RESEARCH ARTICLE

Development of trilayered mucoadhesive tablet of itraconazole with zero-order release

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Itraconazole is practically insoluble in water; large interindividual and intraindividual variations of its oral bioavailability are reported. A mucoadhesive drug delivery system is useful to prolong the retention time of a dosage form in the stomach, thereby improving the oral bioavailability of the drug. Solid dispersion of itraconazole with Eudragit E100 was prepared by spray-drying method to improve dissolution. Trilayered mucoadhesive tablet was prepared, with inner core containing solid dispersion of the drug and with carbopol and HPMC sandwiched between two layers of hydrophilic mucoadhesive polymer mixture of carbopol and Hydroxypropyl methyl cellulose (HPMC). Amounts of Carbopol 934P (CP) and Methocel K4M (HPMC) were varied in the outer coat around the solid dispersion. The drug-release pattern for all the formulation combinations was found to be nonfickian, approaching zero-order kinetics. Suitable combination of two polymers provided adequate bioadhesive strength and sustained-release profile with zero-order kinetics.

Key words: *Eudragit E100, itraconazole, mucoadhesive, solid dispersion, trilayer*

INTRODUCTION

Itraconazole is an oral antifungal agent with a broad spectrum of activity. Itraconazole is weakly basic (pKa = 3.7) and highly hydrophobic (octanol/water partition coefficient at pH = 8.1, log *P* = 5.66).[1] It is practically insoluble in water. Hence it is a challenging task to prepare a formulation for oral route of administration. Itraconazole is most effective when drug concentration is maintained above the minimum effective concentration. Studies in immunocompromised patients have shown that plasma concentration below the MEC not only results in poor clinical response but may cause relapse of disease.[2] Large interindividual and intraindividual variations of its oral bioavailability have been reported.[3]

A mucoadhesive drug delivery system can overcome this problem and is particularly useful to prolong the retention time of a dosage form in the stomach, thereby improving the oral bioavailability of the drug.[4]

The strategy for designing Buccal adhesive dosage form is based principally on the utilization of polymers with suitable Physicochemical properties such as hydrophilicity. Combined usage of HPMC and carbopol in delivering clotrimazole for oral candidiasis has been reported.[5]

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Trilayered compacts of metoprolol tartarate have been reported, where one layer consisted of ethyl cellulose; the core consisted of drug with combination of sodium alginate and HPMC K4 M; while the third layer, which was responsible for bioadhesion and release control, consisted of carbopol and HPMC K4 M. Results reinforce the fact that increase in concentration of carbopol increased bioadhesion.[6]

The aim of the current study was to develop trilayered mucoadhesive tablet of itraconazole. The first step involved preparation of solid dispersion of drug with Eudragit E100. This dispersion was then blended and compressed with rate-controlling polymer carbopol and HPMC K4M to form the core. The core was sandwiched between two layers of mixture of hydrophilic mucoadhesive polymers HPMC and carbopol. Drug release and bioadhesive strength (f) was investigated and optimum formulation was arrived at.

MATERIALS AND METHODS

Materials

Itraconazole was a gift sample from Muralikrishna Pharmaceuticals Ltd. (Chennai, India); Methocel K4M, from Colorcon Asia Pvt. Ltd. (Goa, India); Carbopol 934P, from M/s Loba Chemie Ltd. (Mumbai, India); Eudragit E100, from Degussa, India; and lactose, from M/s Loba Chemie Ltd. (Mumbai, India). All other chemicals used in the study were of analytical grade.

Preparation of solid dispersion

Solid dispersion of itraconazole with Eudragit E100 was prepared by spray-drying technique.[7,8] Drug and carrier were dissolved in dichloromethane in different ratios and spray-dried using Labultima spray dryer, model LU 222, and employing following parameters:

Aspiration speed: - 60
Feed rate: - 10 mL/min
Inlet temperature: - 80°C
Outlet temperature: - 40°C

Preparation of trilayered mucoadhesive compressed tablet

Table 1 lists the composition of different mucoadhesive formulations containing outer layers prepared using varying amounts of carbopol and HPMC. Inner core of the tablet was compressed using homogeneously blended solid dispersion of drug and mixture of carbopol and HPMC [Figure 1] into flat-faced tablets (600 mg, 12-mm diameter) using a Rimek MINI PRESS-II MT tablet machine (Karnawati Engg. Ltd., Mehsana, India).

