Original Article

Journal of Pharmaceutical and Medicinal Chemistry
Volume 9 Number 2, July – December 2023
DOI: http://dx.doi.org/10.21088/jpmc.2395.6615.9223.1

Formulation & Evaluation of Famotidine Transdermal Patches by using Different Polymers

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How to cite this article:
Lakshman Vinod Kumar V, Lakshmana Rao A, Sai Datri A, *et al.*/Formulation & Evaluation of Famotidine Transdermal Patches by using Different Polymers/J Pharmaceut Med Chem. 2023;9(2): 51-58.

Abstract

Purpose: The main objective of the present research investigation is to formulate transdermal patches of famotidine using different polymers. Famotidineis a H^2 blockers.

Methods: The transdermal patches of famotidine were prepared employing different concentrations of HPMC, and Ethyl cellulose.

Results and Discussion: All patches exhibited satisfactory characteristics regarding integrity, flexibility, dispersion of drug, and other quality control parameters. In the invitro release studies of transdermal patches, formulation F10 showed the prolonged release of drug (88%) for 12 h, which indicates the maximum availability of the drug. The kinetic studies were carried out and it was found that all the formulations follow zero order and the release mechanism of drugs was found to be diffusion rate limited, Non-Fickian mechanism which was confirmed by Korsmeyer–Peppas model.

Conclusion: This suggests the transdermal application of Famotidine holds the promised controlled release of the drug for an extended period of time.

Keywords: Famotidine; Transdermal patches; HPMC; and Ethyl cellulose.

INTRODUCTION

The transdermal drug delivery system (TDDS) is also called as "patches." Conventional dosage forms such as tablets or capsules have limitations like poor bioavailability owing to hepatic first pass metabolism or degradation of drug by enzymatic reactions in gastrointestinal tract (GIT). TDDSs have the ability to enhance bioavailability by preventing the first pass metabolism and enzymatic or acid mediated degradation.[1] Delivery through the transdermal route is a fascinating and patient compliant novel drug delivery system and delivers the drug through epidermis in controlled rate within the therapeutic window.[2]

Famotidine belongs[3] to a class of drugs known as H^2 blockers. Famotidine is available under the following different brand names: Pepcid, Zantac 360, Act, Dyspep HB, Fluxid, and Acid Controller.

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Received on: 01.06.2023 **Accepted on:** 30.08.2023

Famotidine is used to prevent and treat heartburn due to acid indigestion and sour stomach caused by eating or drinking certain foods or drinks. Prescription famotidine comes as a tablet and a suspension (liquid) to take by mouth. It is usually taken once daily at bedtime or two to four times a day.

MATERIALS

Famotidine was obtained as a gift sample from Dr. Reddy's Laboratories Ltd, Hyderabad. PVA, Potassium dihydrogen phosphate, Sodium hydroxide were purchased from Thomas Baker (Chemicals) Pvt Ltd, Mumbai. HPMC E5 was purchased from Loba Chemie Pvt Ltd, Mumbai. PVP, Methanol, Chloroform, Dibutyl phthalate, DMSO were purchased from Research Lab Fine Chem Industries, Mumbai. Eudragit L100 was purchased from Rohm Pharma, Germany. All the other reagents were all of the analytical grades.

METHODS

Pre-formulation Studies of Drug:

Organoleptic Properties: Color, odor, taste, and state were determined.

Determination of Melting Point: The melting point was determined by the capillary method. The temperature at which the drug melted was recorded.

Determination of UV Absorption Maxima: The identification of drug was done by UV spectrophotometric method. From the spectra, λ max of Famotidine was observed at 263 nm. The spectral data from this scan was used for the preparation of a calibration curve of Famotidine.[4]

Fourier Transform Infrared Analysis: FTIR analysis of the sample was employed for compound identification (FTIR-8400S Shimadzu). The powdered drug was scanned from 400 to 4000 cm^{-1}.

Determination of Solubility: The solubility analysis for Famotidine was done by solubility determination in different solvents like Water, Chloroform, DMSO, Ethanol, Methanol, etc.

