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Original Article

Preparation and *in vitro* and *in vivo*characterization of Solid Dispersions tablets of Azithromycin by melting method

Pawan Kumar and Rupa Mazumder

Department of Pharmaceutical Technology, Noida Institute of Engineering and Technology Greater Noida, India

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ABSTRACT: Azithromycin is a cyclic-structure macrolide, shows prolonged anti-bacterial, anti-inflammatory and immunomodulatory effects. Azithromycin belongs to BCS class II drug i.e. drug with poor solubility and good permeability. The major problems with this drug is its very poor solubility in biological fluids that results into poor bioavailability after oral administration. The objectives of the present research work were to develop the formulation with enhanced dissolution rate of poorly soluble azithromycin. The solid dispersion of azithromycin was prepared using carrier PEG - 6000 by melting method. Tablets were formulated containing solid dispersion products and compared with tablet formulated by pure drug without any carrier. The *in vitro* dissolution studied showed improved dissolution rate and it was compared with *in vivo* studied using animal model. Dissolution enhancement of the drug being caused by change in crystalline nature of drug in to amorphous nature.

⇑ Corresponding author at:
Pawan Kumar, Department of Pharmaceutical Technology, Noida Institute of Engineering and Technology Greater Noida, India
E-mail address:pawan.mpharmacy@gmail.com

INTRODUCTION

Azithromycin(9-deoxy-9a-aza-9a-methyl-9a-homoerythromycinA) is a cyclic macrolide with a wide antimicrobial spectrum [1]. Azithromycin treatment has been used in treatment of pulmonary exacerbations, improve lung function in patients with cystic fibrosis (CF) [2], chronic obstructive pulmonary disease, and non-CF bronchiectasis [3,4]. One of the major problems with this drug is its very poor solubility in biological fluids that results into poor bioavailability after oral administration [5].

Oral bioavailability of azithromycin is about 37% Its Peak plasma concentrations are achieved 2 to 3 hours after a dose, but Azithromycin is extensively distributed to the tissues, and tissue concentrations subsequently remain much higher than those in the blood. Small amounts of Azithromycin are demethylated in the liver, and it is excreted in bile as unchanged drug and metabolites [6].Solid dispersions of azithromycin were prepared by using hydrophilic carrier PEG 6000 [7].

The purpose of the present investigation is to increase the solubility and dissolution rate of azithromycin by preparing its solid dispersions with poly ethylene glycol (PEG) 6000 using melting method technique. Polyethylene glycols (PEGs) having molecular weights of 1,500–20,000 are used for the preparation of solid dispersions (SDs).

Solubility of PEGs in water is generally good, but decreases with increase in molecular weight. Other advantages of PEGs for formation SDs is that they also have good solubility in many organic solvents. The melting points of PEGs lies under 65°C [8].

MATERIAL AND METHODS

Materials: Azithromycin was purchased from Century Pharmaceuticals Ltd (Vadodara, Gujrat) and PEG 6000 was purchased from Sigma-Aldrich (St. Louis, MO, USA).All other materials used were of analytical grade.

Preparation of Solid dispersion: Solid dispersion of Azithromycin were prepared by using hydrophilic carrier PEG

6000 having different ratios such as 1:0.5, 1:1 and 1:1.5 by weight. Solid dispersions were prepared by melting method [9]. Weighed quantities of PEG 6000 and azithromycin were thoroughly mixed and melted on hot plate with constant stirring to obtain a uniform melt. The melt was than cooled on an ice cooled bath. The solid mass was removed from the stainless-steel plate, powdered and kept in a desiccator for two-three days. The powder was passed through sieve #22 and stored in closed airtight container [10].

Preparation of Tablet Dosage Form: Two types of tablets were prepared. First type of tablet consists of pure drug and second type consist of tablets with SDs having different ratio of PEG -6000. The drug and polymer were taken in the ratio of 1:0.5, 1:1 and 1:1.5 respectively All the ingredients are passed through sieve # 22 and mixed in double cone blender. These mixtures were then mixed with drug polymer mixtures and lubricated with magnesium stearate by further blending for 3 minutes in double cone blender. Compression was done on 16 station automatic punching machine directly by dry granulation technique using 8mm punch [11]. All the formulations are reported in Table 1.

Table 1:Formulation of Tablets

Ingredients (mg)	F_0	F_{10}	F_{11}	F_{12}
Azithromycin	100	100	100	100
PEG 6000	-	50	100	150
Microcrystalline Cellulose	50	50	50	50
Lactose anhydrous	246	196	146	96
Mg Stearate	4	4	4	4
Total Wt(mg)->	**400**	**400**	**400**	**400**

***In vitro*dissolution studies:** Azithromycin (250 mg) was weighed accurately and transferred to a 100 ml volumetric flask. It was dissolved in glacial acetic acid (20 ml, 3 M), and diluted to 100 ml with distilled water. An aliquot (5.0 ml), was further diluted with water in 50 ml volumetric to get final concentration of 250 mg/ml.