Tablet assay

Five tablets from each batch were powdered individually, and a quantity equivalent to 100 mg of itraconazole was accurately weighed and extracted with a suitable volume of 0.1-N HCl. Each extract was suitably diluted and analyzed spectrophotometrically (Jasco V-530 UV/Vis spectrophotometer) at 254 nm.

Physical evaluation

Ten tablets from each batch were evaluated for uniformity in tablet weight and thickness. Six tablets from each batch were examined for friability, using a Roche-type friabilator (Tropical Equipment Pvt. Ltd., Mumbai, India); and hardness, using a Monsanto-type hardness tester (Campbell, Mumbai, India).

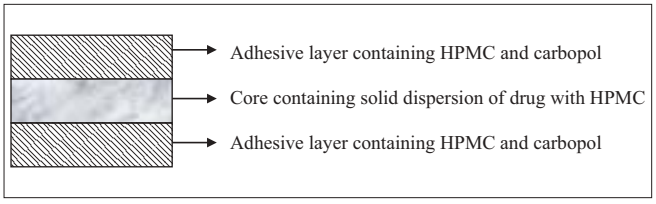

Figure 1: Schematic explanation of the structure of mucoadhesive trilayered device

In vitro bioadhesion studies

The *in vitro* bioadhesion studies were conducted using a modification of a bioadhesion test assembly described by Gupta *et al.*[9] Porcine buccal mucosa was used as the model membrane. The mucosa was kept frozen in 0.1-N HCl and thawed to room temperature before use. The mucosal membrane was excised by removing the underlying connective and adipose tissue and was equilibrated at 37°C ± 1°C for 30 min in 0.1-N HCl before bioadhesion evaluation study. The tablet was kept in intimate contact with mucosa under constant weight of 5 g for a total contact period of 1 min. Bioadhesive strength was assessed in terms of weight (grams) required for detaching the tablet from the membrane.

In vitro release study

Drug release studies ($n = 3$) were conducted for all the formulation combinations using dissolution test apparatus (DA-6D USP Standard). Nine hundred milliliters of 0.1 N hydrochloric acid was taken as the release medium at 100 rpm and 37°C ± 1°C, employing USP II paddle method (Apparatus 2). Aliquots were periodically withdrawn, and the sample volume was replaced with an equal volume of fresh dissolution medium. The samples were analyzed spectrophotometrically at 254 nm.

RESULTS AND DISCUSSION

Solid dispersion of itraconazole with Eudragit E100 prepared by spray-drying method in the ratio of 1:2 showed 100% drug release within 3 h in 0.1-N HCl using USP 24 dissolution assembly at 37°C ± 1°C. Figure 2 shows dissolution profile of prepared solid dispersion. The prepared solid dispersion was used in formulation of mucoadhesive tablet.

No interaction between carrier and drug was seen as shown in IR and differential scanning calorimetry (DSC) studies [Figures 3 and 4]. FT-IR spectra of itraconazole powders were noticed at 400 to 1800 cm^{-1}. They might have arisen from the stretching and vibration of functional groups such as -C = C- of aromatic groups. A peak observed at 1600 to 1800 cm^{-1} is attributed to -C = O stretching and vibration, whereas peaks for alkane and amine groups were noticed at 2800 to 3200 cm^{-1} and are retained in solid dispersion; while in DSC the pure drug shows the sharp endotherm at 167°C, indicating the melting point of the pure drug. Same

Table 1: Composition of itraconazole mucoadhesive trilayered hydrophilic matrices

Layer	Contents	T1	T2	T3	T4	T5
1	C934P	25	37.5	50	62.5	75
	HPMC K4 M	75	62.5	50	37.5	25
2	Solid dispersion of itraconazole and Eudragit E 100 (1:2)	300	300	300	300	300
	CP934P:HPMC K4M (1:1)	100	100	100	100	100
3	C934 P	25	37.5	50	62.5	75
	HPMC K 4 M	75	62.5	50	37.5	25

endotherm is seen in Solid dispersion with reduced intensity, indicating lack of interaction between itraconazole and Eudragit E100.

Physical evaluation

Physical evaluation of compressed matrix tablets showed all physical parameters to be within specifications. Tablet weights varied between 595 and 605 mg; thickness, between 3 mm and 4 mm; and hardness, between 6.5 and 7.5 kg/cm^2. The assay content of itraconazole varied between 98.2% and 99.8%, and the friability ranged between 0.3% and 0.6%.

