ORIGINAL ARTICLE

Physicochemical Characterization and Dissolution Study of Solid Dispersion Tablet of Azithromycin

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Abstract

Aim: To increase the solubility of azithromycin by formulating solid dispersion (SD) and then SD tablets (SDT) were prepared from the best formulation of SDs. **Material and Methods:** SDs were prepared using polyethylene glycol 6000 and β-cyclodextrin (β-CD) by solvent evaporation method. To investigate drug-excipient interaction and for selection of suitable excipient for formulation differential scanning calorimetry study was done, and each excipient was selected for formulation development only if it showed compatible results. **Results and Discussion:** Tablets were prepared by direct compression technique using hydroxypropylmethylcellulose (HPMC)-K 100 and guar gum in different concentrations. SDs were evaluated for drug content, *in vitro* dissolution profiles, and developed SDT were evaluated for various pharmaceutical characteristics, viz., hardness, friability, weight variation, thickness, drug content, and *in vitro* drug release. **Conclusion:** Study indicates that among various formulations SDT of azithromycin: β-CD (1:2) complexes prepared using HPMC and guar gum in 1:4 combination showed maximum drug release.

Key words: β-cyclodextrin, azithromycin, direct compression, dissolution, solid dispersion, solid dispersion tablet, solvent evaporation method

INTRODUCTION

Azithromycin is an azalide a subclass of acid-stable macrolide antibiotics with a 15-membered azalactone ring. It was approved by the food and drug administration for clinical use in 1992. Azithromycin is derived from erythromycin; however, it differs chemically from erythromycin in that a methyl-substituted nitrogen atom is incorporated into the lactone ring. It is a member of a new generation of macrolide antibiotics and has several advantages over erythromycin. It also has enhanced antimicrobial activity which allows for once daily dosing but it has low bioavailability.[1-3]

Azithromycin is a broad spectrum antimicrobial agent with oral bioavailability about 37%. The drug has pKa values around 8.74 and is sparingly soluble in water (~1.8 μg/mL).[3,4]

According to the biopharmaceutical classification system, azithromycin can be classified as a Class II drug; therefore, the drug dissolution may be a rate-limiting step in the drug absorption process.[5] Furthermore, it is a substrate of p-gp which is also responsible for low bioavailability of anal transition zone (ATZ) due to ileal clearance (biliary plus intestinal clearance).[4,6]

The sparingly water-soluble drugs often show an erratic dissolution profile in gastrointestinal (GI) fluids, which consequently results in variable oral bioavailability. To improve the dissolution and bioavailability of sparingly soluble drugs, researchers have employed various techniques, such as micronization, solubilization, salt formation, complexation with polymers, change in physical form, use of prodrug and drug derivatization, alteration in pH, addition of surfactants, and others. Chiou and Rigelman and Serajuadin *et al.* have used the solid dispersion (SD) technique for dissolution enhancement of poorly water-soluble drugs.

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Among the various approaches, the SD technique has often proved to be the most successful in improving the dissolution and bioavailability of poorly soluble active pharmaceutical ingredients like azithromycin because it is simple, economic, and advantageous.[7]

In this investigation, SD tablets (SDTs) of ATZ were prepared using the different ratio of hydroxypropylmethylcellulose (HPMC) and guar gum. In the previous study, SDs of AZT using β-cyclodextrin (β-CD) and polyethylene glycol (PEG) 6000 were prepared in different ratios using the solvent evaporation method.[8] SDT from the best formulation of SDs were formulated using direct compression method; which were evaluated on various parameters.

MATERIALS AND METHODS

Materials

Azithromycin was obtained as gift sample from Cadila Health Care Ltd., Ahmedabad. β-CD, HPMC-K 100, guar gum was procured from Micro Labs, Bangalore. All other polymer, chemical and reagent used were of analytical grade.