In a 100 ml volumetric flask, standard azithromycin solution (2.0 ml) and glacial acetic acid solution (1.0 ml) were pipetted successively. Potassium permanganate solution (0.25 % w/v, 0.025 ml) was added. The flask was heated on a water bath at 37° for 10 min. Excess of potassium permanganate was neutralized with oxalic acid (10 % w/v). The reagent solution (2.0 ml) was added to it, and mixed thoroughly. The reaction flask was heated on a water bath at 37° for 1 min, cooled, and the volume was adjusted up to the mark with distilled water.

Absorbance of the colored solution was scanned on Shimadzu UV visible spectrophotometer from 600 nm to 200 nm, against reagent blank. Maximum absorbance was obtained at 412 nm. 1 ml of Standard solution of azithromycin (25 mg/ml) diluted in 100ml volumetric flask. Resulting solution (1, 2, 3, 4 & 5 ml) was pipette out into a series of 10 ml volumetric flasks, colour was developed as described above, and absorbance was measured at 412 nm. The Beer's law is obeyed in the concentration range of 25-125 µg/ml of azithromycin [12] (table 4).

***In vivo*dissolution studies:** Albino rabbits of weight (2000-3000gm) were obtained from Animal House, NIET, Greater Noida. The animals were kept under standard laboratory conditions (12:12 h dark/light cycle) and a free access to food and water for 14 days. Animals described as fasted will be deprived of food for 12 h but free access to water. Then animals were dosed by the prepared powder by means of oral catheter. After blood sample were collected from marginal ear pinna of rabbit at an interval of 0, 2 ,4, 6, 8 & 10 hrs[13,14] (table 2).

Table 2: Experimental Summary

1	Animal	Albino rabbit
2	Weight	2000-3000g
3	Gender	Either sex
4	No. To be used	6 (3 in two group)
5	Doses	60mg/Kg body weight
6	Blood withdrawal Volume	0.5 ml
7	Site	Marginal ear vein
8	Sampling time	0, 2 ,4,6, 8 and 10 hrs

Collected blood were centrifuged at 2000 rpm for 10 min where upon the separation of plasma were obtained. Further, the drug concentration was determined by using HPLC Method (table 3).

Table 3: Chromatographic Conditions

Column	C-8, 250mm X 4.6mm, 5µ,
Flow rate	1.2 ml/min
Wavelength	210
Column temperature	45°C
Injection volume	20µL
Run time	15 minutes
Diluent	Mobile phase
Elution	Isocratic
Needle wash	Water: Methanol 90:10 (v/v)

RESULT AND DISCUSSION

***In vitro* dissolution studies:** The *in vitro* dissolution studies performed in USP apparatus No -1 (Paddle Type) at 100 rpm at the interval of 10, 20,30,40,50 & 60 min using sodium phosphate Buffer pH- 6.Following result were obtained as shown in table 5.From the *in vitro* studies, performed in dissolution apparatus tablet consist of pure drug shows poor drug release but when its solid dispersion (SD) were prepared using PEG 6000 at different ratio has improved the dissolution rate of formulation F10, F11 and F12 to a great extent (table 5).

***In vivo*dissolution studies:** Plasma drug concentration of pure drug and solid dispersion drug were determined by using HPLC Method. Following result were obtained as shown in table 6.The maximum plasma concentration (C_{max}), $T_{max,}$ AUC, absorption rate constant Ka and were determined from the curve between plasma drug concentration versus time. C_{max} and T_{max} were directly determined from the plasma concentration versus time data. The area under curve was calculated using the linear Trapezoidal rule (table 6).

Pharmacokinetic parameters of Pure drugs and drug with polymer (Solid dispersion using PEG 6000) were shown in table 7.

Table 4: Standard curve of Azithromycin

Concentration(µg /ml)	Absorbance
0	0
25	0.212
50	0.408
75	0.573
100	0.715
125	0.824

