Research Article

Formulation, Development and Evaluation of Intraconazole Gastro Retentive Tablet

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ABSTRACT

The aim of this research was to prepare and evaluate sustained release mucoadhesive tablets of Itraconazole. Solid dispersion of Itraconazole was prepared to improve solubility and bioavailability of Itraconazole. The prepared solid dispersion was subjected for different evaluation such as FTIR spectroscopy and in vitro drug release from solid dispersion and the data for such studies gives the satisfied results. The tablets were prepared by direct compression of solid dispersion (drug and Poloxamer 188) of ratios 1:1 and 1:2. In the present study, various mucoadhesive polymers such as sodium alginate, guar gum was selected. All the formulated tablets were subjected for different evaluation parameters such as Hardness, Friability, Weight Variation, thickness, Swelling study, In-vitro drug release and Diffusion from mucoadhesive tablets. The optimized formulation was subjected for accelerated stability study for the six months. When values of absorbance of the formulations were put in PCP disso software we get best fit model and value for that formulation. As seen that the best fit model for formulations FG3 and FG5 is peppas with n value of 0.6929 and 0.6954 respectively. This shows the Non fickian diffusion of drug and release mechanism of drug from guar gum is due to water penetration, gelatinization and diffusion. From the result of present work it was concluded that this drug delivery system can be a better alternative to the conventional drug delivery systems by the virtue of its enhanced bioavailability and site specific absorption.

Keywords: Itraconazole, Mucoadhesive drug delivery systems, Solid dispersion, Chitosan, sodium alginate.

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INTRODUCTION

The triazoles are first-line agents for the prevention and treatment of invasive and allergic fungal infections. Itraconazole (cis-4[4-4-4[[2-(2-4-dichlorophenyl)- 2-(1H-1,2,4-triazol-1-methyl)-1,3-dioxolan-4-yl]-1-piperazinyl]phenyl]-2,4-dihydro2-(1-methyl-propyl)-3H-1,2,4 triazol-3-one) was initially synthesized in 1980 and has broad-spectrum antifungal activity. Itraconazole was the first orally bioavailable triazole with activity against medically important opportunistic filamentous fungi such as Aspergillus spp.[1]. Itraconazole is still used for the treatment of allergic and invasive aspergillosis, superficial candidiasis, dermatophyte infections, sporotrichosis, blastomycosis, histoplasmosis, penicilliosis and coccidioidomycosis[2]. Mucoadhesive drug delivery systems are delivery systems which utilize the property of bioadhesion of certain polymers which become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for extended periods of time. Bioadhesion is an interfacial phenomenon in which two materials, at least one of which is biological, are held together by means of interfacial forces. The attachment could be between an artificial material and biological substrate, such as adhesion between a polymer and a biological membrane. In the case of polymer attached to the mucin layer of a mucosal tissue, the term "mucoadhesion" is used[3]. This study aimed at developing mucoadhesive dosage forms containing a solid dispersion of itraconazole with amount of two swellable polymers.

MATERIALS AND METHODS

The drug Itraconazole was a gift samples. Sodium alginate, Chitosan 86.60% DOD, Guar gum, Pluronic F-68 was procured from Loba chem, Mumbai. All other chemicals used in the study were of analytical grade.

Preparation of solid dispersion of Itraconazole

Solid dispersions of itraconazole were prepared by the hot melt method. The mixture of Itraconazole and poloxamer 188 was heated to a liquid state and cooled in an ice bath immediately, leading to rapid solidification. Itraconazole in poloxamer- 188 in various proportions such as 1:0.5, 1:1 and 1:2 was taken for preparation of Solid dispersion[5].

Evaluation of solid dispersions

FTIR spectroscopic studies

The FTIR spectra of the free drug, poloxamer 188 and selected solid dispersion of drug and poloxamer 188 ratio were recorded with Jasco FT/IR spectrophotometer -4100.

The samples were prepared by using potassium bromide and scanned for absorbance 4000-400 cm^{-1}.

In-vitro drug release from solid dispersion

The dissolution rate of various solid dispersions was studied using Electrolab Dissolution Apparatus. An accurately weighed sample of solid dispersion equivalent of 100 mg drug was filled in capsule and dissolution study performed in 900 ml Simulated gastric juice pH 1.2. USP method (apparatus I) at 37º C ± 1º C and stirred at 100 rpm. A 5ml aliquot of dissolution medium was withdrawn at various time intervals and analyzed spectrophotometrically at 254 nm using Jasco UV V-530 spectrophotometer [7].

