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Research Article

IMPROVEMENT OF ORAL BIOAVAILABILITY OF AZILSARTAN MEDOXOMIL BY LIPID BASED LIQUISOLID COMPACTS: *IN VITRO* AND *IN VIVO* EVALUATION

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ABSTRACT

The main objective of the current research work is to improve the oral bioavailability of azilsartan medoxomil (BCS Class IV molecule) using lipid based liquisolid approach. Azilsartan liquisolid compacts (ALC) have been prepared using Capmul MCM and Captex as lipid based non-volatile vehicles, Pearlitol SD 200, Avicel PH 102 and Flowlac 90 as carrier's materials and Syloid® 244FP as a coating material. Carrier to coating material ratio was fixed as 5:1. Percentage of drug in the lipid based non volatile liquid was fixed as 50%w/w. Prepared formulations were evaluated for their micromeritics properties, solubility, dissolution and in vivo bioavailability in selected rats. Among the formulations prepared, formulation (ALC4) containing Capmul MCM as vehicle, Pearlitol SD 200 as carrier has shown enhanced drug release (99.8 ± 1.5 % release in 30 minutes) and solubility (82.54mg/mL) compared to other formulations. Hence, this formulation is evaluated for comparative in vivo bioavailability in rats along with pure drug and marketed formulation (Zilarbi). It was found that relative bioavailability of ALC 4 was increased by 1.29 times compared to pure drug and increased by 1.22 times compared to marketed formulation. Hence, the study demonstrated that lipid based liquisolid technology can lead to improve the bioavailability of poorly soluble drugs like azilsartan medoxomil significantly.

Key Words: Lipid based, Liquid solid compacts, Bioavailability, Dissolution, Solubility

INTRODUCTION

Recent drug developments in high-throughput screening and combinatorial chemistry used in discovery resulted in increase in number of drugs with poor aqueous solubility and/or poor membrane permeability. Approximately 90% of the new chemical entities (NCEs) are considered poorly soluble with either high or low permeability (Biopharmaceutics Classification System (BCS) class II and IV)[1-5]. BCS class IV drugs have low aqueous solubility and low membrane permeability. The absorption/bioavailability of these drugs is limited by both dissolution rate and permeability rate. These drugs exhibit varying bioavailability and small increment in dissolution and/or permeability may result in substantial improvement in bioavailability. Hence, dissolution enhancement or permeability enhancement is the key factor in formulating BCS class IV drugs[6-10].

Azilsartan medoxomil, a prodrug, is hydrolyzed to azilsartan in the gastrointestinal tract during absorption. Azilsartan is a selective AT1 subtype angiotensin II receptor antagonist. Till the date, several techniques have been reported including self-emulsifying drug delivery (SEDDS), solid dispersions, liquisolid compacts and complexation with cyclodextrin were aimed at improving the dissolution rate. However, all those techniques were only aimed to improve only the drug dissolution rate. Hence, there is a need of delivery system which can able improve both the drug dissolution rate and membrane permeability[11-13].

The drug substance is chemically described as (5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylate salt. Its empirical formula is $C_{30}H_{23}N_4O_8$. It is used in the treatment of essential hypertension. It is BCS class IV drug with 60% oral bioavailability[14-17].

Hence, the current research work is aimed to improve both the drug dissolution rate and permeability by which we can improve the oral bioavailability using lipid based liquisolid approach.

Liquisolid technique is a newly developed and advanced method for dissolution enhancement. This technique was first introduced by Spireas et al. and applied to incorporate water-insoluble drugs into rapid release solid dosage forms. The design principle of liquisolid system is to contain liquid medications (i.e., liquid drugs, drug solutions or suspensions) in powdered form and delivery drug in a similar way to soft gelatin capsules containing liquids. Liquisolid technique refers to the conversion of liquid medications into apparently dry, non-adherent, free flowing and compressible powder mixtures by blending the liquid medications with suitable excipients, which are generally termed as carriers and coating materials. The liquid medication is first absorbed into the interior framework of the carrier. Once the interior of the carrier is saturated with liquid medication, a liquid layer is formed on the surface of carrier particles, which is instantly adsorbed by the fine coating materials. Consequently, an apparently dry and free flowing and compressible powder mixture is formed. Usually, orally safe, and preferable water-miscible organic solvents with high boiling point, such as propylene glycol and polyethylene glycol (PEG) 400, are used as the liquid vehicles. If we use the lipid based liquid vehicles like captex, capmul, transcutol etc., along with the drug solubility drug permeability is also expected to be increased. Carriers refer to porous materials with large specific surface area and high liquid absorption capacity to absorb liquid medication. Various grades of cellulose, starch and lactose can be adopted as carriers. However, only excipients with very fine particle size and highly adsorptive

property, such as silica powder, can be used as coating materials[6-10].

