer percentages were (20%, 25%, 27% and 30%) of the total formulation weighs. The thickness and elastic modulus of the optimized film was evaluated using dynamic mechanical analyzer. Epinephrine content uniformity was assessed using UV at wavelength 280 nm. For the dissolution test, fast dissolving films (FDFs) were evaluated in 500 Simulated Saliva, with 50 rpm. *In vivo* taste and disintegration evaluation was performed on six healthy volunteers.
Results: Films formed by formulations 1, 2 and 3 were too sticky after drying, while formulation 4 that has 30% polymer content formed smooth, transparent, flexible and uniform film, and therefore, it was selected for further testing. The value of elastic modulus was determined at 1.325 MPa. The thickness of the film at different locations was measured at 0.29 mm. Drug content in film was measured at 93% ±10. More than 90% of epinephrine was released from the film within 7.2 min. Bitterness of epinephrine was masked efficiently according to volunteer's comments with average disintegration time of 20 s.
Conclusion: This study presents potential proof for using FDFs as a replacement therapy of epinephrine injections for pediatrics.

Keywords

Anaphylaxis, epinephrine, fast dissolving film strip, Lycoat

History

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Introduction

Epinephrine is considered the primary choice for the treatment of anaphylaxis which is a life threatening allergic reaction that might lead to death if untreated especially in children[1]. A study reported that one in every 10 000 children has an anaphylactic attack per year[2]. The administration of proper therapeutic agents, such as epinephrine, must be prompt. This is usually performed through the usage of autoinjectors, such as EpiPen® or Twinject®, that deliver the required dose in the midouter thigh either subcutaneously or intramuscularly[3]. However, many disadvantages were reported with the usage of these injectors, such as high cost, inaccurate administration, short half-life, patient's fear of needles, accidental injections, and unavailability of enough number of fixed prefilled doses[4]. These shortcomings affects greatly the patient compliance and adherence to these injectors[4]. In addition, it is very challenging to adjust the dose to different children ages, as there are only two premeasured fixed epinephrine doses (0.15 and 0.3 mg)[5]. Recent study showed that only 17% of pediatric patients who have experienced anaphylactic symptoms, have used prescribed auto injectors[6]. Other available delivery systems, such as syringes or inhalers, are also underused due to their lack of rapid and accurate dosing. Therefore, there is growing interest in the development of an alternative noninvasive delivery system that can easily provide accurate doses of epinephrine.

Fast dissolving films (FDF) could be a promising alternative for the delivery of epinephrine. These are very thin strips that disintegrate or dissolve very rapidly in the oral cavity, releasing the medication to be absorbed through the oro-mucosal route[7]. Rapid bioavailability of the drug is achieved due to the high blood flow and permeability of the buccal cavity[8]. Actually, FDF has acquired more acceptance over the last few years due to their many advantages, such as prompt onset of action, ease of administration (no water needed), convenience of dosing and the availability of different shapes and sizes[7]. For instance, more than 80 FDF brands were launched since 2003 in North America[8]. Many reports showed that fast dissolving films to be used in various acute conditions such as pain, migraine, asthma or hypertension[7]. FDFs are typically formulated from a plasticized hydrocolloids or mixtures that can be laminated by special techniques, such as solvent casting, hot-melt extrusion and gel rolling[9]. However, several parameters should be optimized during the development of FDF, such as physical properties (tensile strength, thickness and elasticity), dissolution profile, content uniformity and taste. Therefore, the objective of this work is to develop a fast dissolving film strip containing epinephrine HCl for the potential treatment of pediatric anaphylaxis.

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Materials

Epinpherine hydrochloride, sodium metabisulfite, citric acid monohydrate and sodium citrate monobasic were purchased from Sigma Aldrich (St. Louis, MO). Lycoat® RS720 was obtained from Roquette (Lestrem, France). Glycerin and tween 80 were purchased from Fisher Chemicals (Pittsburg, PA). Xylitol was purchased from Gallipot (St. Paul, MN). Tutti frutti was obtained from LorAnn Oils (Lansing, MI).