Preparation of mucoadhesive tablet of Itraconazole containing its solid

Dispersion

The tablets were prepared by direct compression of solid dispersion (drug and Poloxamer 188) of ratios 1:1and 1:2. In the present study, various mucoadhesive polymers such as sodium alginate and guar gum were selected. Tablet batches were designed considering formulations containing single polymers. Tablets were prepared as per the compositions shown in Table 1 for 1:2 ratio and Table No.2 and Table No.3 show composition of 1:1 ratio of solid dispersion. All ingredients were sieved through mesh #100. Each tablet contained 100 mg equivalent of itraconazole in selected solid dispersion; Solid dispersion and polymers were homogeneously blended using mortar and pestle and directly compressed into 11 mm flat beveled tablet using a tablet compression machine (Karnavati) [6].

Table 1: Batch prepared by direct compression using 1:2 ratio of solid dispersion.

Ingredients	AA1	AA2	AA3	AA4	AA5	AA6	AA7	AA8
Sodium alginate (mg)	50	50	50	50	60	60	60	60
Chitosan (mg)	10	15	20	30	35	50	60	70
Solid dispersion (mg)	300	300	300	300	300	300	300	300
Total Weight (mg)	360	365	370	380	395	410	420	430

Sodium alginate as mucoadhesive polymer

Table 2: Optimized batch prepared by direct compression using solid dispersion.

Ingredients	FA1	FA2	FA3	FA4	FA5	FA6	FA7	FA8
Sodium alginate (mg)	50	50	40	50	50	50	50	35
Chitosan (mg)	50	60	75	75	80	85	90	75
Solid dispersion (mg)	200	200	200	200	200	200	200	200
Tablet TotalWeight (mg)	300	310	315	325	330	335	340	310

Guar gum as mucoadhesive polymer

Table 3: Optimized batch prepared by direct compression using solid dispersion

Ingredients	FG1	FG2	FG3	FG4	FG5	FG6	FG7	FG8
Guar gum (mg)	80	80	70	70	65	65	60	60
Chitosan (mg)	20	10	15	10	25	15	25	10
Solid dispersion (mg)	200	200	200	200	200	200	200	200
Tablet TotalWeight (mg)	300	290	285	280	290	280	285	270

Evaluation of mucoadhesive tablets of Itraconazole containing its soliddispersion

All the formulated batches were subjected for basic evaluation of tablets such as Hardness, Friability, Weight Variation, and Thickness [6].

Swelling study

The swelling of the polymers can be measured by their ability to absorb water and swell. The swelling property of the formulation was determined by various techniques the water uptake study of the tablet was done using USP dissolution apparatus II. The medium used was 0.1N HCL, 900 ml rotated at 100 rpm. The medium was maintained at 37±0.5°C throughout the study. After a selected time interval, the tablets were withdrawn, blotted to remove excess water and weighed. The weight of the swollen tablet was calculated. The swelling index (S.I.) was determined from the following relation:

Swelling Index (%) = (Wt – W0 / W0). 100

Where, Wt is the weight of the swollen tablet at each interval t,

Wo is initial wt of the tablet.

In-vitro drug release from mucoadhesive tablets of Itraconazole containing its solid dispersion

The drug release studies were performed by USP Type II dissolution test apparatus. The 0.1N HCl was used as dissolution medium. The temperature and speed of the apparatus were maintained at 37±0.50C and 100 rpm respectively. The samples were withdrawn at predetermined time interval and analyzed for drug concentration at 254 nm by UV-Visible spectrophotometer after filtration. The readings were taken in triplicate [7].

