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Original Article

DEVELOPMENT AND CHARACTERIZATION OF BILAYER TABLETS OF CANDESARTAN CILEXETIL

Dr. Vijaya Kuchana,[1] Ayesha Farooqui*[1], Peddireddy. Pravalika Reddy[1], Bathula. Bharathi[2]

[1]Department of Pharmaceutics, Teegala Krishna Reddy College of Pharmacy, Medbowl, Meerpet, Saroornagar, Hyderabad-500079, Telangana, India.

[2]Syncorp Clincare Technologies Pvt. Ltd, Hyderabad, India.

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Abstract

Candesartan is primarily used as Anti- Hypertensive which is poorly soluble drug. It is available as salt form of Cilexetil i.e., Candesartan Cilexetil included under Class –II of Biopharmaceutical classification system. The objective of the current investigation is development and characterization of bilayer tablets containing Candesartan Cilexetil. Frequent administration and variable low bioavailability after oral administration are problems of conventional dosage forms which can be overcome by designing a suitable form of bilayer Tablets. Candesartan bilayer tablets were formulated by using sodium alginate, HPMC, ethyl cellulose. All the formulations evaluated for Pre-compression parameters. Bilayer tablets then evaluated for post compression parameters such as weight variation, hardness, disintegration, friability, thickness and dissolution studies. The optimized formulation showed 99.85% drug release in 12hours. Thus F8 was chosen as best formulation. All the formulations showed uniformity in hardness, weight variation, thickness, friability and content uniformity within limits. The kinetic models used were Zero-order equation, First order equation, Higuchi's model and Peppa's models. The correlation coefficient values (R^2) indicate that the drug release was following zero order release kinetics and Higuchi diffusion mechanism. Stability studies were carried out in accordance with ICH Guidelines Q1 showed that there was no significant change in % release of drug after 3 months indicating that the formulation is stable.

Keywords: Candesartan Cilexetil, HPMC, Sodium alginate, Ethyl cellulose, Bilayer tablets, in vitro drug release studies

Correspondence Address:
Ayesha Farooqui Department of pharmaceutics, Teegala Krishna Reddy College of Pharmacy, Medbowl, Meerpet, Saroornagar, Hyderabad-500079, Telangana, India. Email Id: Ayesha_farooqui12@yahoo.com.

1. INTRODUCTION

Candesartan is a nonpeptide angiotensin II type 1 receptor antagonist used in the treatment of hypertention and congestive heart failure.[1]

Bilayer tablet is new era for successful development of controlled release formulation along with various features to provide successful drug delivery system[2]. Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in

which one layer is immediate release as loading dose and second layer is maintenance dose.[3] The immediate release layer of bilayer tablet has worked as the loading dose and the sustained release layer has maintained therapeutic plasma drug concentration for prolonged time[4].

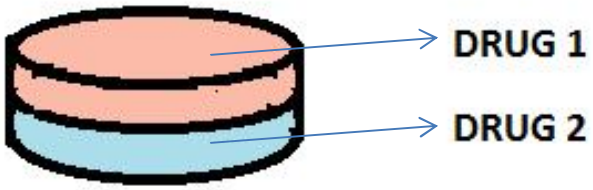

Figure-1: Bilayer tablet

2. MATERIALS AND METHOD

MATERIALS

Candesartan was obtained from Aurbino laboratories, India. HPMC k 100M, Ethylcellulose, Sodium alginate, Crospovidone, Sorbital, Microcrystalline cellulose, Povidone, Isopropyl alcohol, Magnesium stearate and talc were purchased from S. D. Fine Chem. Labs. (Mumbai, India) All other ingredients used throughout the study were of analytical grade and were used as received.

METHOD

Direct compression method[6,7]

Preparation of tablets

Preparation of Immediate layer

Drug and superdisintegrant (Crospovidon) pass through 40 # mesh separately and then transfer it to poly bag and mix it for 3 minutes. Add other excipients to the above mixture. Finally add the Glidant (Magnesium Stearate) to the above blend mix it for 2min.

Preparation of Sustained layer

Drug and polymer (Sodium alginate or HPMC K100 or Ethylcellulose) pass through 40 # mesh separately and then transfer it to poly bag and mix it for 3 minutes. Add other excipients to the above mixture. Finally add the Glidant (Magnesium Stearate) to the above blend mix it for 2min. Compressed the above lubricated blend by using 8mm round punches.