Determination of Partition Coefficient: The partition coefficient was determined by dissolving 10 mg of drug in separating funnels containing 10 ml portion of each of n-Octanol and PBS pH 7.4. The separating funnels were shaken on mechanical shaker for 24 hours. Two phases were separated and aqueous phase was filter through what man filter paper and the amount of the drug in aqueous phase was determined spectrophotometrically at 263 nm.[5]

Calibration of Famotidine: Stock solution was prepared by dissolving 100 mg of Famotidine in 100 ml methanol in a volumetric flask. An aliquot of desired concentration was prepared. The absorptivity coefficient of the drug at 263 nm was determined.

Drug-excipients Compatibility Studies: A small quantity of drug with an excipient was placed in a vial, and stoppered from above by rubber cork and sealed properly. A storage period of about 2 weeks at 60°C and the same sample was retained for 2 months at 40°C. After storage, the sample was observed physically for liquefaction, caking, odor or gas formation, discoloration.[6]

Preparation of Famotidinetransdermal patches:

The method adopted for preparing transdermal patches was the solvent casting technique. Drug along with polymer was dissolved in methanol and sonicated for 30 mins until to get a homogenous semisolid consistency. PEG 4000 is added finally as a plasticizer. The prepared solution was cast into petridish containing mercury as a substrate and allowed to dry at room temperature for 48 hours. The dried patches were collected andstored in a desiccator until used for further study.

Evaluation of Transdermal Patches:

Physical Evaluations:

Thickness: The thickness of films was measured by digital Vernier calipers with least count 0.001mm. The thickness uniformity was measured at three different sites and average of three readings was taken with standard deviation.[7]

Flatness: The constriction of patches cut out from a drug loaded matrix patch is an indicator of its flatness. Longitudinal strips were cut out from the prepared medicated patch, the lengths of each strip were measured and then variation in the lengths due to the non uniformity in flatness was measured. Flatness was calculated by measuring construction of strips and a zero percent constriction is equal to a hundred percent flatness.[8]

Constriction (%) = L1 L2/ L2 x 100

Where L1 = initial length of each strip, L2 = final length of each strip.

Folding Endurance: A strip of specificarea is to be

cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of the folding endurance.[9]

Drug Content: The patch of specified area was cut and dissolved in phosphate buffer 6.8 pH. It is kept aside for some time to make polymer soluble, then 1 ml was withdrawn from the solution and diluted to 10 ml. The absorbance of the solution was taken at 263 nm and concentration was calculated by correcting dilution factor, the drug content was calculated.[10]

Weight Variation: The three disks of 3.14 cm^2 was cut and weighed on electronic balance for weight variation test. The test was done to check the uniformity of weight and thus check the batch-to-batch variation.[11]

Swellability: The patches of 3.14 cm^2 was weighed and put in a petridish containing 10ml of double distilled water and were allowed to imbibe. Increase in weight of the patch was determined at present time intervals, until aconstant weight was observed.[12]

The degree of swelling (%S) was calculated using the formula

S (%) = Wt – Wo/Wo x 100

In-vitro Permeation Study: The release studies from formulated patches were carried out by using Franz diffusion cell in order to determine delivery and permeation of drug from the skin in to the body.[13] The drug release data of all formulations were fitted to various mathematical models such as zero order as cumulative % of drug released vs. time, first order as log cumulative % of drug remaining vs. time and Higuchi's model as cumulative % drug released vs. square root of time. To determine the mechanism of drug release from formulations, the data were fitted into Korsmeyer Peppas equation as log cumulative % of drug released vs. log time.[14]

Stability study (As per ICH guidelines): Stability studies of formulations was conducted according to ICH guidelines by storing at 40°C and 75% RH for 3 months. The samples were withdrawn at 30, 60 and 90 days and evaluated for physical appearance and drug contents. The ex-vivo permeation study was performed after 90 days and compared with fresh batch.[15]

RESULTS

Pre-formulation studies:

The pre-formulation study was performed in order to assure the accuracy of drug sample and determination of various parameters for formulation of transdermal patch.

Table 1: Composition of Famotidine transdermal patches

Formulation Code	Ingredients				
	Drug (mg)	Ethyl cellulose (mg)	HPMC K15M (mg)	PEG 4000 (mg)	Methanol (mg)
F1	20	10	_	50	10
F2	20	20	_	100	10
F3	20	30	_	150	10
F4	20	40	_	200	10
F5	20	50	_	250	10
F6	20	_	10	50	10
F7	20	_	20	100	10
F8	20	_	30	150	10
F9	20	_	40	200	10
F1	20	_	50	250	10

Identification of drug:

Organoleptic properties: Organoleptic properties of the drug were found within limits as shown in Table 2.