Diffusion from mucoadhesive tablets of Itraconazole containing its solid dispersion

The diffusion study of Itraconazole through the stomach mucosa was performed using Franz-type diffusion cells at 37º C ± 1º C. Mucosa was obtained from a local slaughterhouse and used within 3 hours of slaughter. The mucosa was Stored in Krebs buffer at 4ºC upon collection. The epithelium was separated from underlying connective tissues with surgical scissors and mucosa was clamped between donor and receiver chambers of the Franz-type diffusion cell. The temperature was maintained at 37º C ± 1º C by a jacket surrounding the receiver chamber that was stirred gently with a magnetic bead. After the membrane was equilibrated with mixture of ethanol/ phosphate buffer saline (PBS) pH 7.4 solution between both the chambers, the receiver chamber was filled with a mixture of fresh ethanol/Phosphate buffer saline (PBS) pH 7.4 solutions. Itraconazole permeation from the mucoadhesive tablet was measured by sticking the tablet wetted with 300 µL of PBS to the mucosa in the donor side. Aliquots (2 ml) were collected from receiver chamber at predetermined time intervals (every hour for 8 hours) and the equivalent volume of fresh dissolution medium, which was prewarmed at 37ºC, was then replaced into the diffusion cell. The amount of Itraconazole permeated through the stomach mucosa was then determined by measuring the absorbance at 254 nm using Jasco UV V-530 spectrophotometer. The experiments were performed in triplicate (n = 3) and mean value was used to calculate the flux [8-9].

Accelerated Stability Study

The best formulation (DS) selected after the evaluation of preliminary data was considered for stability studies. Stability studies were done at a temperature of 40 ºC ± 2ºC and humidity 75% ± 5%RH. The formulation was evaluated initially and after a period of 6 months for the following parameters: Drug content, Water Sorption Study (Swelling study), Measurement of the mucoadhesive strength, Thickness, Hardness, weight variation, invitro drug release[10].

RESULTS AND DISCUSSION

FTIR spectroscopic studies

The FTIR spectrum of Itraconazole Solid dispersions with ratios (1:2, 1:1) dispersedin KBr are shown in figure 01. In the case of solid dispersion of itraconazole and poloxamer -188 both the drug and polymer peaks were present. The spectra have no difference in the position of the absorption band especially with respect to –OH, -CH and =O hence providing the evidence for the absence of hydrogen bonding interaction in solid state between itraconazole and poloxamer -188. Poloxamer -188 contains around 70% polyoxyethelene units. When solid dispersion is prepared, it forms a eutectic mixture. Both the compounds may simultaneously crystallize out as very small particles. The increase of specific areas due to reduction of particle size generally increases rate of dissolution of drug.

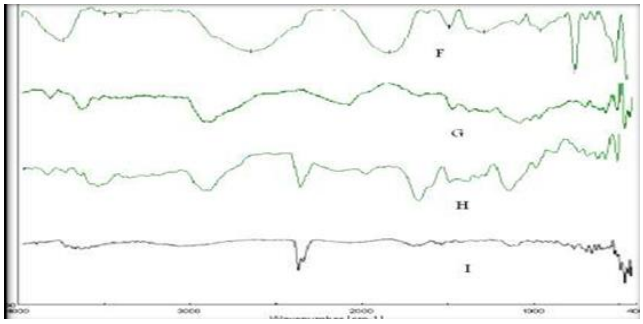

Figure 1: FTIR spectra of F (Solid dispersion of drug and poloxamer 1:1 ratio), G (FG5 Formulation prepared using guar gum as polymer), H (FA4 Formulation prepared using Sodium alginate as polymer), I (Chitosan)

***In-vitro* drug release from Solid dispersion**

Percent drug release of solid dispersions prepared by various ratios of drug and poloxamer-188 i.e.,1:0.5, 1:1 and 1:2 is depicted in Table 04. From the table it is cleared that solid dispersion prepared by using 1:0.5 ratio of Drug: Poloxamer 188 gives drug release of only 70.29% in 60 minutes. Solid dispersion of 1:1 ratio gave drug release of 76.077 % in 60 min. and 1:2 ratio of solid dispersion gave 79.605% drug release in 60 min. Based on above results it was observed that solid dispersion 1:0.5 did not provide intended drug release so it was not included in further study. Further study was carried out on the solid dispersions having 1:1 and 1:2 ratios.

Table 4: Percentage release of Itraconazole from solid dispersion powder atvarious ratios.