Methods

Film preparation

Several FDFs were prepared by solvent casting technique to choose the optimum film formulation. The formulations compositions of the FDFs are mentioned in Table 1. In details, Lycoat and xylitol were dissolved in warm water. The solution was then placed in a sonicator for 2 h, and then, the solution was left overnight to ensure the removal of all entrapped air bubbles. Other excipients and epinephrine HCl were added to the solution on the next day at room temperature. The mixture was then placed again in a sonicator for 40 min. The mixture was then spread onto a checkered paper covered by plastic sheet using a stainless steel bar applicator. The film was left to dry overnight and was cut into 9-mm^2 small film strips.

Physical properties

The thickness and elastic modulus of the optimized film was evaluated using dynamic mechanical analyzer (Q800 DMA, TA instruments, New Castle, DE). This is important to evaluate tensile properties of the films. Three strips of the optimized films were tested at 25 °C according to ASTM International Test Method for Thin Plastic Sheeting (D 882–02)[10]. Each film was positioned between the grips of the instrument. The preload force was set at 0.01 N and the final force at 15 N. The initial grip separation was set to 60 mm and crosshead speed was set to 500 mm/min. The test was terminated when the film breaks. Elastic modulus was determined as the slope of the straightline part of the stress–strain curve and it was expressed in force per unit area (MPa).

Drug content uniformity

Specific areas were cut from six different films and weighted to calculate the estimated amount of drug in each area. Films were then dissolved in 100 ml of citric acid buffer. The media were stirred and then filtered using 0.45-um filters (Millipore Corporation, Millipore, Vimodron, Italy) and epinephrine content was assessed using UVmini-1240 UV-Vis Spectrophotometer (Shimadzu, Kyoto, Japan) at wavelength 280 nm. Epinephrine content was determined by calculating the percentage of the measured epinephrine to the estimated amount in each film.

In vitro dissolution test

For the dissolution test, FDFs were evaluated using USP dissolution apparatus II, paddle (Distek Evolution 6100, North Brunswick, NJ). Six strips were placed in different 1-l vessels containing 500 ml simulated saliva. The temperature of the dissolution media was set to 37 °C and rpm was set to 50 rpm. Samples were taken at different time points throughout the time of the experiment (15 min), and the amount of epinephrine release in the media was determined by UVmini-1240 UV-Vis Spectrophotometer (Shimadzu, Japan) at 280 nm.

Human taste panel

To evaluate the palatability of optimized epinephrine film, taste evaluation study was performed on six healthy volunteers. The study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki), and all volunteers were informed in advance of the related details and the goal of the study and their consents were obtained. Volunteers were asked to place the film on the interior surface of their buccal cavity until film is fully disintegrated. Volunteers then rinsed their moths with drinking water. Volunteers have to report their findings of the presence of bitterness or not, any tongue restriction and how long it took for full disintegration of the film.

Results and discussion

Fast dissolving films have received wide acceptance from pharmaceutical industry due to their numerous advantages, such as precise dosing, convenient administration and rapid bioavailability[11]. Several reports showed that 80% of patients prefer fast dissolving dosage forms over conventional solid oral dosages forms especially pediatric and geriatrics[12].Therefore, various drugs have been formulated and marketed into FDFs, such as dextromethorphan, doneprezil and rotavirus vaccine[13,14]. One important criterion for consideration when formulating a drug into FDF is the limitation of the dose size. A dose range of 5 mg to 30 mg of a drug can only be incorporated into the film[7].

Drugs with larger doses are difficult to formulate into FDF due to the thickness requirement of the film as a good film should be thin, small and does not hinder the tongue's movement. The typical dose of epinephrine for anaphylactic treatment is 0.3 to 0.5 mg in adults and 0.01 mg/kg up to a maximum of 0.3 mg in children administered through intramuscular route[5]. In this study, 13 mg/9 mm^2 of epinephrine (5.9% w/w) were used as the dose

Table 1. List of the compositions of the four FDFs formulations.