Table 2: Organoleptic properties of the drug

Properties	Inference
Color	White to off-white
State	Crystalline powder
Odor	Odorless

Melting Point: Melting point of drug was found to be 163 ± 1 °C which compared with previously reported value (162 to 163 °C) indicated that the drug sample was pure.

UV Absorption Maxima: The maximum absorbance of drug in methanol was found to be at λ max 263 nm.

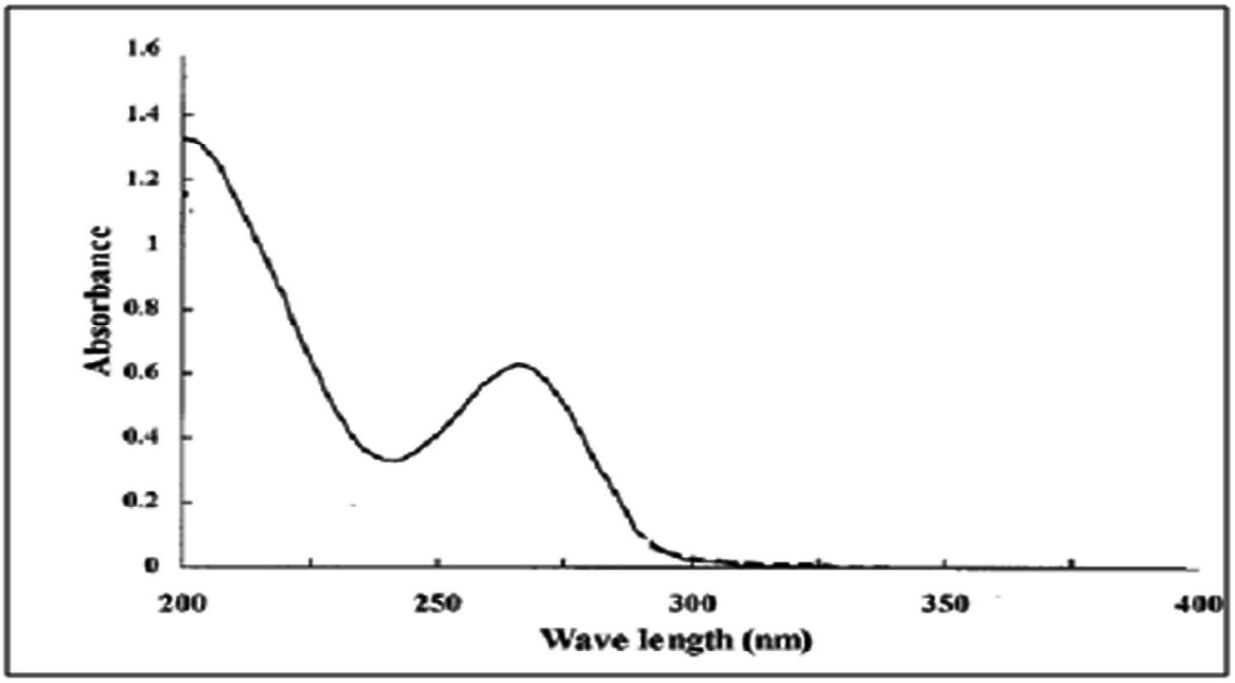

Fig. 1: UV spectra of Famotidine in methanol

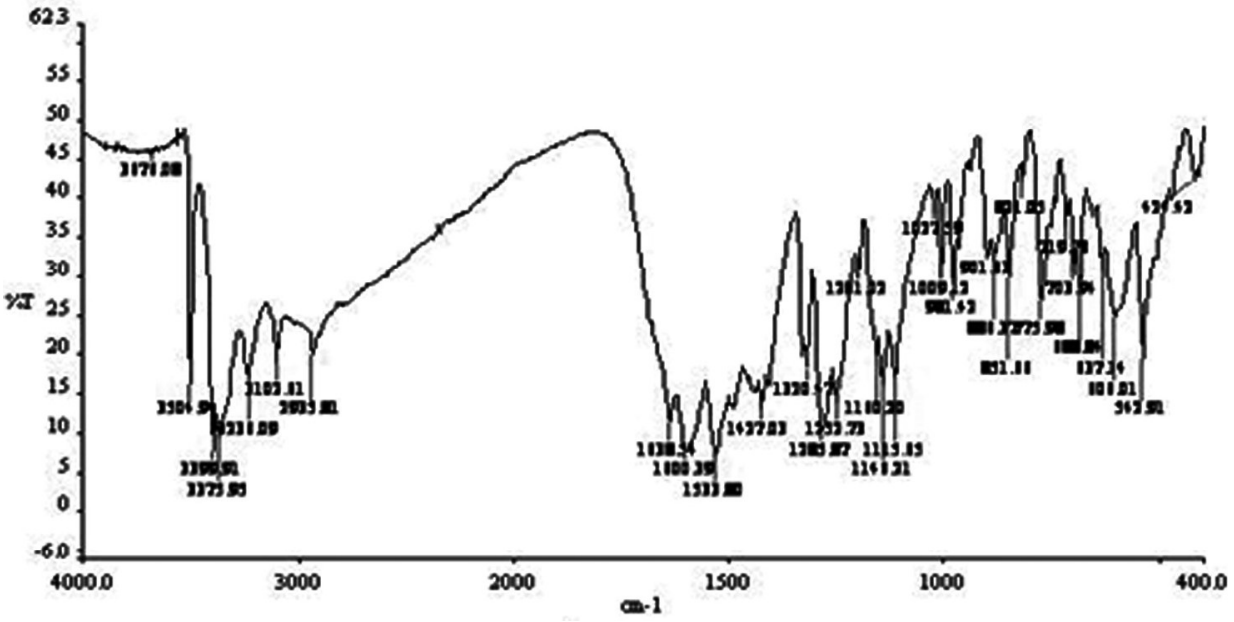

Fig. 2: FTIR spectra of pure drug

Fourier Transform Infrared Analysis: The FTIR analysis of the drug was carried out for compound identification. The powdered drug was placed carefully over sample holder for scanning. The FTIR spectrum for pure drug is shown in Fig. 2.