In vitro bioadhesion strength determination

The phenomenon of bioadhesion is related to the ability of some synthetic or biologic macromolecules and hydrocolloids to adhere to biological tissues. During the process of bioadhesion between materials, the surface energy of the system is decreased and a new interface is formed by destroying the two free surfaces.[10] The bioadhesion may occur by one mechanism or a combination of mechanisms such as electronic interaction, hydrogen bonding, and interpenetration of macromolecules.[11] Hydrophilic polymers show good bioadhesion on account of their hydrogen-bonding abilities. This property of polymer is closely associated with bioadhesion because polymer swelling depends upon water imbibitions, which in turn increase the diffusion and interpenetration of macromolecules.[12] An increase in the amount of polymer will increase the bioadhesive strength (with procaine mucosa). Application of one-way ANOVA, keeping the levels of one of the polymers fixed, also showed a statistically significant difference amongst the observed data of bioadhesive strength ($P < .001$), confirming the significant positive influence of each polymer on bioadhesion. Results concur with observed facts - that increase in concentration of carbopol increased bioadhesion.[6] The HPMC K4M, because of its ability to take up water, causes polymers to swell and interpenetrate quickly and to a greater extent.[13] The water uptake reduces glass transition temperature below ambient conditions; hydrogels become progressively rubbery due to coiling of polymer chains; and subsequently, mobility of polymer chains is increased.

Figure 5 indicates bioadhesive strength (with procaine mucosa) in grams for all formulations. The value of bioadhesive strength ranged between 19.54 ± 1.25 and 34.59 ± 2.15 g. The bioadhesion is highest when both the polymers are used in equal amounts. Further increase in concentration of carbopol shows slightly lesser adhesion.

In vitro release studies

The data was analyzed using PCP disso software version 2.08, developed by Poona College of Pharmacy, Pune. Table 2 lists

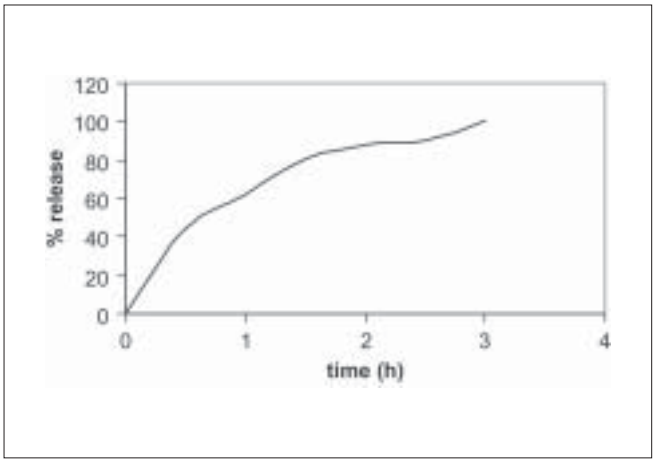

Figure 2: Dissolution profile of solid dispersion

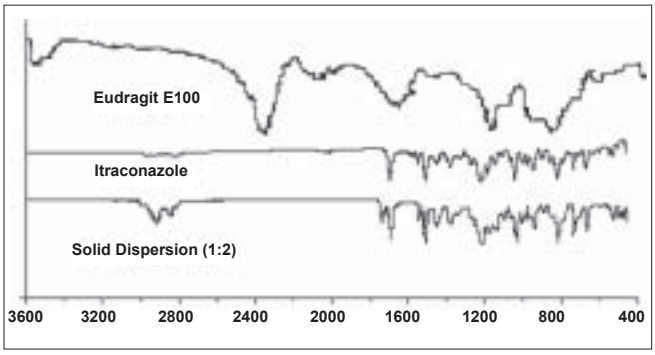

Figure 3: Infrared spectra of itraconazole, Eudragit E100, and solid dispersion (1:2)

Table 2: Dissolution parameters for trilayered mucoadhesive hydrophilic matrix formulations (*n* = 3)

Trial no.	n	k	%Release ± SD (7 hours)	Model	r^2
F1	0.8435	14.24	76.89 ± 0.11	Zero	0.9939
F2	0.9578	11.85	85.06 ± 0.23	Zero	0.9858
F3	0.9449	10.54	72.98 ± 0.20	Zero	0.9792
F4	0.8363	14.24	75.25 ± 0.15	Zero	0.9863
F5	0.7453	18.68	93.82 ± 0.34	Zero	0.9841

*SD - Standard deviation, *k- Kinetic constant, r^2- Coefficient of determination, n - Diffusion coefficient.