Ingredient (% w/w)	Use	F1	F2	F3	F4
Epinephrine HCl	Drug	5.9	5.9	5.9	5.9
Sodium metabisulfite	Antioxidant	5.9	5.9	5.9	5.9
Lycoat® RS720 (hydroxypropyl starch)	Film-forming polymer	20	25	27	30
Glycerin	Plasticizer	3	3	3	3
Tween 80	Surfactant	2	2	2	2
Citric acid monohydrate	Buffer; increases absorption in oral cavity	0.5	0.5	0.5	0.5
Sodium citrate monobasic	Buffer	0.5	0.5	0.5	0.5
Xylitol	Sweetener	10	10	10	10
Tutti Frutti	Flavor	6	6	6	6
Water		46.2	41.2	39.2	36.2

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size (Table 1). This quantity was calculated for 6–7-year-old child according to Clark's rule[15]:

$$\text{Pediatric dose} = \text{Adult dose} \times (\text{child's weight}/150)$$

A typical adult dose was determined to be 40 mg based on a study that showed dose bioequivalence between 40 mg epinephrine table administered sublingually and 0.3 mg epinephrine administered intramuscularly using E. injectors [5].

Different techniques have been used to prepare films such as solvent casting, hot melt extrusion, solid dispersion extrusion, semisolid casting and gel rolling[7]. However, the most common ones in industry are solvent casting and hot melt extrusion. Nevertheless, hot melt extrusion has main drawback as it needs thermal process to operate which might affects the stability of some heat-sensitive drugs[16]. In this work, solvent casting technique was used to prepare epinephrine film. This technique has been used in many studies where it showed to provide high quality films that have thickness uniformity, high clarity, good flexibility and physical properties[11,14].

A typical FDF consists of a drug, water-soluble polymer, plasticizer, saliva-stimulating agent, surfactant and other fillers, such as sweetening agents and flavors in case of bitter taste drugs and colors[13,14]. The composition of the film should be taken into high consideration as it highly affects the mechanical properties of the film and subsequently its delivery profile[13].

In this work, four different formulations have been prepared where the percentages of the polymer were changed (Table 1). The polymer percentages were (20%, 25%, 27% and 30%) of the total formulation weighs. The selection of optimal amount of polymer is crucial for obtaining nonsticky and functional film. Ideal film-forming polymer should have good wetting property, high spreadability, good feeling in the mouth and should be safe and nonirritant[7]. Many studies have showed that polymer content of at least 10–15% is needed in order to formulate proper film of proper thickness after drying in order to peel the film off from the release line[17]. The polymer used in this study was Lycoat, which is according to the manufacturer's information, and it was a modified starch that specifically manufactured for aqueous film coating in immediate release solid oral dosage forms[18]. However, Lycoat is considered a water-soluble polymer, which has been used in many FDFs studies that showed its efficiency in developing high-quality films[14,19]. Water-soluble polymers have the advantages of providing good mechanical properties, quick disintegration and pleasant mouthfeel[13].

Glycerin was used as a plasticizer to provide the proper elasticity for the film (Table 1). The plasticizer imparts certain level of flexibility to the film by decreasing its brittleness[20]. It also enhances the flow of the polymer and improve the tensile strength and elongation of the film[20]. Several plasticizers are commonly used in FDFs preparation, such as glycerol, di-butylpthallate and polyethylene glycols, and they are usually used up to 20% concentration of dry polymer weight[7]. Films in this study were prepared using 3% glycerol which is equivalent to 10–15% of the amount of polymer used.

