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APPLICATION NUMBER: *60/458,922*
FILING DATE: *March 28, 2003*
RELATED PCT APPLICATION NUMBER: *PCT/US04/09387*

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03-31 A/PROV

Docket Number: IVAX0012-P-USA

PROVISIONAL APPLICATION FOR PATENT COVER SHEET (Large Entity)

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c).

INVENTOR(S)/APPLICANT(S)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Nicholas	Bodor	Miami, FL

☐ *Additional inventors are being named on page 2 attached hereto*

TITLE OF THE INVENTION (280 characters max)

ORAL AND TRANSMUCOSAL DELIVERY OF CYCLODEXTRIN BASED FORMULATIONS

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ Specification — *Number of Pages* 23

☐ Drawing(s) — *Number of Sheets*

☒ Other (specify) Postcard

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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

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Respectfully submitted,

SIGNATURE Jeffrey J. Miller DATE March 28, 2003

TYPED or PRINTED NAME Jeffrey J. Miller REGISTRATION NO. *(if appropriate)* 39,773

TELEPHONE 617-535-4421

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

SEND TO: Box Provisional Application, Assistant Commissioner for Patents, Washington, DC 20231

P19LARGE/REV04

EV345335370US

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application:	Nicholas Bodor
Serial Number:	Not Yet Assigned
Filing Date:	March 28, 2003
Title:	**ORAL AND TRANSMUCOSAL DELIVERY OF CYCLODEXTRIN BASED FORMULATIONS**
Docket Number:	IVAX0012-P-USA

CERTIFICATE OF MAILING UNDER 37 C.F.R.§ 1.10

"Express Mail" Mailing Label Number **EL945335370US** Date of Deposit **March 28, 2003**

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Assistant Commissioner for Patents
Washington, DC 20231

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TRANSMITTAL LETTER

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[✓] Provisional Application for Patent Cover Sheet (Large Entity);
[✓] Provisional Patent Application (5 Pages Specification, 18 Pages Appendix);
[✓] Authorization to charge Deposit Amount for filing fee of $160.00; and
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If the enclosed papers are considered incomplete, the Mail Room and/or the Application Branch is respectfully requested to contact the undersigned collect at (617) 535-4421, Boston, MA.

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Dated: 3-28-03

Respectfully submitted,

Jeffrey J. Miller, Reg. No.39,773
McDERMOTT, WILL & EMERY
28 State Street
Boston, MA 02109-1775
617-535-4421 (Telephone)
617-535-3800 (Facsimile)

Docket Number:	IVAX0012-P-USA

PROVISIONAL APPLICATION FOR PATENT COVER SHEET (Large Entity)

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Given Name (first and middle [if any])	Family Name or Surname	Residence (city and either State or Foreign Country)

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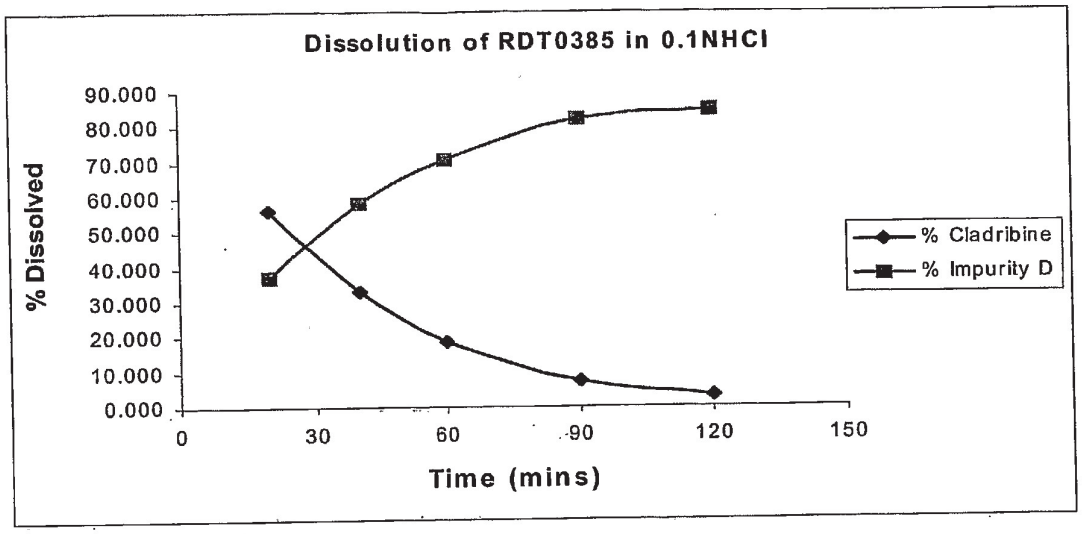
8 **Phase solubility testing**