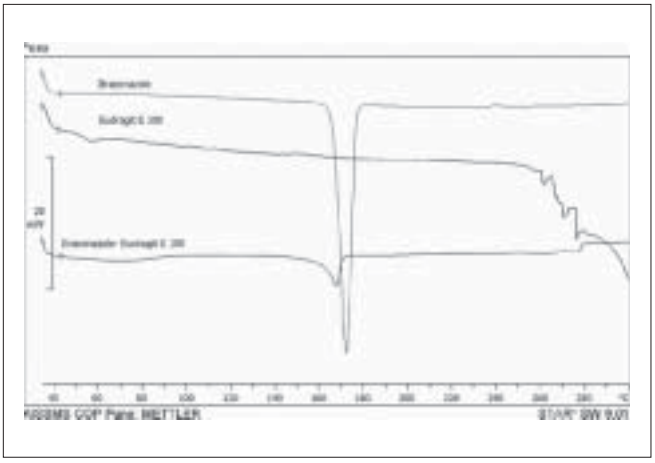

Figure 4: DSC study for itraconazole, Eudragit E100, and solid dispersion (1:2)

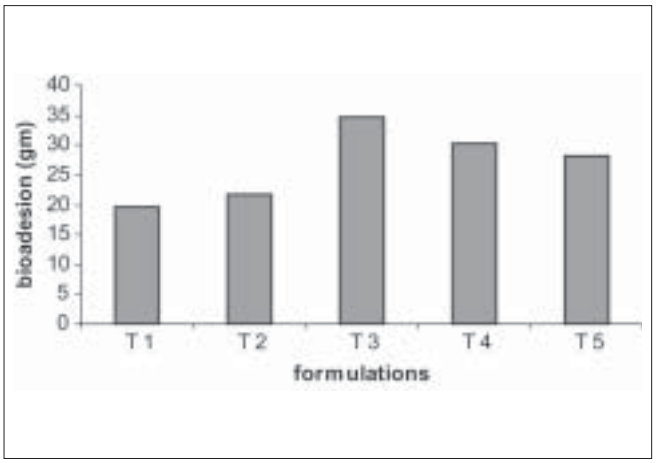

Figure 5: Bioadhesive strength of all mucoadhesive formulations (*n* = 5)

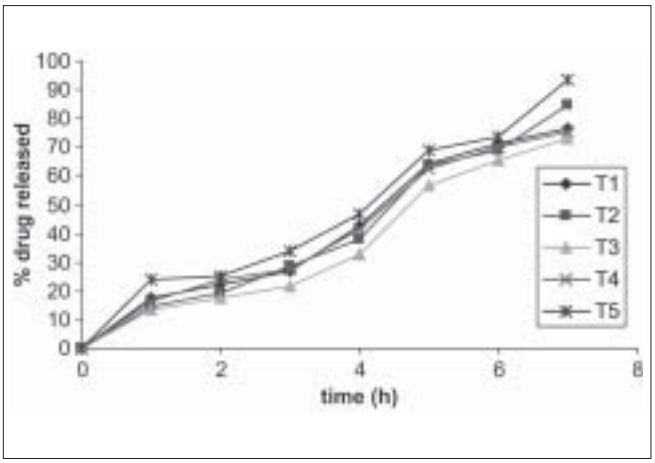

Figure 6: *In vitro* release profile of trilayered mucoadhesive hydrophilic matrices

various dissolution kinetic parameters computed for all five batches. In the current study, all five formulations followed the zero-order release pattern [Figure 6]. According to correlation obtained for the Ritgers and Peppas model, drug release from the swellable tablet system was mainly driven by anomalous transport (not Fickian), as seen by values of release exponent, which varied between 0.7453 and 0.9578. Further the magnitude of kinetic constant (k) ranged between 10.54 and 18.68. Consequently, the value of $t_{50\%}$ was found to vary in between 1.1341 and 2.2097 h according to the content of polymers of the outer layer of bioadhesive polymers.

CONCLUSION

The prepared trilayered formulation of itraconazole gave zero-order drug release. This may be useful to overcome the variable and incomplete absorption of itraconazole through Gastrointestinal tract.

The combination of polymers gave controlled release and better mucoadhesion, and this approach can be useful to overcome formulation problems associated with other BCS class II drugs.

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