Tween 80 was used as a surfactant (Table 1). The function of the surfactant is to facilitate the solubilization or wetting of the film and subsequently causing the film to disintegrate quickly, releasing the drug to be absorbed through the buccal cavity[21]. This is very essential for the anaphylaxis treatment using rapid bioavailable delivery system. Citric acid was use to adjust the pH and can be used in FDFs as saliva simulating agent to increase the secretion rate of saliva which will further improve the disintegration time of the film[7]. Typically, acids, such as citric acid, malic acid, lactic acid and ascorbic acid, are used as chemical stimulants of saliva secretion. However, citric acid is the most preferred among them[22]. Xylitol and tutti frutti flavor were used for taste masking (Table 1). Xylitol is an effective sweetening agent that has equal sweetness to sucrose[23]. However, the cooling feeling that xylitol imparts in the mouth makes it very attractive in film development[23]. In addition, it has been reported that xylitol has no aftertaste and it is marketed as safe for diabetics people with hyperglycermia conditions. Xylitol was selected because as compared to regular sugars, it has extremely low glycermic index of 7 (glucose has glycemic index of 100)[24]. Tutti frutti is an appealing flavor for children due to its sour taste. Children tends to love sweet and sour flavored materials[25]. Finally, the addition of antioxidant is very important for the stability of epinephrine. Prompt oxidation of epinephrine in aqueous solution results in a colored inactive product which has been reported[26]. Therefore, different types of antioxidants are used in the commercial injectors such as sodium metabisulfite, ethylene diamine tetra-acetic acid (EDTA) and ascorbic acid achieving shelf life of 2 years[26]. The addition of sodium metabisuflite to the film, herein, will ensure the stability of epinephrine in the film (Table 1). However, further stability studies should be performed to assess this claim. However, films formed by formulations 1, 2 and 3 were too sticky after drying rendering them unusable. While formulation 4 that has 30% polymer content formed smooth, transparent, flexible and uniform film, and therefore, it was selected for further testing. The difference in stickiness is clearly related to the variation of the polymer content. This comes in agreement with previous study that showed that using 22.5% of Lycoat polymer formed a thin and flexible but sticky film at that concentration concluding that higher percentage of polymer is needed[27]. Physical properties of the film prepared by formulation 4 were evaluated such as elastic modulus, thickness, content uniformity and dissolution time. Assessing these parameters is essential to determine the efficiency and usability of the film by patients.

Elastic modulus was first studied as it represents clear measure of the stiffness level of the film. It is calculated as the ratio of the applied stress over strain on specific section[13].

Elastic's modulus = (Force at corresponding strain/cross section area) × 1/(corresponding strain)

The profile of the film was illustrated in Figure 1 where small increase in the applied strain to the film caused quick increase in stress reaching a value of 0.1 MPa at 20% strain level. As the strain increases further above 20%, the increase magnitude in stress decreases gradually until it reaches semi-plateau at value 0.16 MPa where % stress is 80% (Figure 1). The value of elastic modulus was determined at 1.325 MPa which is indication of very good flexibility of the film (Table 2). The thickness of the film at different locations was measured at 0.29 mm with very small

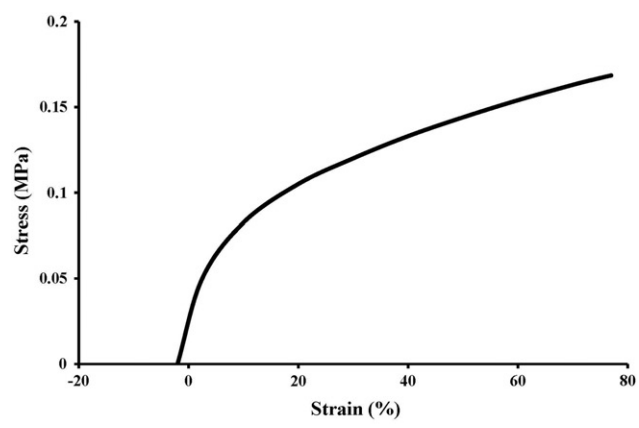

Figure 1. Stress–strain profile of the optimized epinephrine FDF.

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Table 2. List of physical properties of the optimized film.