Preformulation study

The differential scanning calorimetry (DSC) thermograms were recorded for ATZ, physical mixture (PM) and SD using a DSC (Perkin-Elmer). The thermograms of the pure drug and polymer or carrier showed respective endothermic peaks corresponding to their melting points. From the thermograms of SD and PM, it was observed that there was no peak corresponding to melting point of drug, suggesting amorphous form of ATZ in SD as well as PM.[8]

To study the interaction between drug and polymers used in the preparation of formulation Fourier transform infrared (FTIR) spectroscopy was carried out for the test samples. FTIR spectrum of pure drug and mixtures were recorded using FTIR 8400S. (Shimadzu, Kyoto, Japan)

Preparation of PM and SD and *in vitro* dissolution studies

PM of azithromycin with PEG 6000 and β-CD were prepared by mixing in mortar and SD was prepared by solvent evaporation method using methanol as solvent. PM and SDs formulation were designated as F1-F8. Dissolution studies of prepared SDs were performed for 90 min. The objective was to achieve the complete drug release within this period; and the SDs with different ratio of drug, PEG 6000 and β-CD failing to achieve this objective were not studied further.[8] Azithromycin: β-CD (1:2) complexes showed maximum drug release; hence this complex was selected for the preparation of tablets.[9-11]

Preparation of azithromycin: β-CD complex tablets

Tablet containing 400 mg of azithromycin SD β-CD (1:2) was prepared by direct compression method. These formulations are designated as F1-F6.

Drug β-CD complex equivalent to 400 mg and all the excipients except the lubricant were passed through a #20 mesh screen. The drug blend was prepared by mixing them manually in a polyethylene bag for 10-12 min. The lubricant was added to this blend and mixed properly again for 2 min. All formulations were prepared according to the experimental design, as shown in Table 1. Powdered lubricated blend was compressed into tablet by compression machine.[12,13]

Evaluation of precompression characteristics of ATZ: β-CD blend

Powder mixture formulated was assessed for different rheological properties using standard procedures. The evaluation was done thrice time (n = 3) and mean data were reported.[10,14]

Evaluation of SDT

The various parameters were used for evaluation of prepared SDT. The thickness, friability, hardness, weight variation, and drug release were determined for prepared tablets using standard procedures.[12,15]

Drug content

The drug content was calculated by triturating the three tablets in a mortar with pestle to get fine powder. Powder was taken as equivalent weight of one tablet and was dissolved in 0.1 N HCl. Measure the absorbance of diluted sample of azithromycin: β-CD tablets at 298 nm, using ultraviolet-visible spectrophotometer.[16,17]

Table 1: Composition of various SDTs formulations

Ingredient	F1	F2	F3	F4	F5	F6
SD (β-CD, 1:2)	400	400	400	400	400	400
HPMCK 100	100	150	200	50	50	50
Guar gum	50	50	50	100	150	200
Aerosil	10	10	10	10	10	10
Magnesium stearate	10	10	10	10	10	10
Theoretical weight	570	620	670	570	620	670

SDTs: Solid dispersion tablets, SD: Solid dispersion, β-CD: β-cyclodextrin, HPMC: Hydroxypropylmethylcellulose

In vitro drug release study

In vitro dissolution has been properly established to develop oral dosage form. It is used to predict *in vivo* dissolution of tablets.[18-20]

The *in vitro* release of SDTs was determined using tablet USP dissolution test apparatus. The media used in dissolution apparatus was 0.1 N HCl (900 mL) and maintained it at 37°C ± 1°C. The sample of 10 mL was withdrawn at different interval and volume of media was maintained by putting fresh media in chamber.[15,17] The aliquots were evaluated spectrophotometrically at 298 nm.

RESULTS AND DISCUSSIONS

After performing FTIR of the ATZ and mixture of ATZ with excipients, it was found that the peaks obtained in drug mixture were in between the range of main principle peaks and were found to be very near to previously performed FTIR of pure drug. No major deviation in peaks was obtained in IR spectra, hence this indicates that drug was compatible with other ingredients [Figures 1 and 2]. Hence, it cannot alter the therapeutic efficacy of ATZ; and it also support to continue further research works.

The bulk density tapped density of the formulation F1-F6 containing different ratio of excipients was in the range from 0.49 ± 0.29 to 0.55 ± 0.85 g/cm^3 and 0.63 ± 0.75 to 0.67 ± 0.19 g/cm^3, respectively, as shown in Table 2. Similarly, the range of Carr's index, Hausner's ratio, and angle of repose were 16.17 ± 0.89 to 23.43 ± 0.5, 1.21 to 1.30 and 19.24 ± 0.12 to 24.72 ± 0.45, respectively.