Table 1-: Formulation development

1	Candesartan	16	16	16	16	16	16	16	16	16
2	Sodium alginate	20	---	---	40	---	---	20	---	20
3	Hpmc k100m	---	20	---	---	40	---	---	20	20
4	Ethyl cellulose	---	---	20	---	---	40	20	20	---
5	Microcrystalline Cellulose	160	160	160	160	160	160	160	160	160
6	Mg.stearate	2	2	2	2	2	2	2	2	2
7	Talc	2	2	2	2	2	2	2	2	2
8	Wt	300	300	300	300	300	300	300	300	300
	Immediate layer									
S. no.	**Ingredients**	**F1 (mg)**	**F2 (mg)**	**F3 (mg)**	**F4 (mg)**					
1	Candesartan	5	5	5	5					
2	Crospovidon	8	8	8	8					
3	Sorbitol	85	85	85	85					
4	Magnesium stearate	2	2	2	2					
5	Talc	2	2	2	2					
S. no.	**Ingredients**	**F5 (mg)**	**F6 (mg)**	**F7 (mg)**	**F8 (mg)**	**F9 (mg)**				
1	Candesartan	5	5	5	5	5				
2	Crospovidon	8	8	8	8	8				
3	Sorbitol	85	85	85	85	85				
4	Magnesium stearate	2	2	2	2	2				

5	Talc	2	2	2	2	2	

EVALUATION PARAMETERS

Drug excipient compatibility studies[8]

Drug excipients compatibility studies were performed to know the compatibility of excipient with drug at accelerated conditions. The study was conducted by preparing homogenous mixture of excipients with drug and filled in HDPE bags and LDPE bags Samples were observed periodically for any physical change.

I. Pre compression parameters[9,10]

A. Angle of repose

Weigh accurately of the powder was passed through a funnel. In this funnel put at a height 2 cm from the base. Then the powder is passed till it forms a heap and touches the tip of the funnel. The radius the base of the conical pile, and the height of pile were measured and the angle of repose was calculated using the formula.

$$\tan^{-} = h/r$$

Where,

h=height of the pile

r=radius of the base of the conical pile

θ=angle of repose

B. Bulk density and Tapped density

Weighed quantity of the Candesartan was poured into 100 ml measuring cylinder. The volume occupied by the drug was measured, and then subjected to 500, 750, 1250 taps in the tap density tester (electro lab USP II), the blend was subjected to 500, 750.taps respectively then the percentage variation in volume was calculated, if it is more than 2 then the blend has to be subjected for 1250 taps and the percentage variation in volume has to be calculated.

Bulk density is denoted by (ρ_i)

$\rho_i = m/v_i$

Tapped density is denoted by (ρ_t)

$\rho_t = m/v_t$

m=mass of the blend

V_i = initial volume

V_t =tapped volume

C. Compressibility index (CI)

The compressibility index was expressed in percentage calculated using the formula

$$CI = \frac{TD - BD}{TD} \times 100$$

D. Hausner's ratio

It is determined by the ratio of tapped density and bulk density.

$$\text{Hausner's ratio} = \left(\frac{v_i}{v_i}\right) \text{or} \frac{TD}{BD_S}$$

II. Post compression parameters[12,13,14]

A. Weight variation

Take prepared 20 tablets were unsystematic selected form each batch and separately weighed. After that average weight of tablets was calculated.

B. Thickness

Ten tablets were unsystematically selected form single batch and these 10 tablets thickness was measured by using vernier caliper. Thickness of three tablets from each batch was measured and mean was calculated.

C. Hardness

The hardness of the tablets was determined using Pfizer hardness tester. It is expressed in kg/cm. Take 3 tablets were unsystematically choose and hardness of the tablets were determined.