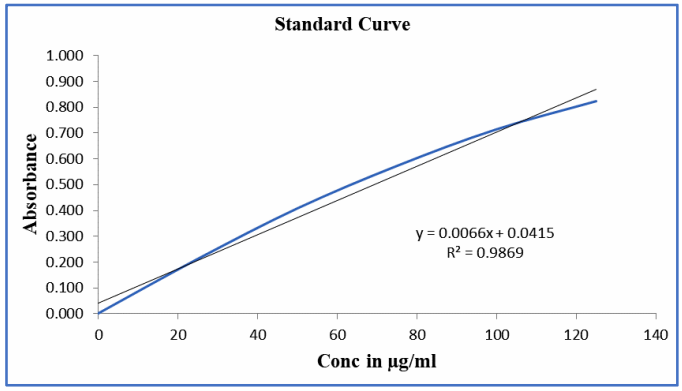

Figure 1: Standard Curve of Azithromycin

Table 5: Comparative drug release of Azithromycin tablet using PEG 600

TIME(min)	Drug without polymer(F0)	Drug: Polymer (1:0.5)(F_{10})	Drug: Polymer (1:1) (F_{11})	Drug: Polymer (1:1.5)(F_{12})
0	0	0	0	0
10	5.09	26.24	32.05	35.05
20	8.50	37.68	45.12	51.04
30	10.25	50.24	59.51	68.36
40	15.24	62.10	77.25	85.02
50	17.28	74.25	87.45	92.06
60	20.09	93.50	95.04	98.12

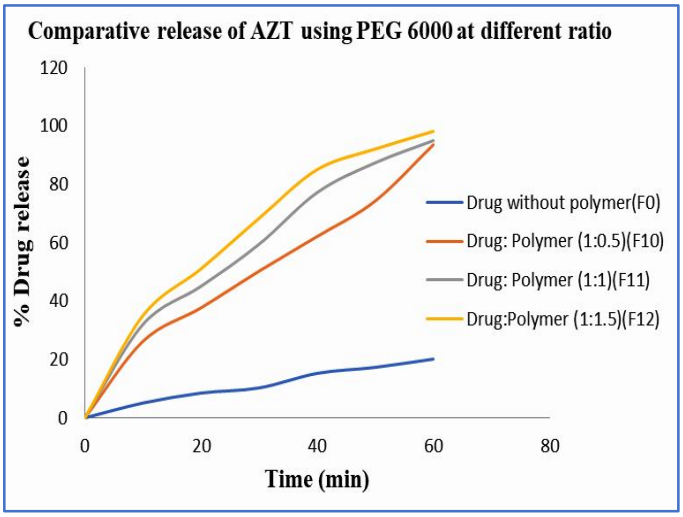

Figure 2: Comparative release of AZT with and without PEG 6000 at different ratio

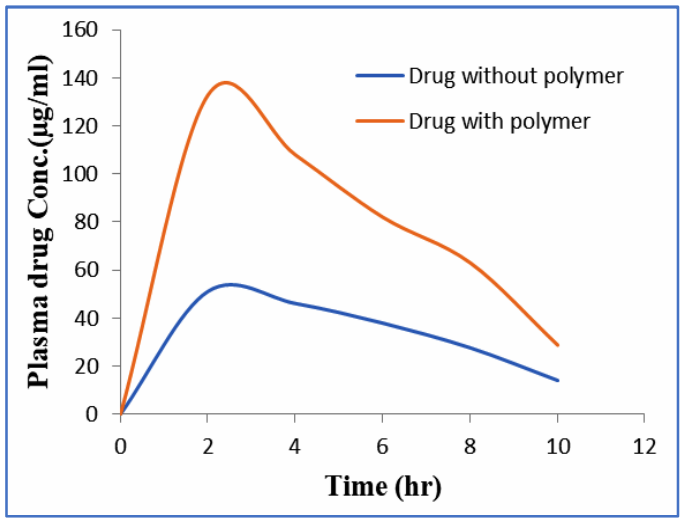

Figure 3:Plasma drug concentration profile

Table 6: Plasma Concentration of drug (With & Without Solid dispersion)

Time(hr)	Drug without polymer(µg/ml)	Drug with polymer PEG (µg/ml)
0	0.0	0.0
2	51.2	133.0
4	46.1	108.0
6	37.9	82.0
8	27.6	63.0
10	14.0	28.7

Table 7: Pharmacokinetic parameters of azithromycin

Parameters	C_{max} (µg/ml)	T_{max} (hr)	AUC (µg.hr/ml)	MRT=$C\int_0^\infty dt$ / $Ct\int_0^\infty dt$ (hrs)	Absorption rate Constant(Ka) hr^{-1}
Drug without polymer	51.3	2.1	288	0.187	0.71
Drug with polymer	133	2.3	667.7	0.190	0.83

CONCLUSION

The present study showed that the solid dispersions of azithromycin were prepared by using PEG 6000. It was observed that the solid dispersion prepared with PEG 6000 by melting method showed improved *in vitro* dissolution rate as compared with formulation containing pure drug. This result was confirmed by *in vivo* studies. The plasma concentration versus time curves of azithromycin after single dose administration to the rabbit, curve obtained from solid dispersion of azithromycin showed a rapid rise in peak as compared to the curved obtained from pure drug. There was significant change in AUC and C_{max}but other parameters like Ka, MRT does not show any significant changes.

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