Test	Results
Elastic modulus	1.325 ± 0.2 MPa
Thickness	0.29 ± 0.01 mm
Content uniformity	93%±10%

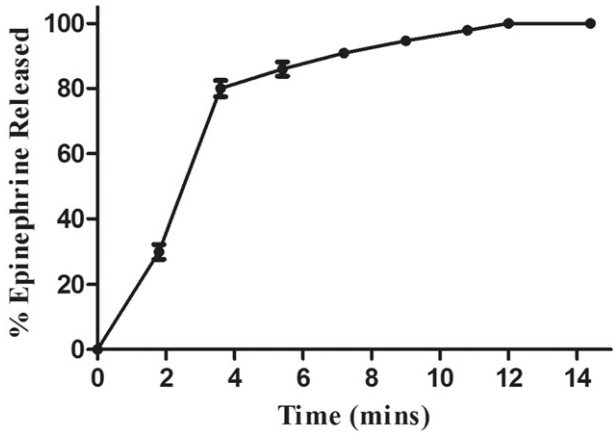

Figure 2. The release profile of the epinephrine from the optimized FDF in 500 ml simulated saliva at 37°C.

Table 3. *In vivo* taste and disintegration time evaluation of the optimized epinephrine FDF.

Volunteer	Bitterness	Tongue constriction	Disintegration time
1	None	None	~10 s
2	None	None	~10 s
3	Slight	None	~20 s
4	None	None	~30 s
5	Very slight	None	~20 s
6	None	None	~30 s

margin of variability which is an indication of the high uniformity of the film (Table 2). A maximum thickness variation of 5% is permitted in the preparation of FDFs[7]. It is very crucial to obtain uniform thickness across the film as it directly correlate with the accuracy of the dose in the film[8]. Drug content in film was measured at 93%±10 indicating high level of consistency of epinephrine dose within the film (Table 2), as a limit of 85–115% of content uniformity is acceptable according to USP[7]. The dissolution profile of epinephrine from the film in terms of rate and extent in simulated saliva was determined on six samples of the optimized film. More than 90% of epinephrine was released from the film within 7.2 min (Figure 2). This is very significant as the time to reach maximum epinephrine concentration after 0.3 mg EpiPen injection of children was reported at 8 ± 2 min[28]. In another study, maximum plasma epinephrine concentration was reached within 34 ± 14 min using 0.01 mg/kg dose injection of epinephrine subcutaneously in the deltoid region. Future pharmacokinetic studies should be performed to assess the C_{max} of epinephrine released form the film[28]. Nevertheless, fast dissolving films have shown to improve the bioavailability of many drugs. For example, about 151.06% improvement in bioavailability was achieved of flupentixol when formulated into FDFs as compared to the oral marketed product[29]. Other study has shown the advantage of fast dissolving films in reaching higher C_{max} and T_{max} of amitriptyline as compared to the commercial solution[30]. These studies and many others clearly indicate the potential use of fast dissolving films as a delivery system for epinephrine.

Taste and disintegration time of the optimized film were evaluated on six volunteers (Table 3). The disintegration time is the time when the film starts to break or disintegrates. Volunteers reported 10–30-sec disintegration time (Table 3). This comply with the regulations set by United States Pharmecopeia (USP) for disintegration time of oral films (not exceeding 30 seconds)[31]. Bitterness of epinephrine was masked efficiently according to volunteer's comments (Table 3). Four volunteers sensed no bitterness of the film, while the two others volunteers reported slight to very slight sensation of bitterness. Moreover, no tongue constriction was reported by any of the volunteers. This data presents clear proof of the efficiency of FDFs in taste masking the bitterness of epinephrine and an indication of strong potential for using FDFs as a replacement therapy of epinephrine injections for children.

Conclusion

Four films with different polymer contents were evaluated in this study. The formulation with the highest concentration of the polymer Lycoat (30%) formed smooth and clear film. The optimized formulation showed good mechanical properties attaining high level of flexibility, thickness uniformity and rapid disintegration (20 s) and dissolution time (90% within 7.2 min). Moreover, a content uniformity of 93% was reported of different strips of the film. Furthermore, tasked masking of the bitterness of epinephrine was achieved based on the opinions of 6 volunteers. Therefore, it was concluded that epinephrine was successfully incorporated into fast dissolving film strip for potential use in pediatrics. However, future research is needed, such as evaluation of the stability of the drug in film strips and performing animal studies, to determine the absorption rate of epinephrine HCl through the buccal cavity.

Declaration of interest

The authors report no declarations of interest.

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