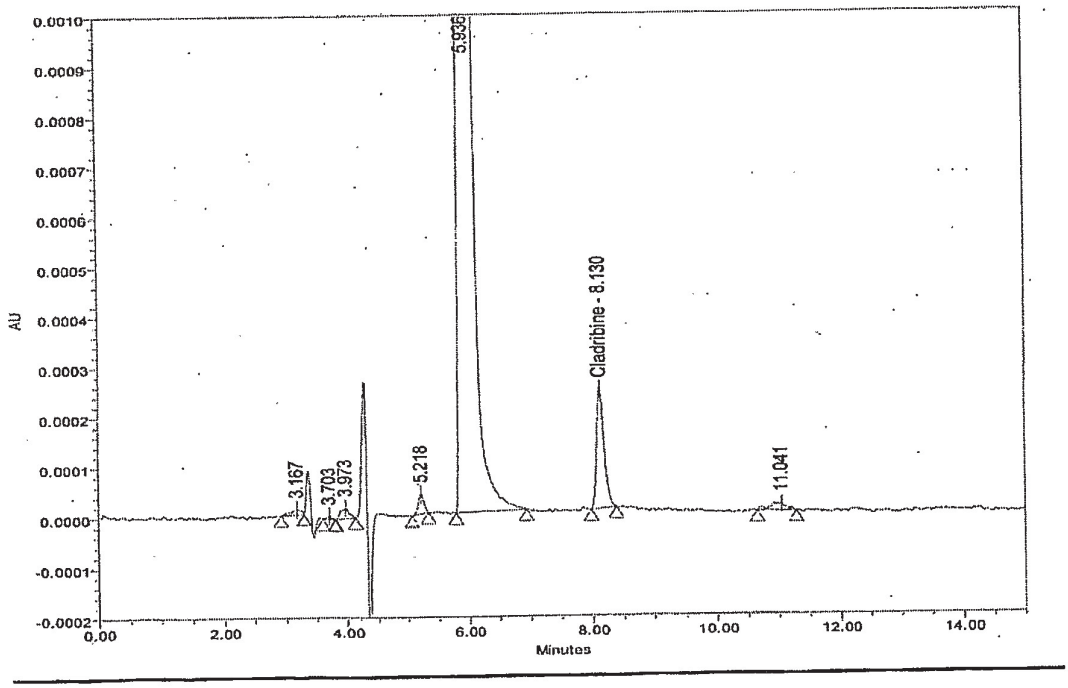
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1. API ANALYSIS

1.1 Dissolution in 0.1N HCl

Initial analysis of active by UV showed 10% degradation of API over 2 hours.
Following from this HPLC analysis of active in 0.1N HCL showed degradation of Cladribine and growth of Impurity D (RRT 0.701). Approx 3% Cladribine remaining after 120 minutes dissolution.

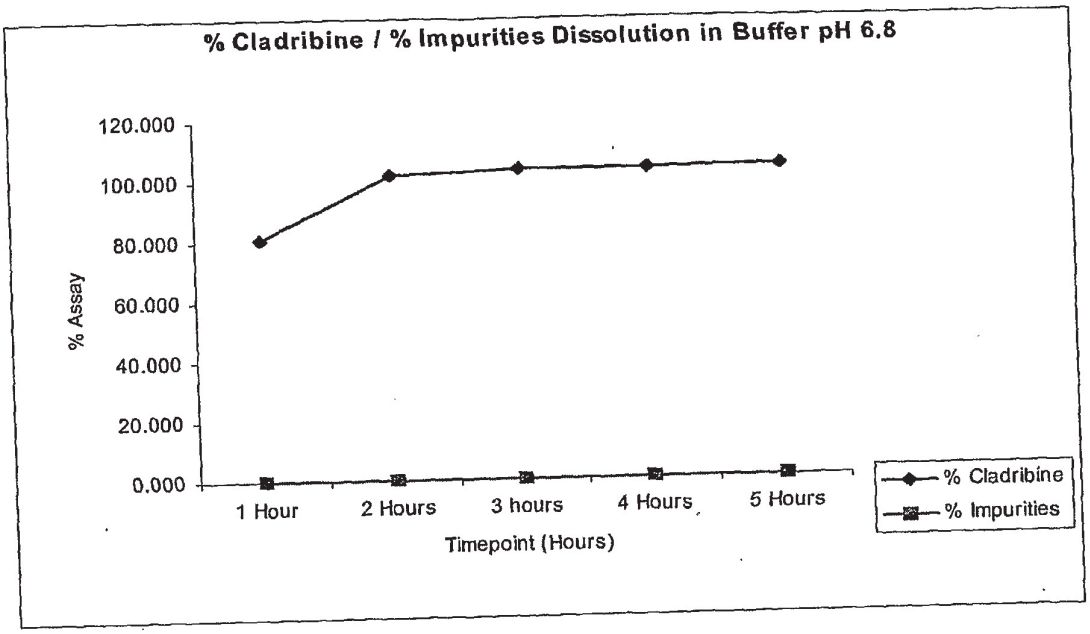




Chromatogram of Cladribine after 2 hours dissolution in 0.1N HCl. Growth of impurity D at retention time 5.936 minutes

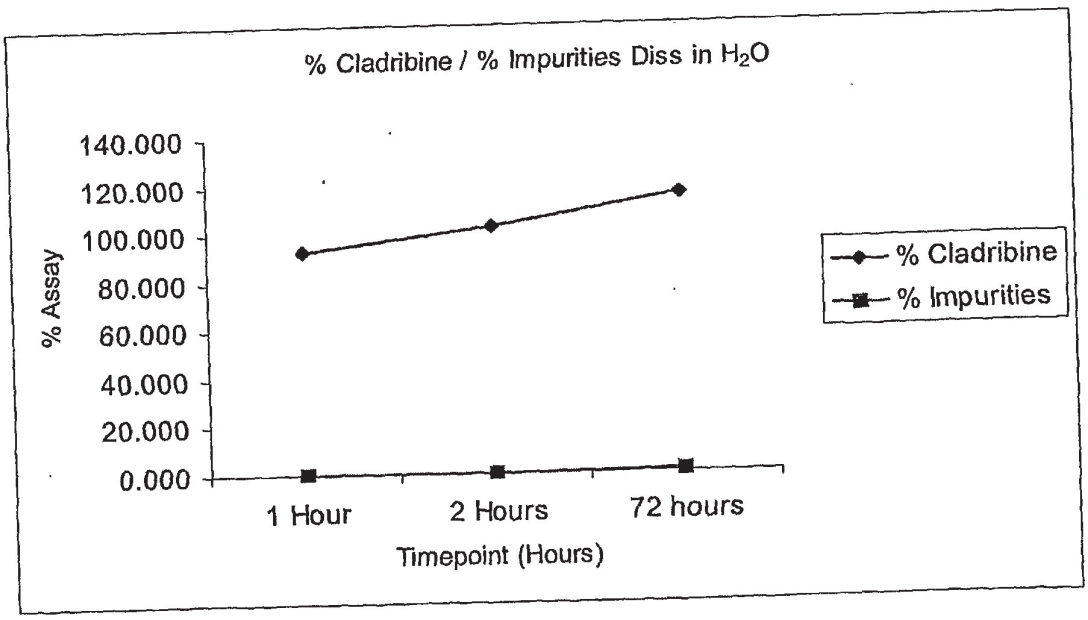
1.2 Dissolution in Phosphate buffer pH 6.8 (HPLC)

102% dissolved after 2 hours. No observed degradation after 5 hours. No increase in related substances.