D. **Friability**

It is the disposition for a tablet to chip, break following compression. This tendency is normally restricted to uncoated tablets during handling and storage. Ten tablets were weighed and placed in the Roche friabilator, which was then operated for 25 rpm for 4 min. After revolution Tablets were dedusted and reweighed. Compressed tablets should not lose more than 1% of their weight.

$$\% F = \{1-(Wo/W)\} \times 100$$

Where,

% F = friability in percentage

Wo = Initial weight of tablet

W = weight of tablets after revolution**.**

E. Content Uniformity

Twenty tablets from each batch were powdered and weighed accurately equivalent to 300mg Candesartan . Required amount of tablet powder transferred into 100 ml of 7.4 phosphate buffer solution by stirring it for 15 min. 1 ml of solution was pipette out into 10 ml volumetric flask and make up the volume with distilled water. After that sample solution analyze the drug by taking absorbance at 257 nm using reagent blank.

F. *In- Vitro* Release study

In vitro drug release was studied using USP II apparatus, with 900 ml of dissolution medium maintained at 37±1°C for 15 h, at 50 rpm. 0.1 N HCl (pH 1.2) was used as a dissolution medium for the first 2 h, followed by pH 7.4 phosphate buffers for further 10 h. 5ml of sample was withdrawn in different time intervels, and was replaced by an equal volume of fresh dissolution medium of same pH. Collected samples were analyzed spectrophotometrically at 257 nm, and cumulative percent drug release was calculated. The study was performed in triplicate.

G. Stability studies[16, 17]

The purpose of stability testing is to obtain a stable product which assures its safety and efficacy up to the end of shelf life at defined storage conditions and peak profileCandesartan bilayered tablets were placed on desiccant and stored at ambient conditions such as 37 ^{o}c and 40±2^{o}c and refrigerator 2-8^{o}c for a period of 3 months.

3. RESULTS & DISCUSSION

Table-2: Calibration curve of Candesartan in 0.1 N Hcl

S. No.	Concentration(µg/ml)	Absorbance
1	0	0
2	10	0.179
3	20	0.401
4	30	0.612
5	40	0.836
6	50	1.056

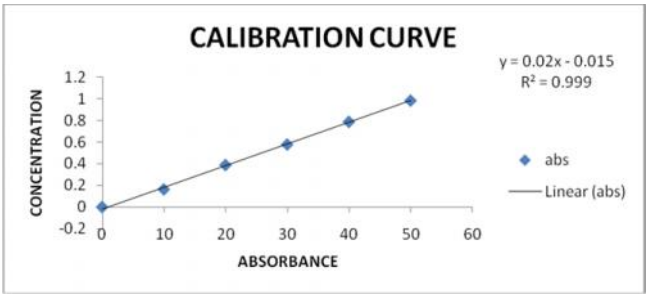

Figure-2: Calibration curve of Candesartan

Standard curve of Candesartan in 6.8 phosphate buffer**Table-3: Calibration curve of Candesartan in 7.4 phosphate buffer**

S. no.	Concentration (µg/ml)	Absorbance
1	0	0

2	10	0.164
3	20	0.389
4	30	0.579
5	40	0.789
6	50	0.985

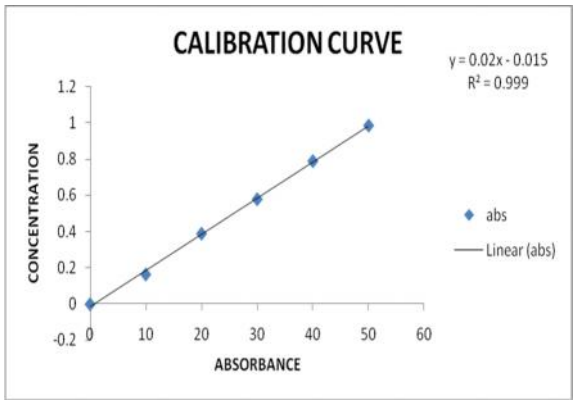

Figure-3: Calibration curve of Candesartan in 7.4 phosphate buffer

FTIR Studies

Infra-red spectroscopy analysis was performed by Fourier Transformation Infrared Spectrophotometer Alpha Brooker FTIR (Tokyo, Japan).The instrument was calibrated by using polystyrene film.