MATERIALS AND METHODS

Azilsartan medoxomil was received as a gift sample from Aurabindo Pharma Pvt Ltd, India. The following materials were gifted by Abitec Corp., USA and were used as received: Capmul MCM (Glyceryl monocaprylate) and Captex 200 (Propylene glycol dicaprylocaprate). Tween 80, Propylene glycol and PEG 400 were received as gift samples from Signet. Cottonseed oil and Olive oil were procured as a gift samples from Corel Pharma Chem., Ahmedabad, India. Pearlitol SD 200, Aviel PH 102, Flowlac 90 were received from Signet, India. Syloid FP 244 was purchased from Ashland India.

Saturation Solubility Studies

Saturation solubility studies of Azilsartan medoxomil was done in different non volatile liquid vehicles including lipid based vehicles and various buffers. Excess amount of drug was added to two mL of each solvent in a screw capped vial and were kept on isothermal mechanical shaker at 25°C for 48-72 hours until the saturation point occurs. After equilibrium/saturation, each solution was centrifuged at 5000 rpm for 30 minutes. Supernatant was collected and filtered through membrane filter using 0.45 µm filter disk. Filtered solution was appropriately diluted with methanol, and UV absorbances were measured at 266 nm wavelength. Concentration of dissolved drug was determined using standard equation of calibration curve (y = 0.009x - 0.002).

Preparation of Liquisolid compacts

Based on the results of saturation solubility, two lipid based solvents such as capmul MCM and captex 200 were selected as non volatile lipid based liquids. Several lipid based liquisolid compacts of Azilsartan medoxomil were prepared using 50%w/w of each of two liquid vehicles. Each vehicle formulation contains three different carriers, Pearlitol SD 200, Avicel PH 102 and Flowlac 90 as carriers and syloid FP200 as coating material at carrier/coat ratio of 5:1. The liquid medication was produced by mixing Azilsartan (40mg/formulation) in nonvolatile liquid vehicle using mortar and pestle. To this liquid medication, the calculated amount of the carrier was added by continuous mixing in the mortar. Then, coating material was carefully added and mixed until mortar contents start to look dry. Composition of liquids solid compacts batches are shown in Table 1.

Evaluation of Liquisolid Formulations

Flow properties of the any prepared formulation should be as good as possible at industrial scale level. Therefore, it was essential to study the flow behaviour of the prepared liquisolid powder admixtures. Flowability was evaluated using parameters such as Carr's index, angle of repose, and Hausner's ratio.

Angle of Repose

The angle of repose of powder blend was determined by fixed height funnel method. Angle of repose (θ) was calculated using the following equation:

$$\theta = \mathrm{Tan}^{-1}(h/r)$$

Where 'h' and 'r' are the height and radius of powder cone.

Compressibility Index

$$\text{Carr's index (\%)} = \text{Tapped density} - \text{Bulk density} / \text{Tapped density} \times 100$$

The compressibility index of the powder blend was determined by Carr's compressibility index. The formula for Carr's index is as below:

Hausner's Ratio

Hausner's ratio was calculated from the equation:

$$\text{Hausner's Ratio} = \text{Tapped Density/Bulk Density}$$

Content Uniformity

Weight equivalent (200mg) to one unit dose of azilsartan medoxomil (40mg) of each formulation was accurately weighed and transferred into a 100 mL volumetric flask. Initially, 10 mL of methanol was added and shaken for 10 min. Then, the volume was made up to 100 mL with phosphate buffer pH 6.8. The solution in the volumetric flask was filtered, diluted suitably, and analyzed spectrophotometrically at 266 nm using UV-visible double-beam spectrophotometer (UV1800, Shimadzu, Japan).

Saturation Solubility Studies

Saturation solubility studies of all the prepared formulations were done in water using the same method as mentioned above

In Vitro Drug Release Study

The *in vitro* drug release study of the prepared liquisolid formulations, marketed formulation and pure drug were performed using USP type II apparatus paddle (EDT-08L, Shimadzu, Japan) at 37°C ± 0.5°C using phosphate buffer pH 6.8 (900 mL) as a dissolution medium and 50 rpm. At the predetermined time intervals, 10 mL samples were withdrawn and replaced with fresh dissolution media. Withdrawn samples were filtered through a 0.45 µm membrane filter, diluted, and assayed at 266 nm using a Shimadzu UV-1800 double-beam spectrophotometer. Cumulative percentage drug release was calculated using an equation obtained from a calibration curve.

Ex vivo permeability studies

The *ex vivo* permeability studies were conducted by using goat intestinal membrane after approval from Institutional Animal Ethics Committee (IAEC Number: 517/01/A/CPCSEA). Intestinal membranes of goats were collected from local animal slaughter house. Male goats were used to obtain freshly excised fully thickness intestinal membrane. Care was taken while collecting the intestinal membrane to prevent the damage of epidermal layer. An open ended glass tube was taken; goat intestinal membrane (0.025cm) was stretched over the one end of the glass tube. Tube was immersed in 250 ml beaker containing 100 ml of 7.4pH phosphate buffer and kept in vertical position so that the membrane touches the (1-2mm deep) surface of the buffer solution. The surface area available for the drug diffusion was 1.76 cm^2. The glass tube (donor) and beaker (acceptor) both were maintained at 37°C±0.5ºC by keeping the entire set up on hot plate magnetic stirrer. Beaker was maintained at 100 rpm throughout the experiment. Weight equivalent to 40 mg of optimized formulation (ALC4), pure drug and marketed formulation (Zilarbi; powdered) was added in 5ml of 7.4 pH phosphate buffer and placed in donor compartment. At predetermined time intervals 5mL samples were collected from acceptor compartment and replaced with fresh buffer. Samples were analyzed spectrophotometrically after suitable dilution with buffer at 266nm. The study was conducted for a period of 6 hrs and amount of drug diffused was calculated from standard graph at each time interval.