Time (Minutes)	Ratio 1:0.5	Ratio 1:1	Ratio1:2
0	0.00%	0.00%	0.00%
10	49.539 %	50.951%	56.142%
20	66.841%	68.759%	73.647%
30	67.875%	72.212%	76.214%
40	68.788%	73.441%	77.630%
50	69.331%	74.759%	78.719%
60	70.077%	76.077%	79.211%

Table 5: Evaluation of plain Itraconazole tablets

Sr. no	Formulation code	% Friability	Thickness (mm)	Hardness (Kg/Cm^2)	Weight variation
1	F1	0.69	3.0 ± 0.02	3.5 ±0.9	185 ± 0.25
2	F2	0.62	3.4 ± 0.03	3.8 ±0.5	220 ± 0.28
3	F3	0.59	3.1 ± 0.04	3.6 ±0.7	195± 0.37
4	F4	0.62	3.6 ± 0.01	3.7 ± 0.9	230± 0.48
5	F5	0.56	3.2 ± 0.04	3.4 ± 0.6	150± 0.45
6	F6	0.62	3.2 ± 0.05	3.7 ±0.9	160 ± 0.57
7	F7	0.59	3.1 ± 0.03	3.8 ±1.1	140 ± 0.12
8	F8	0.57	3.2 ± 0.06	3.4 ±0.9	150 ± 0.24
9	F9	0.47	3.0 ± 0.04	3.5 ±1.1	140 ± 0.47
10	F10	0.48	3.0 ± 0.02	3.7 ±0.6	135 ± 0.33
11	G1	0.59	3.3 ± 0.05	3.7 ±1.0	170 ± 0.36
12	G2	0.62	3.3 ± 0.07	3.6 ±0.7	165 ± 0.42
13	G3	0.57	3.2 ± 0.01	3.4 ±0.5	160 ± 0.51
14	G4	0.52	3.2 ± 0.04	3.7 ±0.4	155 ± 0.19
15	G5	0.41	3.1 ± 0.09	3.5 ± 0.7	150 ± 0.18
16	G6	0.57	3.0 ± 0.06	3.5 ±0.7	145 ± 0.24

Table 6: Swelling index mucoadhesive table of itroconazole solid dispersion

Batchcode	1 hrs.	2 hrs.	3 hrs.	4 hrs.	5 hrs.	6 hrs.	7 hrs.	8 hrs.
FA1	40.2	100.2	160.1	266.1	275.4	270.1	262.4	255.3
FA 2	50.2	117.2	185.1	276.4	299.4	290.1	285.4	279.2
FA 3	51.1	120.2	187.2	280.2	303.2	292.3	284.4	276.3
FA 4	55.2	130.2	210.5	303.1	340.3	310.2	280.2	276.1
FA 5	58.4	135.4	210.5	299.3	321.1	310.1	298.2	292.4
FA 6	62.4	142.3	219.2	304.2	327.1	321.5	315.1	311.0
FA 7	65.4	155.2	238	333.2	317.2	310.4	304.1	280.4
FA 8	49.9	112.2	178.2	269	289.2	280.4	271.2	263.4
FG1	22.4	30.2	45.7	58.2	65.4	87.2	101.2	115.4
FG2	20.1	27.4	39.2	51.1	69.7	82.2	96.2	96.9
FG3	22.4	37.8	45.2	57.5	70	87.6	86.2	82.4
FG4	19.9	32.4	42.2	59.4	72.2	79.4	82.2	81.1
FG5	21.2	35.2	42.2	54.4	68.2	84.1	80.1	76.4
FG6	17.1	26.3	32.1	39.4	50.2	66.2	75.1	75.7
FG7	18.1	29.1	35.4	52.2	65.4	79.2	87.6	86.4
FG8	14.5	21.2	29.1	45.3	59.4	73.2	78.2	77.3

Evaluation of mucoadhesive tablet of itraconazole

Swelling Study

Swelling index of various tablets comprising of Sodium alginate, Guar gum and Chitosan with solid dispersion of drug and poloxamer-188 are shown in Table 08. As the amount of polymer in the formulations increases swelling increases for all the polymers. In Formulation FA1 to FA8, high initial swelling was observed with erosion in the latter stages. This high initial swelling was observed due to the greater amount of Chitosan present in the formulation. Guar gum does not swell rapidly. It swells slowly initially and

hence initial burst release of drug from the guar gum matrices occurs. Table 06 shows formulation FA7 swells more i.e., 333.2% in 4 hrs. This is because it contains a large amount of Chitosan. After 4 hrs., erosion mechanism starts those results in decrease in percent swelling. Optimum formulation i.e.FA4 gave a swelling of 340.3% in 5 hrs. While Formulation FG4 gave swelling of 87.6% in 6 hrs., FG5 gave swelling of 82.2% in 7 hrs. Above results suggest that tablet having higher amount of Chitosan swell rapidly and to higher extent while the tablet containing guar gum swell to lesser extent.