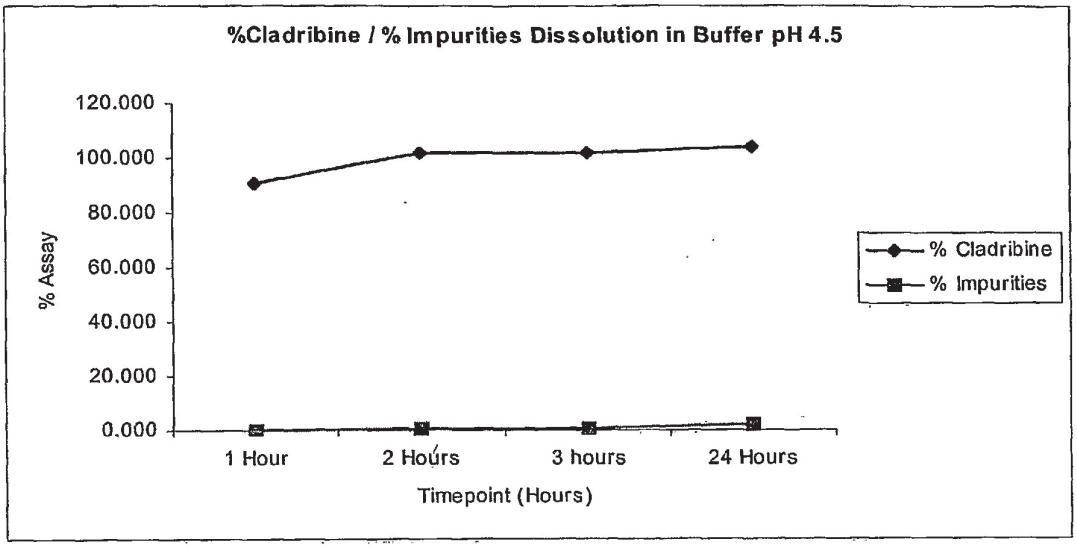
1.3 Dissolution in DI Water (HPLC)

102% dissolved after 2 hours. No observed degradation after 5 hours. Increase in assay of Cladribine after 72 hours due to evaporation of medium. No increase in related substances



1.4 Dissolution in Buffer pH 4.5 (HPLC)

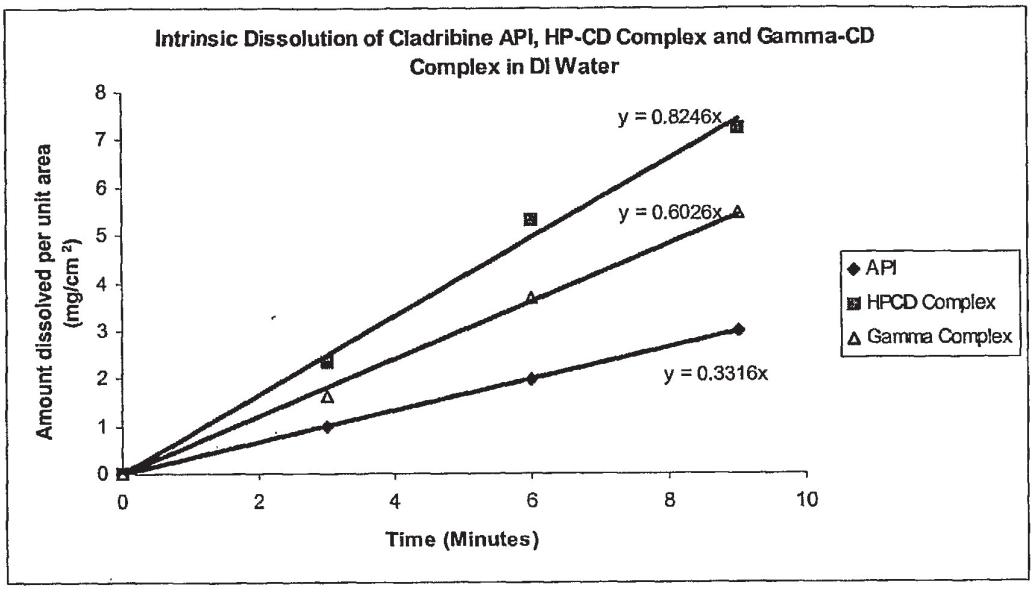
102% dissolved after 2 hours. No observed degradation after 2 hours. Increase in impurities (0.1%) of Cladribine after 24 hours.