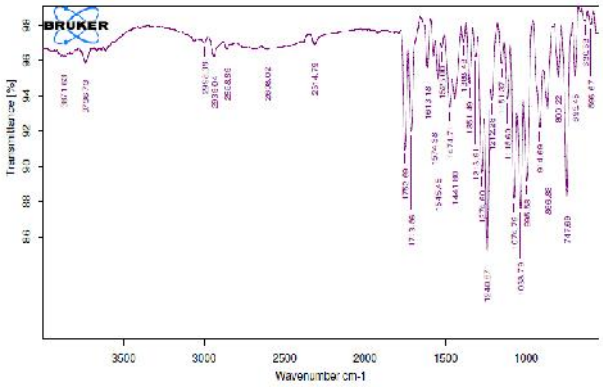

Figure-4: FTIR Spectra of Candesartan

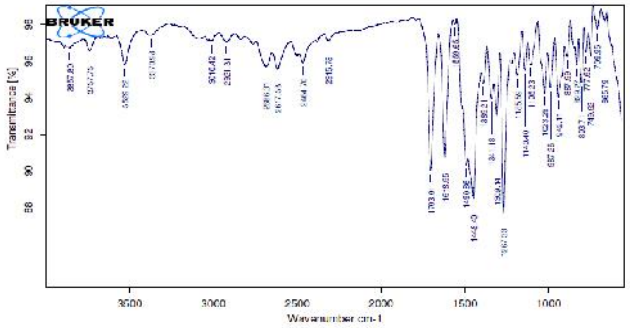

Figure-5: FTIR Spectra of Optimized formulation

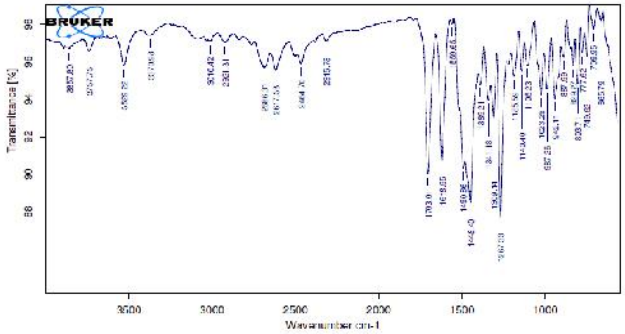

Figure-6: FT-IR Sample for Best Formulation for Immediate Release

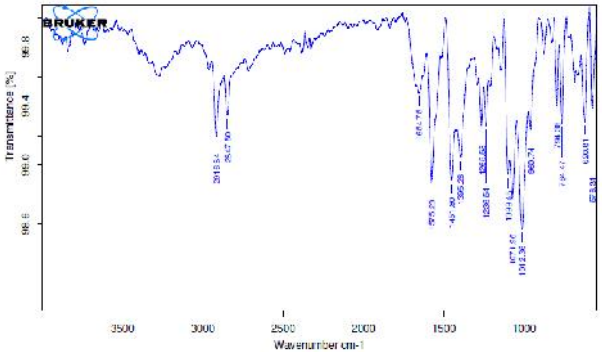

Figure-7: FT-IR Sample for Best Formulation Sustained Release Formulation

Evaluation parameters

All formulations were tested for Physical parameters like Hardness, thickness, Weight Variation, Friability and found to be within the Pharmacopoeial limits. The results of the tests were tabulated. The drug content of all the formulations was determined and was found to

be within the permissible limit. This study indicated that all the prepared formulations were good.

Table -4: Results for Evaluation parameters of all formulations

parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
Weight variation	300±0.4	299±0.3	298±0.7	300±0.1	299±0.3	300±0.2	299±0.9	300±0.8	399±0.1
Thickness (mm)	2.5±0.4	2.6±0.4	2.3±0.4	2.6±0.4	2.5±0.4	2.5±0.3	2.5±0.2	2.5±0.1	2.5±0.2
Hardness (kg/cm^2)	7.9±1.4	7.2±1.2	7.2±1.2	7.9±0.9	7.4±1.9	7.1±1.7	7.2±1.5	7.3±1.6	7.2±1.4
Friability	0.19%±0.2	0.26%±0.23	0.19%±0.19	0.17%±0.26	0.18%±0.22	0.15%±0.1	0.10%±0.4	0.18%±0.5	0.13±0.7
Content uniformity	95.01%±0.2	96.4%±0.4	98.7%±0.3	98.8%±0.2	99.8%±0.3	99.19%±0.2	99.98%±0.2	99.56%±0.2	99.46%±0.2