Ex-vivo mucoadhesion studies

The amount of sodium alginate in the formulation increases the mucoadhesion of the tablet also increases. Formulation FA7 gives maximum mucoadhesion i.e., 14gm. Formulations of Guar gum as mucoadhesive polymer FG1 and FG3, gave same mucoadhesion i.e., 14gm.

In-vitro drug release from Itraconazole mucoadhesive tablets containing its solid dispersion

In vitro drug release from mucoadhesive tablets prepared by using solid dispersion 1:2 ratio of drug and poloxamer. From the results it is observed that Chitosan and sodium alginate are not able to control the drug release for predetermined time. A tablet prepared by using drug and poloxamer 1:2 ratio of solid dispersion does not remain intact for 8 hrs. It gets disintegrated within 6hrs. This showed that the controlled release of drug was not obtained. The amount of Chitosan is increased for Formulation AA1 to AA6 i.e., from 10mg to 50 mg to control the release but tablet does not remain intact for 6 hrs., so it was decided to increase the amount of Chitosan in next formulation. Formulation AA7 and AA8 contains 60mg and 70 mg of Chitosan respectively. The amount of sodium Alginate was same in both the formulations, but controlled release is not obtained. It means that Chitosan and sodium alginate are not able to provide the required drug release if used in the ratio 1:2. The total weight of the tablet with batch code AA8 is 430mg but we were required to add more amount of Chitosan in formulation to control the drug release, therefore it has been decided to check first the result of drug release from tablet prepared by 1:1 ratio of solid dispersion. The result of drug release of tablet prepared by using 1:1 ratio of solid dispersion for FA1 to FA8 formulations. It is seen that in formulation FA1 and FA2 tablet does not remain intact for 8 hrs., it is due to the presence of less amount of Chitosan in that formulation. Therefore, it has been decidedto increase the amount of Chitosan in the next formulation. Formulation FA3 shows good, controlled release property but due to less amount of sodium Alginate present in the formulation, it does not give required mucoadhesiveness, hence in the next formulation that is FA4, the amount of sodium alginate has been increased. The results show that the tablet gave better control release as well as mucoadhesive property. Percent drug release from the formulation FA4 in 8 hrs. was 75.73% and mucoadhesion was 13.4 gm. That means formulation FA4 gave desired result for both, drug release and mucoadhesion. Increasing amount of Chitosan in next formulations i.e.FA5 to FA7 lead to decrease in drug release. From the result it is observed that formulation FA4 gave optimum result of drug release and mucoadhesion. Drug release of FA4 formulation depends upon the amount of Chitosan present in the formulation. As the amount of Chitosan increases in the formulation, the drug release is decreased. This is because the increase in the amount of Chitosan increases the viscosity of gels formed by Chitosan. In general, the drug release from the tablet is controlled by gel formation of Chitosan in acidic environment, diffusion of drug through the gel and followed by diffusion erosion of gel taking place as a result of dissolution of Chitosan. Sodium alginate present in theformulation also contributes to controlled release of tablets to smaller extent because Sodium alginate has an ability to hydrate and swell. Controlled release of drug may be due to stability of alginate at lower P^H and conversion of sodium alginate to insoluble but swelling alginic acid. When values of absorbance of the formulations were put in PCP disso software we get best fit model and n value for that formulation. As seen from table 10 the best fit model for optimized formulation i.e., FA4 is peppas with n value of 0.7295. The release mechanism was anomalous i.e., Non fickian diffusion which suggests that the drug release from the tablet occurs by swelling as well as erosion. Guar gum has both the properties of controlled release and mucoadhesion so it is used as a polymer for the next formulations. By using guar gum as a mucoadhesive polymer-controlled release of drug was achieved, which is depicted in table 10. In formulation FG1 and FG2 the required drug release was not obtained within 8 hours. This is because, more amount of guar gum was present in those formulations therefore it was decided to decrease the amount of guar gum in next formulations. Formulation FG3, FG4, FG5 gave almost similar kinds of drug release but showed different mucoadhesive properties. Formulation FG5 gave the highest mucoadhesiveness, that is 14.3gm. followed by FG3 which gave mucoadhesion of 14 gm. In formulation FG6, FG7 and FG8 various compositions of guar gum and Chitosan were tried but it didn't give intended drug release and mucoadhesiveness. Guar gum has both the properties of control release and mucoadhesion therefore the amount of Chitosan required in these formulations i.e., FG1 to FG8 was less ascompared to those required for formulations FA1 to FA8. Controlled release from formulations FG3, FG4 and FG5 was achieved because guar gum dissolves and forms pores filled with liquid from which the drug can diffuse. When values of absorbance of the formulations were put in PCP disso software we get best fit model and value for that formulation. As seen, the best fit model for formulations FG3 and FG5 is peppas with n value of 0.6929 and 0.6954 respectively. This shows the Non fickian diffusion of drug and release mechanism of drug from guar gum is due to water penetration, gelatinization and diffusion.