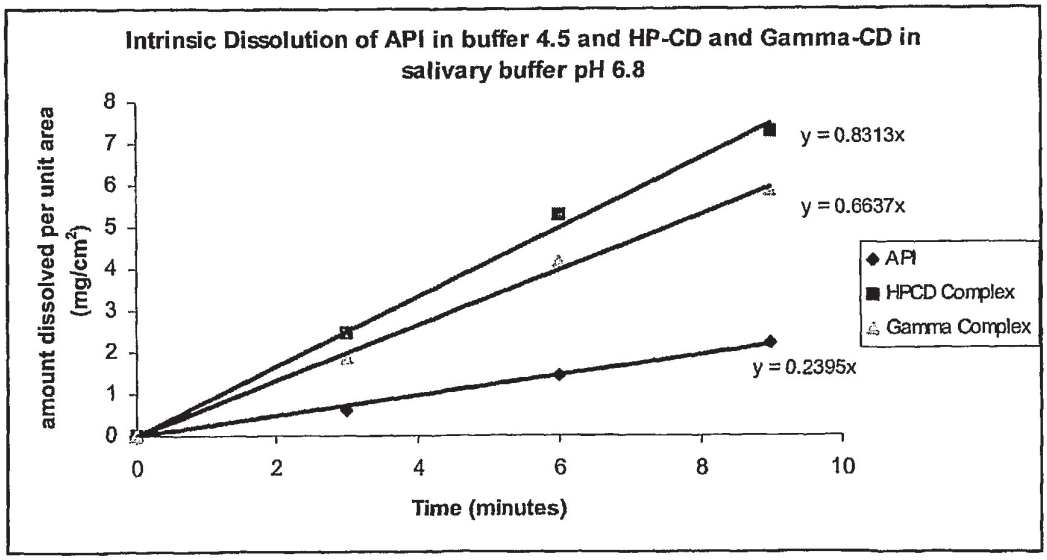
2 INTRINSIC DISSOLUTIONS

Note: IDR of 0.1 mg/min/cm^2 corresponds to solubility of 1 mg/ml.
Cilag estimate solubility of 5mg/ml in water

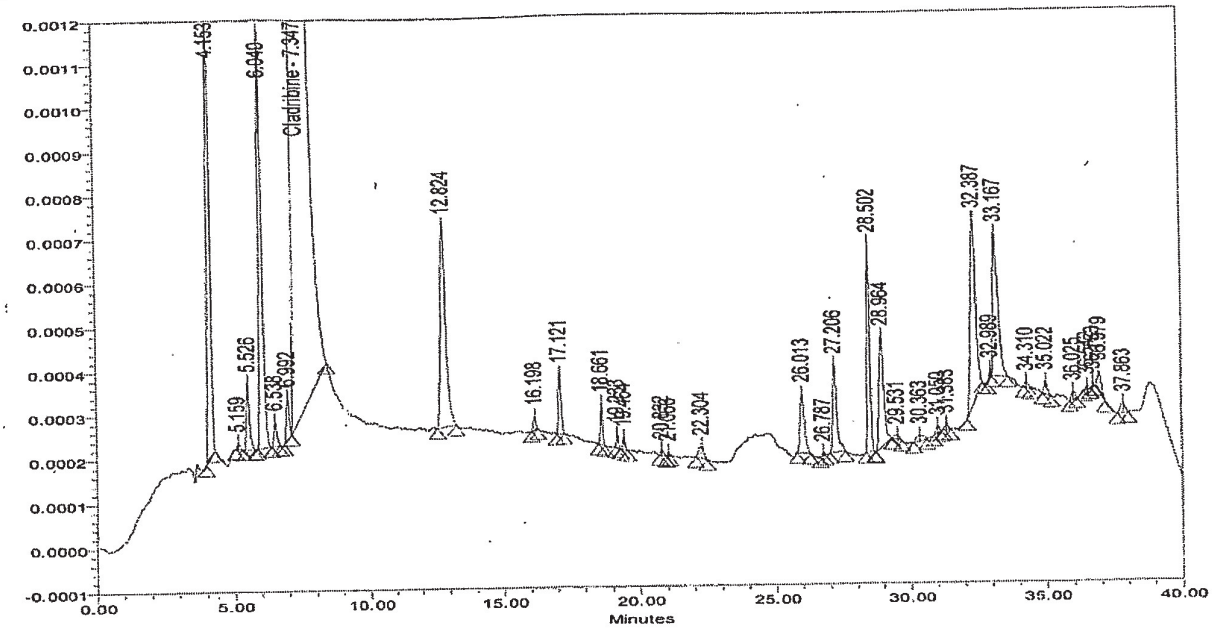
IDR of API in DI water: **0.3316 mg/min/cm^2**
IDR of Gamma-CD complex in DI water: **0.6026 mg/min/cm^2**
IDR of HP-CD complex in DI water: **0.8246 mg/min/cm^2**



IDR of API in phosphate buffer pH 4.5: **0.2395 mg/min/cm^2**
IDR of Gamma-CD complex in salivary buffer pH 7.0: **0.6637 mg/min/cm^2**
IDR of HP-CD complex in salivary buffer pH 7.0: **0.8313 mg/min/cm^2**



3. API RELATED SUBSTANCES



Name	Specification	RRT	Cilag Assay	IVAX Assay
2-Amino-2 deoxyadenosine (Impurity B)	NMT 0.3%	0.563	0.200	0.060
2-Chloro-adenine (Impurity D)	NMT 0.3%	0.701	<0.1	0.002
2-Methoxy-2-deoxyadenosine (Impurity E)	NMT 0.2%	0.821	0.200	0.082
2-Chloro-9-(2 deoxy-α-D-ribofuranosyl)-adenine (Impurity F)	NMT 0.2%	0.951	<0.1	0.01
Cladribine	98% - 102%	1.000	99.8	98.5
Unknown 1	NMT 0.1%	1.763		0.088
Unlnown Impurity RRT (Cilag RRT) = 1.85	NMT 0.2%	1.85		ND
Impurity G	NMT 0.1%	2.123		ND
RWJ-47753-000	NMT 0.1%	3.877		0.043
RWJ-47754-000	NMT 0.1%	4.511		0.056
TOTAL IMPURITIES	NMT 1.0%		0.6%	0.3%

4. FINISHED PRODUCT RELATED SUBSTANCES

Name	RRT	Specification	RDT0385 (Fludaribine formulation)	RDT0398a (Carbomer formulation)	RDT039 (Cyclode formulat
2-Amino-2 deoxyadenosine (Impurity B)	0.563	NMT 0.3%	0.059	0.067	0.056
2-Chloro-adenine (Impurity D)	0.701	NMT 0.3%	0.002	0.002	0.002
2-Methoxy-2-deoxyadenosine (Impurity E)	0.821	NMT 0.2%	0.083	0.093	0.076
2-Chloro-9-(2 deoxy-α-D-ribofuranosyl)-adenine (Impurity F)	0.951	NMT 0.2%	0.010	0.012	0.009
Cladribine	1.000	98% - 102%	96	114	90
Unknown 1	1.763	NMT 0.1%	0.086	0.101	0.082
Unlnown Impurity RRT (Cilag RRT) = 1.85		NMT 0.2%			
Impurity G	2.123	NMT 0.1%	0.001	0.000	0.000
RWJ-47753-000	3.877	NMT 0.1%	0.042	0.050	0.039
RWJ-47754-000	4.511	NMT 0.1%	0.049	0.059	0.047
TOTAL IMPURITIES		NMT 1.0%	0.33%	0.38%	0.24%