Table -5: Results of Dissolution profile for F1-F9

Time	F1	F2	F3	F4	F5	F-6	F-7	F-8	F-9
0	0	0	0	0	0	0	0	0	0
1	25.92	22.67	28.67	21.61	19.61	24.57	18.43	21.41	23.61
2	59.36	57.67	61.91	47.56	43.96	58.63	40.54	42.94	48.56
4	78.21	75.24	82.91	71.62	68.65	73.35	64.65	67.43	70.62
6	97.92	94.72	98.72	85.83	81.44	86.29	78.37	79.94	83.83
10	100	100	100	98.26	94.83	96.21	89.47	93.59	96.26
12	-	-	-	100	100	100	96.28	99.86	100

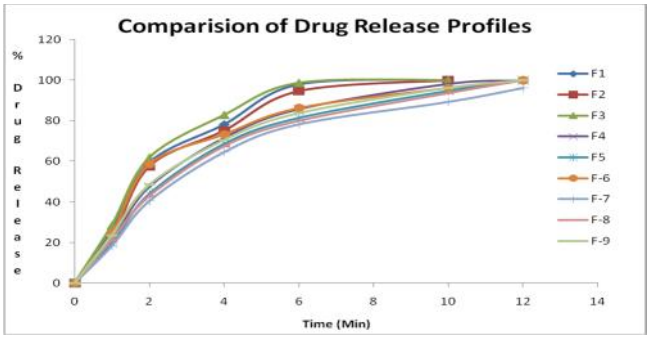

Figure-8: Dissolution studies of all formulations

Kinetic models

Dissolution data of above two methods was fitted in Zero order, First order and Higuchi equations. The mechanism of drug release was determined by using Higuchi equation.

Table -6: Drug release kinetics

S.NO	time	log T	Square root of Time	%CR	%Drug remaining	log %CR	Log % drug retained	cube root of % drug remaining
0	0	0	0	0	100	0	2	4.641589
1	1	0	1	18.43	81.57	1.265525	1.91153	4.336874
2	2	0.30103	1.414214	40.54	59.46	1.607884	1.774225	3.903088
3	4	0.60206	2	64.65	35.35	1.810569	1.548389	3.281934
4	6	0.778151	2.44949	78.37	21.63	1.89415	1.335057	2.786242
5	10	1	3.162278	89.47	10.53	1.951677	1.022428	2.191843
6	12	1.079181	3.464102	96.28	3.72	1.983536	0.570543	1.549462