Diffusion of Itraconazole mucoadhesive tablets containing its solid dispersion

As we prepared mucoadhesive tablets of Itraconazole it was adhering to stomach mucosa from one side, there was diffusion of drug from the mucosa. But as the drug diffuses through mucosa of stomach it enters in blood. The P^H of blood is 7.4 and itraconazole is insoluble at basic pH. It is soluble in acidic pH. So the drug does not show any effect in basic condition because it is in insoluble form, still the drug diffusion was checked to note whether there are changes in the properties of drug duringpreparation of solid dispersion of the drug with poloxamer-188. It is cleared that drug do not show any absorbance at basic pH. From the above data the drug does not have diffusion. As justified earlier under dissolution studies basic mechanism of drug release is dissolution.

Accelerated stability studies

The optimized formulations of Itraconazole i.e.FA4, FG3, FG4 and FG5 were subjected to stability studies at 40 ^{O} C ± 2^{O} C, 75 ± 5% RH. for a period of 6 months. The formulations were evaluated initially and after a period of 2,4 and 6 months. The aim of this study was to check the stability of the formulation along with determination of percent of the drug degraded after a span of 3 months.

Table 7: Assay of Itraconazole mucoadhesive tablets kept for Stability Study

Formulation Code	Drug Content (%)			
	Initial	2 Month	4 Months	6 Months
FA4	99.2 ± 1.3	99.0 ± 1.0	98.9 ± 0.7	98.8 ±1.01
FG3	99.4±1.01	99.2 ± 0.9	99.2 ± 1.1	99.1 ± 0.9
FG4	99.1± 1.2	99.0 ± 0.7	98.8 ± 0.9	98.8 ± 0.6
FG5	99.4± 0.8	99.4 ± 1.01	99.3 ± 1.2	99.2 ± 0.8

* Mean ± S.D for n=3

Table 8: Dissolution profile of Itraconazole mucoadhesive tablets kept For Stability Study

Formulation Code	Drug Release (%) after 8 hrs.			
	Initial	2 Month	4 Months	6 Months
FA4	75.734	75.60	75.44	75.57
FG3	74.577	74.50	74.42	74.46
FG4	74.234	74.11	74.05	74.00
FG5	73.523	73.50	73.40	73.32

As seen from the results the tablets showed a slight decrease in hardness and drug content after 6 months when compared to initial readings and were acceptable. As seen from table No.08 in-vitro drug release when compared with initial and after 6 months, it was almost super impossible with a slight decrease in % release and complying with the specifications for the respective categories of formulation**.** All the formulation showed good mucoadhesion to stomach mucosa of sheep.

CONCLUSION

To remedy the poor solubility profile of Itraconazole, solid dispersion of Itraconazole with poloxamer- 188 was prepared using hot melt technique. It improved the solubility of Itraconazole from 58 % to 76%. Present study demonstrated the potential of gastroretentive drug delivery system for controlled release of Itraconazole. Thus, from the data obtained after evaluation the objective of the present study to formulate a gastroretentive drug delivery system of Itraconazole is achieved successfully with the aid of mucoadhesive polymers and solid dispersion. This drug delivery system can be a better alternative to the conventional drug delivery systems by the virtue of its enhanced bioavailability and site-specific absorption. Moreover, patient compliance may be achieved as the dosing frequency is reduced markedly.

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