Thickness of all formulations was found to be between 2.9 ± 0.03 and 3.4 ± 0.05. From Table 3, it has been observed that tablet weights of all formulation were under USP limits, between 197.3 ± 0.85 and 203.5 ± 0.24 mg. The tablets of all batches exhibited the hardness between 2.7 ± 0.14 and 3.6 ± 0.24 (kg/cm^2) and the result of friability was <1%. The drug content of prepared SDTs was between 97.1 ± 0.47 and 99.2 ± 0.29%.

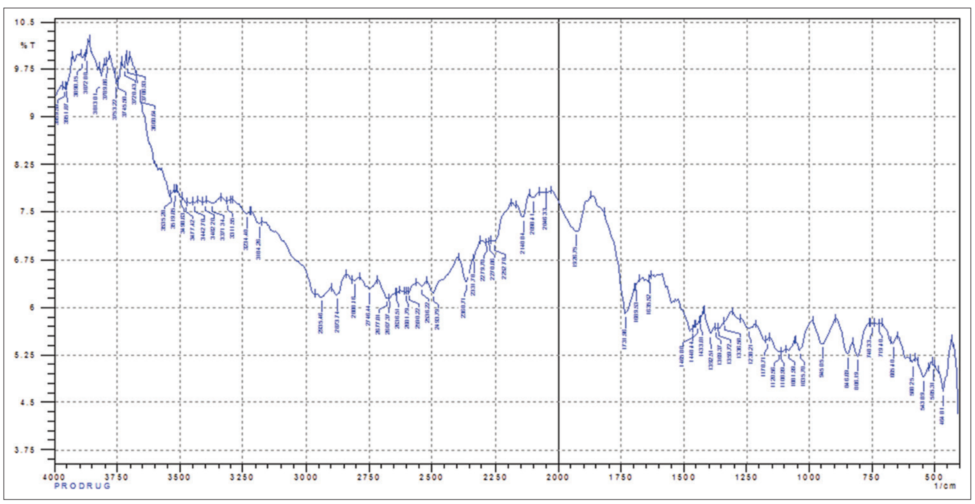

Figure 1: Fourier transform infrared spectra of mixture of anal transition zone and β-cyclodextrin

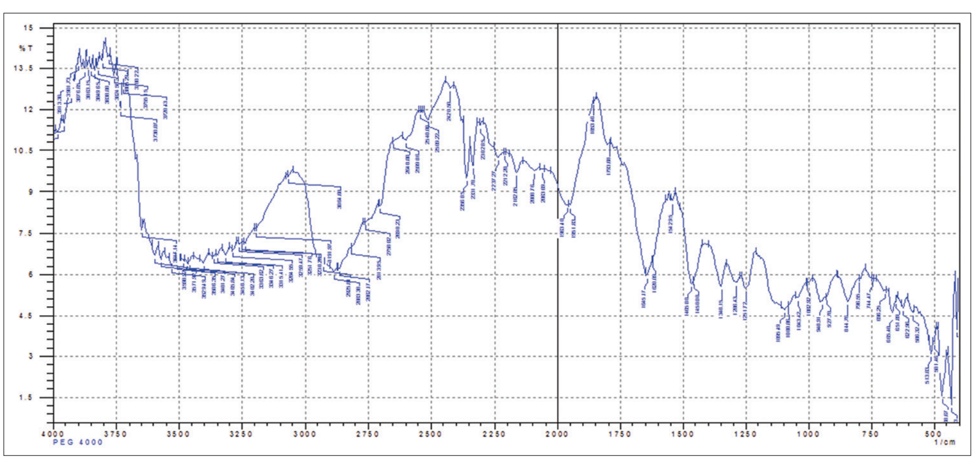

Figure 2: Fourier transform infrared spectra of mixture of anal transition zone and excipient