5. ASSAY AND RELATED SUBSTANCES OF FREEZED DRIED COMPLEX RAW MATERIAL AND TABLETS

Identity	Chemical Name	RRT	Gammá – CD Raw Material	HP-β-CD Raw Material	FD02 (5mg Gamma-CD Tablets)	FD03 (5mg HPCD Tablets)
Imp B	2-Amino-2'-deoxyadenosine	0.54	0.28	0.19	0.31	0.29
Imp D	2-Chloroadenine	0.73	<0.05	ND	ND	ND
Imp E	2-Methoxy-2'-deoxyadenosine	0.83	0.14	0.12	0.13	0.13
Imp F	2-Chloro-9-(2'-deoxy-α-D-ribofuranosyl)-adenine	0.93	ND	ND	ND	ND
API	**Cladribine**	**1.00**	**108**	**100**	**105**	**102**
Theoretical % Active in Complex	Cladribine		2.128	2.347		
Actual % Active in Complex	Cladribine		2.293	2.353		
Unknown	Not Known	1.89	0.06	0.09	0.07	0.07
RWJ-49616-000	Not Known	2.60	ND	ND	ND	ND
Unknown	Not Known	3.06	<0.05	**1.56***	<0.05	<0.05
Unknown	Not Known	3.43	0.05	0.07	0.08	0.06
RWJ-47753-000	Not Known	3.90	ND	ND	ND	ND
Unknown	Not Known	4.18	ND	ND	0.26	ND
Unknown	Not Known	4.39	ND	ND	0.98	0.31
Unknown	Not Known	4.63	ND	0.33	ND	ND
RWJ-47754-000	Not Known	4.68	0.22	0.15	0.34	0.21
TOTAL			0.75	2.51	2.17	1.01

* To be investigated. Possible solvent or carryover.

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SUMMARY

No differences observed in assay for related substances for API and any formulations.
Recommended PDA analysis on API also.

6. FORMULATIONS BASED ON FLUDARIBINE

Three 100g batches using Cladribine API have been manufactured using the following formulations:

Batch	RDT0385 Fludaribine Formulation	RDT0398a Carbomer Formulation	RDT0398b Cyclodextrin Formulation
Ingredient / mg/batch			
Cladribine API	10.00	10.00	10.00
Hydroxypropyl β-Cyclodextrin			41.79
Carbomer 974P		20.00	
Avicel PH101	21.80	16.7	11.25
Lactose DC11	65.00	50.1	33.76
Crosacarmellose Sodium	2.00	2.00	2.00
Collidol Silicon Dioxide	0.20	0.20	0.20
Magnesium Sterate	1.00	1.00	1.00
Total	100.00	100.00	100.00

Measurement	RDT0385 (IR)	RDT0398a (20% Carbomer)	RDT0398b (Cyclodextrin)
Average tablet weight (mg)	100.1	101.1	103.3
Average Hardness (Kp)	4.9	4.4	3.7
Friability (%)	0.18	0.03	0.18
Thickness (mm)	2.86	3.24	2.92
Disintegration (min)	0.50	> 15.00	6.60

6.1 Fludaribine Formulation: RDT0385

- Assay - 101.4%
- CU - 100.5%, RSD = 3.17%
- UV Dissolution (0.1N HCl) - Max 91% 30 minutes.
- HPLC analysis carried out on dissolution in HCl showed breakdown of Cladribine into impurity D. Only 3% Cladribine remaining after 2 hours dissolution.
- UV Dissolution (buffer pH 6.8) - Slow release. 85% after 240 minutes
- UV Dissolution (Water) - Fast release. 101% after 2 hours.

6.2 Enteric-coated tablets: (Fludaribine Formulation). RDT0385b

- UV Dissolution in 0.1N HCl followed by buffer pH 6.8 - 7.0.
- 7% dissolution after 2 hours in acid, (min 5%, max 18%). On addition of pH 7.0 conditions dissolution increased to 97% after 2 hours (min 84%, Max 107%). After 4 hours in acid, dissolution was 116%.

6.3 20% Carbomer Formulation: RDT0398a

Results may be related to tablet weight i.e. heavier tablet gives higher dissolutions

• Assay	-	113.9%
• CU	-	105.7%, RSD = 6.4%. One result at 123.1%
• UV Dissolution (0.1N HCl)	-	Max 80%, 240 minutes. Slow release profile
• UV Dissolution (buffer pH 6.8)	-	Slow release. 86% after 10 hours. 0.1% Carbomer interference. Further HPLC analysis shows possible Carbomer peak at 4 –5 minutes. 0.2% - 1.0%.
• UV Dissolution (Water)	-	Fast release. 97% after 2 hours.

6.4 Cyclodextrin Formulation: RDT0398b

Cyclodextrin formulation is sub-potent due to extra Mag Stearate added. Estimated potency at 95%.

• Assay	-	89.9%
• CU	-	83.2%, RSD = 3.3%
• UV Dissolution (0.1N HCl)	-	Max 83%, 48 minutes. Degradation occurs.
• UV Dissolution (buffer pH 6.8)	-	Max 76%, 1 hour. No Cyclodextrin interference
• UV Dissolution (Water)	-	Max 86% after 1 hour.