Solubility: The solubility study revealed that the drug sample was Freely soluble in dimethylformamide (80) and glacial acetic acid (50), slightly soluble in methanol (0.3) and water (0.1).

Partition Coefficient: The logarithmic value of partition coefficient value was experimentally found to be 0.23. This revealed the hydrophobic nature of Famotidine and further indicated that it is a suitable candidate for transdermal drug delivery.

Calibration:

Table 3: Calibration Curve for the Estimation of Famotidine

Concentration (µg/ml)	Absorbance at 263 nm (x ± SD)
0	0.0000±0.000
2	0.1746±0.0014
4	0.3342±0.0022
6	0.4987±0.0048
8	0.6672±0.00168
10	0.8366±0.0067

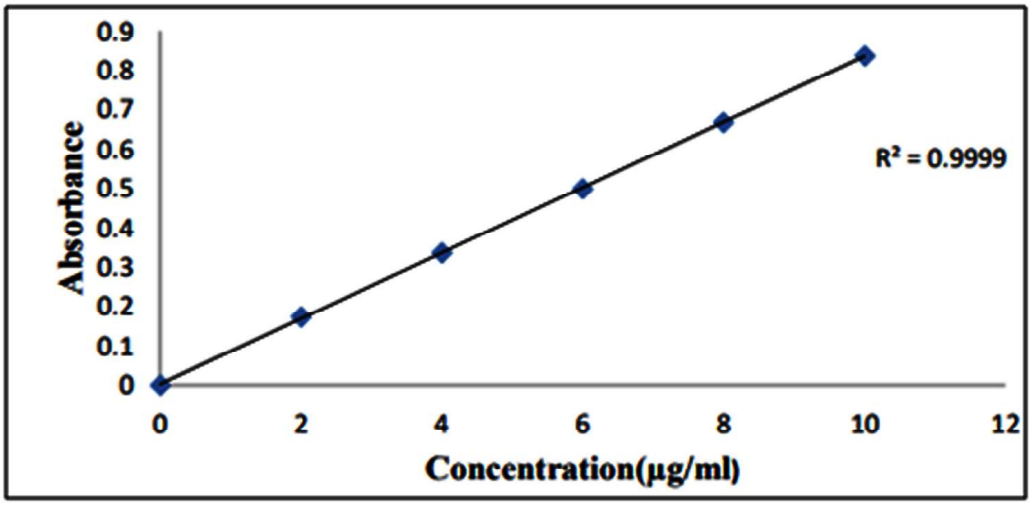

Fig. 3: Calibration Curve for the Estimation of Famotidine in 6.8 pH Phosphate Buffer