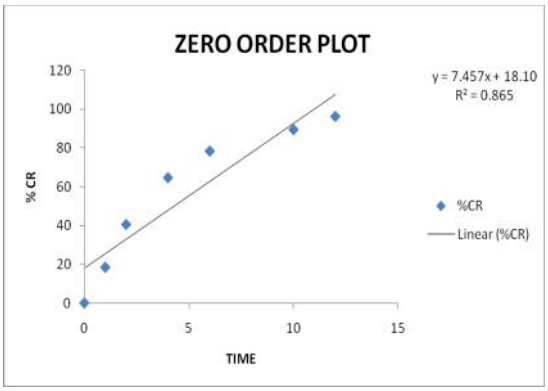

Figure -9: zero order plot for optimized formula

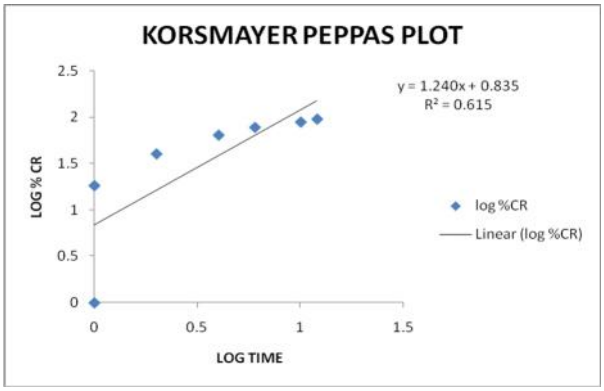

Figure-12: Korsmayer peppas plot for optimized formula

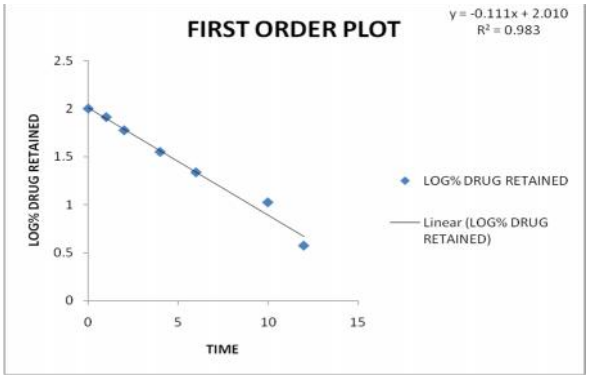

Figure-10 : First order for optimized formula

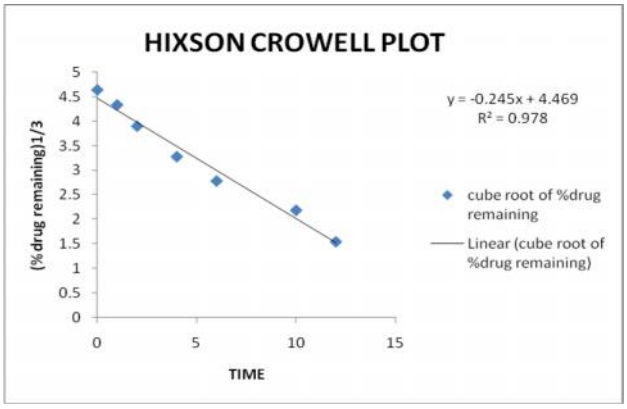

Figure -13: Hixson crowell plot for optimized formula

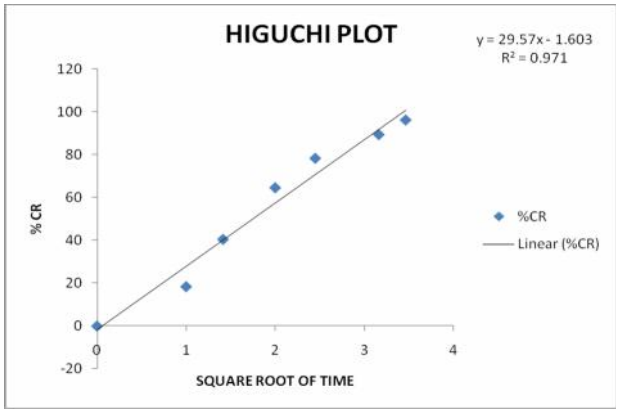

Figure-11: Higuchi plot for optimized formula

4. CONCLUSION

The objective of the present study is to develop bilayered tablets of Candesartan. In this present study an attempt was made to increase the therapeutic effect of Candesartan by continuously releasing the drug up to an extended period of time by formulating the bilayered tablets having two different layers i.e. immediate and sustained layer.

Systematic studies were conducted using different concentration of rate releasing polymers like Sodium alginate, HPMC K100 and Ethyl cellulose for extending the drug release up to 12 hrs. And immediate layer prepared by using croscarmellose sodium as a superdisintegrant. All the prepared systems were evaluated for the different properties. Before the preparation of tablets, preformulation studies to find out the micromeritic properties to assess flowability, compressibility properties and

solubility studies. And all the formulations gave good results for above preformulation studies.

Formulated tablets gave satisfactory results for various physical tablet evaluation parameters like tablet dimensions, hardness, friability, weight variation, content uniformity, all the formulations were found within the permissible range.

Finally it was concluded that:

Amongall the formulations (F1-F9), it was observed that formulation-7 has shown better dissolution profile. So Formulation-8 was found to be the best formulation when compared with other prepared formulations. All the polymers were used at the different concentrations in the formula, much difference were observed in the release characteristics of the bilayered tablets prepared. The release data were analyzed as per zero order, first order, Higuchi, Hixson crowell and Korsmeyer & Peppas models. The correlation coefficient (r^2) values in the analysis of release data as per various models are mentioned. Analysis of the release data as per zero order and first order kinetic models indicated that the drug release from bilayered tablets formulated followed first order kinetics. The correlation coefficient (r^2) values were higher in first order model when compared to zero order models. As per Peppas equation of F-7 shows the release exponent 'n' was found 1.240 in the case of bilayered indicating super case-II transport as the release mechanism from these tablets.

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