SUMMARY

- Cladribine API is acid labile. Formulation needed to avoid acidic stomach conditions.
- No degradation observed in water, buffer pH 4.5 and buffer pH 6.8
- API IDR matches Cilag estimated solubility. Best IDR in water.
- Solubility issue in buffer pH 6.8. Dissolution values are less than assay results.
- Solubility does not seem to be a problem in water. Dissolution results matching assay and CU.
- Fludaribine formualtion shows fast release in water and slow release in buffer pH 6.8.
- Carbomer formulation allows for slow release. Carbomer impurity (approx 1.0%) present in chromatography.

Some spurious CU results (121%) indicating possible processing problems with Carbomer 974P or high levels of Carbomer.

- Possible potency issue with Cyclodextrin formulation. Only getting 90% assay and dissolution. Immediate release in buffer and water.

7 BUCCAL AND GRANULE FORMULATIONS WITH DICLOFENAC API

Six batches using Diclofenac Sodium in place of Cladribine API were manufactured to explore the development of buccal / sublingual and mucoadhesive tablets as patentable cladribine formulations.

Formulation:

	RDT0399a Buccal tablet	RDT0399b Buccal tablet	RDT0399d Granule (Carbopol 974P)	RDT0399e Granule (Carbopol 974P)	RDT0399f DC tablet (Carbopol 71G)	RDT0399g DC tablet (Carbopol 71G
Ingredient/ mg/tablet						
Diclofenac	10.00	10.00	10.00	10.00	10.00	10.00
Sodium CMC	2.50	5.00				
Sorbitol	87.00	84.50				
Carbopol 974P			2.50	10.00		
Carbopol 71G					2.50	10.00
Avicel PH101			86.80	79.30		
Avicel PH102					21.75	19.88
Lactose DC11					65.25	59.63
Aerosil			0.20	0.20		
Mag. stearate	0.50	0.50*	0.50	0.50	0.50	0.50

***Extra 0,5mg/tablet added to minimise picking.**
RDT0399c was manufactured as RDT0399a placebo.

Physical parameters:

Measurement	RDT0399a	RDT0399b	RDT0399f	RDT0399g
Tooling/shape	Concave	Flat /Concave	Concave	Concave
Average tablet weight (mg)	95.8	94.5	95.1	99.7
Average Hardness (Kp)	3.76	2.10	2.94	2.46
Friability (%)	1.35	0.60	0.00	0.00
Thickness (mm)	3.07	2.90	2.95	3.10
Disintegration (min)	2min 34sec	4min 45sec	>15min*	>15min**

*Tablet formed a soft globular mass with adhesive properties
** Tablet formed a globular mass with strong adhesive properties. Mass was dry in center after 15 mins.

NOTE: Diclofenac has solubility problems in 0.1N HCl.
Diclofenac Na dissolves 16% - 20% in 0.1N HCl.

7.1 Buccal / Sublingual:

RDT0399a + RDT0399b:
Manufactured using Sodium CMC at 2.5 – 5 % respectively.

- UV Dissolution of approx 70% after 10 hours in simulated saliva solution. 68% dissolution after 30 minutes.
- Assay of 70%.
- No obvious reason for low results.
- Poor taste from tablets. Possible Diclofenac Na taste. Recommend 2mg drug formulation per 100 mg tablet to inhibit possible taste issues.

7.2 Mucoadhesive granule for HGC fill:

NOTE: Carbopol 71G may offer better flow properties due to its granular nature which may alleviate possible processing problems.

RDT0399d:
Manufactured using Carbopol 974P at 2.5%.

- 5% dissolution in 0.1N HCl after 2 hours. 97% dissolution after 3 hours in pH 7.0 buffer.

RDT0399e:
Manufactured using Carbopol 974P at 10%.

- 6% dissolution in 0.1N HCl after 2 hours. 91% - 99% after 3 hours in pH 7.0

7.3 Mucoadhesive Direct compression tablet:

RDT0399f:
Manufactured using Carbopol 71G at 2.5%.

- 5% dissolution in 0.1N HCl after 2 hours. 76% after 3 hours in pH 7.0

RDT0399g:
Manufactured using Carbopol 71G at 10%.

- 2% dissolution in 0.1N HCl after 2 hours. 90% after 3 hours in pH 7.0

All tablet formulations flowed and compressed well.
The granulated product produced a good strong granule. Milled through a 0.075 inch comil screen.

7.4 Tablet within a tablet formulation:

Outer tablet coat used to protect Cladribine from acidic stomach conditions.

Dissolution in 0.1N HCL followed by buffer pH 6.8. Tablets completely disssolved in acid (86% - 95%) after 25 minutes. No advantage.

8 PHASE SOLUBILITY TESTING

Table 1. Solubility of cyclodextrins in water (g/100 ml)

Temperatur e (°C)	ACD	BCD	GCD	HPCD
20.0	10.1	1.55	23.2	360.0
25.0	13.0	1.85	30.0	--
30.0	16.0	2.25	38.5	--
40.0	25.6	3.52	63.5	--

PROTOCOL FOR PHASE SOLUBILITY STUDIES OF CLADRIBINE IN PRESENCE OF CYCLODEXTRIN

Reported Solubility of Cladribine in Water is 5 mg / ml

TABLE 1

SOLUTION SYSTEMS	Solution of CD, 800 mg in 4ml B.soln	DRUG ADDED
A	2ml B. Soln (400 mg)	25 mg
B	2ml B.soln. + 2ml D.Water (200 mg)	25 mg
C	2 ml soln. B + 2 ml D.Water (100 mg)	25 mg
D	2 ml soln. C + 2 ml D.Water (50 mg)	25 mg
E	2 ml soln. D + 2 ml D.Water (25 mg) * * Use only 2 ml of solution for testing	25 mg
F	2 ml D.Water (0.0 mg)	25 mg