Table 4: Evaluation of Famotidine Transdermal Patches

Formulation Code	Weight Variation (mg)	Thickness (mm)	Drug Content (mg)	Folding Endurance	% Swellability	Flatness
F1	67+0.06	0.066+0.01	7+1.0	97.7±4.1	87.08±0.43	100
F2	120+0.08	0.126+0.04	8+0.6	98.3±3.5	86.00±0.47	100
F3	181+0.09	0.133+0.01	8+0.3	98.3±5.0	87.33±0.58	100
F4	230+0.01	0.240+0.04	9+1.2	94.2±2.0	90.90±0.49	100
F5	301+0.06	0.170+0.01	9+0.5	101.2±2.0	94.33±0.57	100
F6	70+0.08	0.209+0.01	8+0.1	94.3±5.0	85.47±0.54	100
F7	130+0.09	0.130+0.02	9+0.1	93.0±3.6	86.71±0.46	100
F8	180+0.01	0.228+0.02	9+0.3	97.0±4.0	89.66±0.55	100
F9	240+0.06	0.123+0.01	9+0.7	96.3±3.5	80.90±0.49	100
F10	320+0.06	0.140+0.04	9+0.2	98.3±3.5	82.90±0.49	100

Table 5: *In-vitro* Drug Release data of Famotidine Transdermal Patches

Time (hrs.)	Cumulative % drug released									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	8.99	12.45	17.34	20.44	24.55	10.89	14.55	16.11	19.44	22.55
2	13.78	19.55	23.77	28.45	34.22	15.23	25.77	31.55	26.45	31.22
4	20.11	24.44	26.99	33.5	44.63	23.14	34.55	46.88	31.5	42.63
6	28.9	35.14	39.8	46.71	63.23	32.45	39.02	69.09	44.71	60.23
8	33.57	44.66	47.23	55.42	74.63	42.5	57.88	75.55	52.42	71.63
10	49.78	66.23	73.26	77.11	81.54	57.89	65.66	79.67	72.11	80.54
12	62.09	72.11	79.56	80.22	84.89	60.32	71.99	76.35	81.22	88.59