Table 2: Data of precompression characteristics of azithromycin: β-CD blend

Formulation	Angle of repose	Bulk density (gm/cm³)	Tapped density (gm/cm³)	Carr's index (%)	Hausner's ratio
F1	19.24±0.12	0.49±0.29	0.64±0.43	23.43±0.58	1.30
F2	20.35±0.45	0.51±0.39	0.65±0.24	21.53±0.21	1.27
F3	22.19±0.28	0.52±0.67	0.63±0.75	17.46±0.89	1.21
F4	22.95±0.35	0.54±0.47	0.66±0.69	18.19±0.67	1.22
F5	24.72±0.45	0.55±0.85	0.67±0.19	17.91±0.18	1.21
F6	25.17±0.72	0.57±0.62	0.68±0.24	16.17±0.34	1.19

Values are mean±SD. SD: standard deviation, β-CD: β-cyclodextrin

Table 3: Evaluation of azithromycin: β-CD complex tablet

Formulation	Tablet hardness (kg/cm²)*	Friability (%)*	Thickness (mm)*	Average weight (mg)*	Assay (%)*
F1	5.1±0.35	0.36±0.65	2.9±0.03	569.3±0.85	98.2±0.68
F2	5.5±0.49	0.39±0.73	3.1±0.08	621.5±0.24	97.5±0.42
F3	5.8±0.24	0.29±0.18	3.4±0.05	669.6±0.47	99.2±0.29
F4	4.8±0.58	0.48±0.42	3.3±0.04	568.7±0.68	97.1±0.47
F5	5.3±0.69	0.42±0.28	3.1±0.08	619.4±0.75	98.5±0.57
F6	5.5±0.14	0.39±0.53	3.3±0.06	669.5±0.58	

*Values are mean±SD. SD: standard deviation, β-CD: β-cyclodextrin

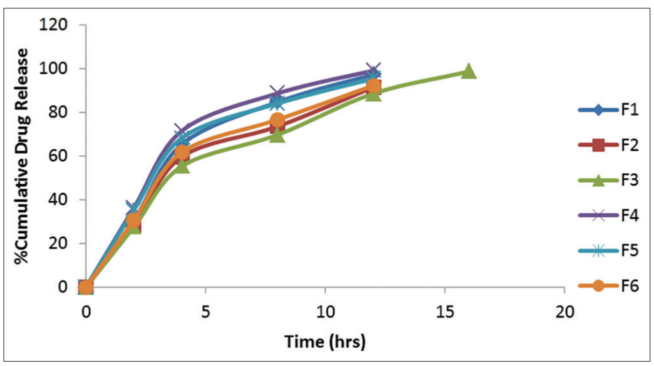

Figure 3: *In vitro* drug release profile of solid dispersion tablets of azithromycin: β-cyclodextrin

In vitro drug release studies of SDTs of azithromycin: β-CD

The *in vitro* dissolution studies exhibited that 92.14-100% of drug release from various formulations [Figure 3]. The 50% of the drug was released from the formulations F1-F6 within 4 h. The F3 released maximum drug, i.e., 98.58%.

The results indicate that the decrease in release rate as the concentration of HPMC increased. At higher polymer loading, the viscosity of the gel matrix was increased, which resulted in a decrease in the effective diffusion coefficient of the drug and was more likely to be resistant to drug diffusion and erosion. This indicates that the drug/polymer ratio is important factors affecting the rate of release of drugs from HPMC matrices.

Formulations formed with guar gum showed an initial burst release and slow drug release with increasing concentration of polymer, which may be due to the formation of a thick gel layer with increasing viscosity around the tablets. In the formulation containing a combination of polymers, when higher concentration of HPMC is replaced by the guar gum, an increase in the drug release was observed which clearly indicates that increasing the concentration of guar gum in the matrix alters the drug release profile significantly.

CONCLUSION

Azithromycin has high permeability but low solubility in GI fluid. Solubility enhancement of ATZ by making its SDT enhanced the dissolution rate of the drug. From above study, it has been noticed that the different formulation exhibited different pattern of drug release and the complexation of drug with β-CD enhance the dissolution rate from the dosage form. The *in vitro* release study findings exhibited that the azithromycin: β-CD (1:2) complexes prepared by solvent evaporation method demonstrated maximum rate of dissolution and SDT of this complex along with 1:4 combination of HPMC and guar gum showed maximum drug release.

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