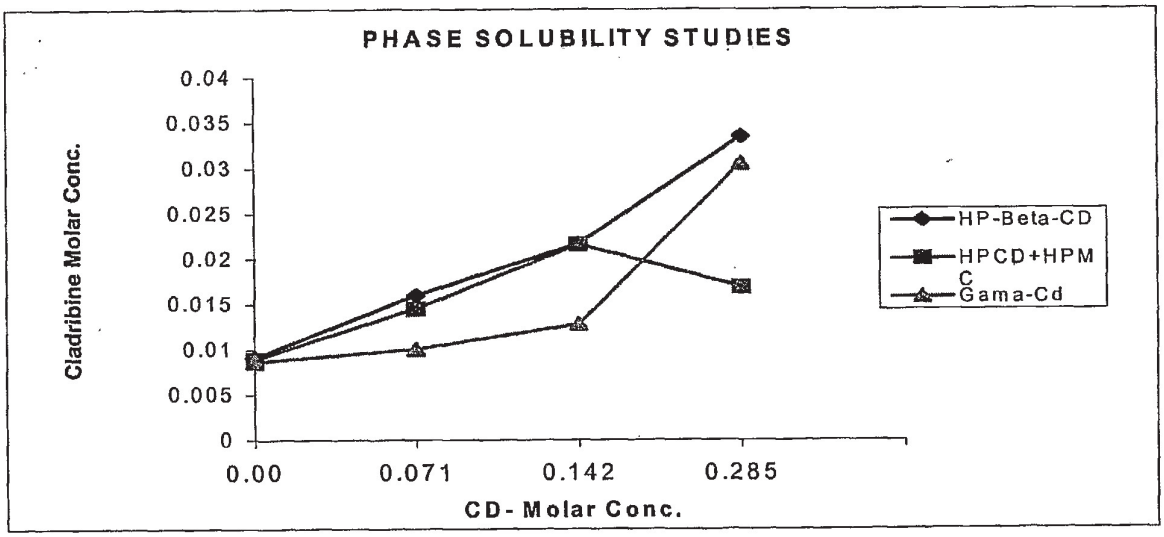
Cyclodextrin
B.soln. – Bulk Solution
D.Water – Deionised Water

Method for preparation.

1. In screw capped vials take 2 ml Cyclodextrin solutions as mentioned in Table 1 .
2. Add respective quantity of drug in each vial.
3. Allow the samples to sonicate for 30 minutes.
4. Remove the samples from sonicator and place on shaker for 8 hrs.
5. The sample after shaking is filtered to get clear supernant.
6. Analyse the sample by UV at 265 nm wavelength.

RESULTS:

CD Conc.	Cladribine –HP betaCD (Trial A)			Cladribine -HP betaCD + HPMC(0.1%) (Trial B)			Cladribine -gama- CD (Trial C)		
CD Conc.	Absorbance	mg/ml	Molar concn.	Absorbance	mg/ml	Molar concn.	Absorbance	mg/ml	Molar c
0.00	0.140	2.610	0.0091	0.137	2.550	0.0089	0.132	2.459	0.0086
0.018	0.169	3.139	0.011	0.146	2.711	0.0095	0.1352	2.519	0.0088
0.035	0.191	3.554	0.0124	0.175	3.262	0.0114	0.1531	2.852	0.0100
0.071	0.245	4.570	0.016	0.223	4.149	0.0145	0.1542	2.873	0.0101
0.142	0.333	6.211	0.0217	0.332	6.185	0.0216	0.1965	3.661	0.0128
0.285	**0.514**	**9.581**	**0.0335**	**0.259**	**4.831**	**0.0169**	**0.4688**	**8.733**	**0.0306**



Observations:

- The best solubility results are obtained with HP-beta CD as complexing agent.
- With HP-beta CD + HPMC (0.1%) results are similar to HP-beta CD , at higher concentration fine precipitation was observed in the vials at the end of the study.

  Absorbance of this sample is low and indicates precipitation of solubised drug
- Absorbance with Gama-Cyclodextrin is low as compared with HP-beta CD.
- Ball park solubility of 9.581 mg/ml in comparison to 5 mg/ml solubility with API alone.

SUMMARY

- Cyclodextrin/Cladribine complex showed increased Cladribine solubility
- Complex sent for freeze-drying.
- Cladribine API ground to decrease particle size (10g)
- Process buccal and sublingual tablets using freeze-dried material
  Issues regarding taste and poor assay, dissolution on previous buccal tablets.
  Information on buccal formulation work in Miami.
- Continued investigation into oral dosage formulations:

  1. **Tablet-within-tablet:**
     High viscosity HPMC in outer formulation for protection against acidic stomach conditions.

  2. **Soft gel capsule:**
     10g API sent to Czechslovakia for trials.

  3. **Dry emulsion formulation:**
     Dummy emulsion to be made with freeze-dried sample

9 CLADRIBINE FREEZE-DRIED CYCLODEXTRIN COMPLEXES

9.1 Cyclodextrin Complex Formulations for Buccal/Sublingual Dosage forms

PRODUCT			Gamma – CD Tablets	Gamma-CD Sorbitol Tablets	Gamma-CD + Cladribine Complex Tablets	HPCD +Cladribine Complex Tablets
Batch No.			RDT 0418A	RDT 0418B	RDT 0418C	RDT 0418D
Code	Ingredient	Lot no.	Mg / Tablet	Mg / Tablet	Mg / Tablet	Mg / Tablet
FD-01	Gamma -CD	N/A	213	213	-	-
FD-02	Gamma-CD +Cladribine	N/A	-	-	235	-
FD-03	HPCD + Cladribine	N/A	-	-	-	218
RE0484	Sorbitol	1F290	-	5.0	-	-
RE0541	Magnesium Stearate	1C130	2.0	2.0	2.0	2.0

9.2 Manufacturing Process

Cyclodextrin FD / Complex

(18 Mesh)

↓

Magnesium Sterate / Lactose pre-mix

(40 Mesh)

↓

Turbula Mixer (5 min)

↓

Manesty Single station F-press
(220 mg, 10.0 mm round concave UP/ Flat Bevelled LP)