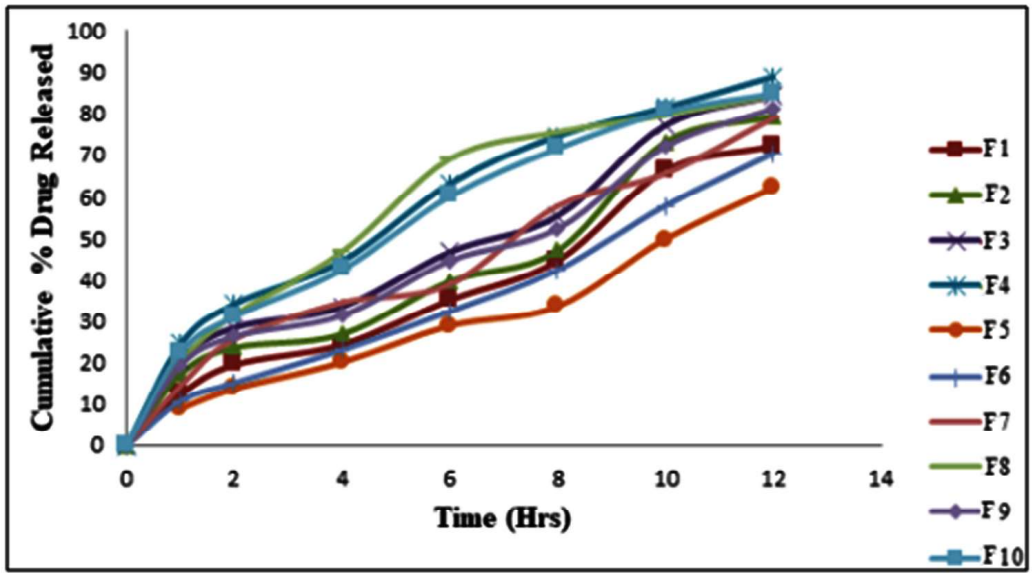

Fig. 4: ***Invitro*** Drug Release Profile of Famotidine Transdermal Patches

Table 6: Diffusion Parameters of Famotidine Transdermal Patches

Formula	Zero order		First order		Higuchi constant		Peppasconstant	
	R^2	K (mg)	R^2	K (hr^{-1})	R^2	K ($mg.h^{1/2}$)	R^2	N
F1	0.801	3.343	0.947	0.092	0.936	2.088	0.942	0.564
F2	0.824	3.603	0.929	0.075	0.978	1.835	0.972	0.656
F3	0.855	3.641	0.964	0.067	0.967	1.734	0.966	0.653
F4	0.981	3.433	0.944	0.071	0.956	2.750	0.992	0.756
F5	0.947	4.35	0.981	0.073	0.992	2.739	0.994	0.799
F6	0.875	3.03	0.955	0.076	0.977	1.983	0.967	0.587
F7	0.888	3.319	0.984	0.073	0.924	2.105	0.978	0.631
F8	0.879	2.345	0.926	0.068	0.971	2.165	0.969	0.757
F9	0.834	3.003	0.949	0.065	0.978	2.806	0.962	0.556
F10	0.805	3.841	0.954	0.077	0.957	1.004	0.936	0.653

DISCUSSION

Transdermal drug delivery is an alternative route for systemic drug delivery which minimizes the absorption and increases the bioavailability. In the present study Famotidine was selected as the drug candidate, Famotidine is an oral medication that belongs to a class of drugs called Histamine receptor blockers (Antihistamines) which is used in the treatment of high stomach acid secretion and allergies. It is soluble in methyl acetate, n-butyl acetate, acetonitrile, N, N-dimethylformamide, dichloromethane, chloroform, alcohol. Slightly soluble in water. Famotidine is readily absorbed from the gastrointestinal tract. After oral doses, it undergoes extensive first pass metabolism in the liver mainly to the primary metabolite.

TDDS are drug containing devices of defined surface area that deliver pre-determined amount of drug to the intact skin at a pre-programmed rate. The transdermal delivery has gained importance in recent years. The transdermal drugdelivery system has potential advantages of avoiding hepatic first pass maintaining constant blood levels for longer period of time resulting in a reduction of dosing frequency, improved bioavailability and decreased gastrointestinal irritation that occur due to local contact with gastric mucosa and improved patient compliance.

In the present study transdermal patches of the Famotidine were prepared using polymers like Ethyl cellulose and HPMC K15M. The drug remained intact and stable in the TDDS during storage, with no significant chemical interaction between the drug and the excipient.

The various formulations of patches were developed for Famotidine using polymers like Ethyl cellulose and HPMC K15M by solvent casting method with the incorporation of PEG 4000 as plasticizer. These transdermal patches were characterized for their physical properties.

Physical parameters such as weight uniformity, thickness uniformity, drug content determination, swellability, Flatness and folding endurance studies were carried out. From the results of the drug content determination, it was inferred that there was proper distribution of drug in the patches and the deviations were within the acceptable limits. The prepared patches exhibited satisfactory physical characteristics such as weight uniformity, thickness uniformity and folding endurance.

CONCLUSION

Transdermal patches of Famotidine have been successfully prepared. Evaluation of the prepared patches in terms of physical appearance, weight, thickness, flatness, tensile strength, moisture absorption, moisture uptake and drug content uniformity recommend that the method employed for formulation of the transdermal patches was reproducible and assured outstanding quality and uniformity in patch characteristics with least variability. Further, in-vitro drug release studies for all the formulations exhibited the drug release and nearly complete release (88%) was achieved in 12 h. These results show that transdermal delivery of Famotidine can have probable applications in therapeutic areas providing advantages by reducing dosing frequency, improving patient compliance, non-invasive character, improved bioavailability, and easy termination of therapy.

Source of Funding: None.

Conflicts of Interest: There are no conflicts of interest.

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