OBSERVATIONS

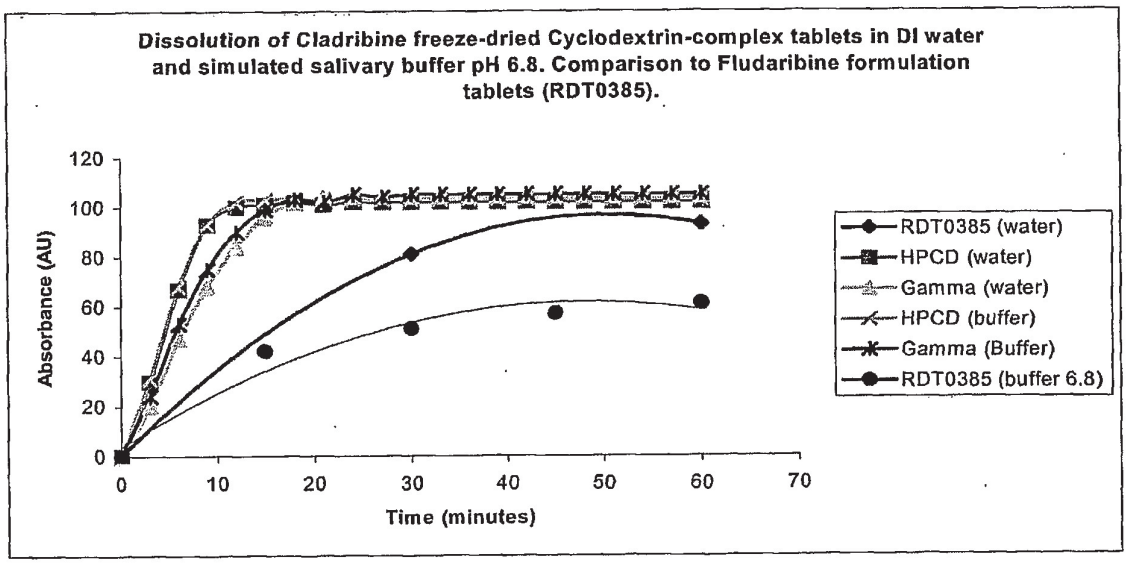
- Flow and compressibility good for all fractions.

- No picking noticed

9.3 Physical Parameters

- Average weight: A) 215 mg, B) 220 mg, C) 237mg, D)220mg.
- Average Hardness: 3- 4 Kp
- Thickness : 3.2 mm - 3.4 mm
- Disintegration Time : 6 – 7 minutes (Water/ Simulated Saliva Buffer)

9.4 Dissolution profiles of freeze-dried buccal tablets in water and simulated salivary buffer solution



Simulated Saliva Solution: 2.38g Na_2HPO_4, 0.19g KH_2PO_4 and 8g NaCl in 1 litre of distilled water, pH 6.75, at 37°C

9.5 Results

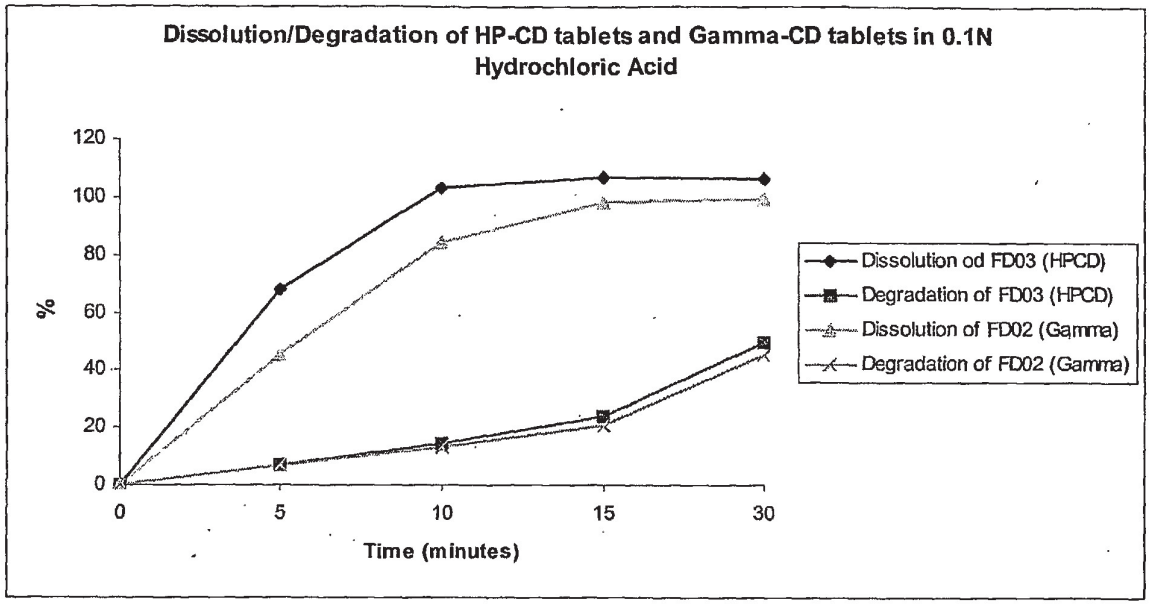
- **Increased Dissolution time.**
  HP-CD. 100% dissolution in salivary buffer after 10 minutes.
  Gamma-CD. 100% dissolution in salivary buffer after 15 minutes

  HP-CD. 100% dissolution in water after 10 minutes.
  Gamma-CD. 100% dissolution in salivary buffer after 15 - 18 minutes

- **Increased Solubility.**

100% dissolution attained for both tablet types in both buffers. Comparison to Fludaribine formulation dissolution in water and buffer show faster dissolution and greater solubility.

9.6 Dissolution and Degradation profiles of freeze-dried Cladribine-Cyclodextrin complex buccal tablets in 0.1N HCl



- Degradation of Cladribine peak to Impurity D observed. 10 – 15% after 10 minutes. 100% dissolution after 10 – 15 minutes.
- By optimising complexation, we can further inhibit acidic degradation of the drug in the stomach whilst increasing drug availability for absorption.