***In Vivo* Pharmacokinetic Studies**

The research protocol of animal experimentation was approved by the Institutional Animal Ethics Committee (IAEC Number: 517/01/A/CPCSEA). Pharmacokinetic evaluation was done in healthy wistar rats. The animals were housed in metallic cages with free access move and provided standard laboratory diet and water in central animal house. Based on the evaluation results of in vitro dissolution studies ALC4 that showed complete release within 30 minutes was selected to carry out *in vivo* performance in comparison with the pure drug solution (APD) and marketed formulation Zilarbi tablets (AZ). Animal dose was calculated using following formula.

AnimalEquivalentDose (mg/kg)
= HumanDose (mg/kg) XKmvalueofanimal
/Kmvalueofhuman

Km value of Rat is 7
Km value of Human is 37

As per the above formula dose of the each formulation administered was 3.5mg. Each formulation was prepared by taking the weight equivalent 3.5 mg of drug and dispersing in 1% Sodium CMC Suspension. All formulations were administered to animal through oral cannula.

An open label, balanced, randomized, three-period, three-treatment, three-sequence, single-dose crossover study design in which six healthy wistar rats received one treatment (product) each with a wash out period of 7 days such that all products are tested in all the six healthy rats during the study. Six healthy rats with body weight range of 200-250g were selected through physical examination. Animals were randomly divided into three groups consisting of two in each group. Each group on three different periods received a single dose of each of the above three treatments in random order with a washout period of one week between each treatment and the scheme of administration of the treatments is shown below table 2.

The animals were fasted overnight before administering the dose. After collecting the zero hour blood sample (blank), a standardized diet was given in the morning.

During each period, 0.5 mL venous blood samples were collected from the retro orbital vein of each animal in Accuvet tubes (Quantum Biologicals Pvt. Ltd., Chennai, India) containing K3EDTA. Blood Samples were collected at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 18 and 24 hrs. Plasma was immediately separated by centrifugation at 5000 rpm for 30 min from the blood samples and stored in frozen conditions at -20°C with appropriate labelling of subject code number, study date and collection time prior to analysis. The concentration of Azilsartan in plasma samples was measured by the HPLC method using Waters symmetry C18 (4.6 × 250 mm, 5 µm) column, 25 mM ammonium acetate buffer (pH 5.5): acetonitrile 55 : 45 v/v as mobile phase and UV detector at 254nm. Pharmacokinetic parameters such as peak plasma concentration (Cmax), time at which Cmax occurred (Tmax), area under the curve (AUC), elimination rate constant (Kel), and biological half life (t½) were calculated in each case using the data by Kinetics Pro 2.0 (PK Solver 2.0) software using non-compartmental approach. Percent relative bioavailability of the optimized formulation vs pure drug suspension and marketed formulation was also estimated to understand the improvement of oral bioavailability with selected method.

Table 1: Composition of Lipid Based Liquisolid Compacts

Name of the Ingredient	ALC1	ALC2	ALC3	ALC4	ALC5	ALC6
Azilsartan Medoxomil API	40	40	40	40	40	40
Capmul MCM	40	40	40	--	--	--
Captex 200	--	--	--	40	40	40
Pearlitol SD 200	100	--	--	100	--	--
Avicel PH 102	--	100	--	--	100	--
Flowlac 90	--	--	100	--	--	100
Syloid FP	20	20	20	20	20	20
Total Unit Weight (mg)	200	200	200	200	200	200
% W/W of Liquid Medication	50	50	50	50	50	50
Ratio of Carrier to Coating Material (R)	5:1	5:1	5:1	5:1	5:1	5:1
Loading Factor (Lf)	0.8	0.8	0.8	0.8	0.8	0.8

Table 2: Three way crossover treatment study for the selected formulations

	Sequence 1		Sequence 2		Sequence 3
Group 1	ALC4	WASH OUT	AZ	WASH OUT	APD
Group 2	AZ		APD		ALC4
Group 3	APD		ALC4		AZ

Table 3: Results of Liquisolid Formulations

Parameters	Formulations						
	Pure Drug	ALC1	ALC2	ALC3	ALC4	ALC5	ALC6
Bulk Density	0.37	0.55	0.54	0.53	0.58	0.61	0.77
Tapped Density	0.66	0.61	0.73	0.77	0.68	0.69	0.84
Angle of Repose (º)	34.54	22.23	18.25	17.58	17.81	19.54	19.52
Carr's Index	43.9	9.8	26.0	31.2	14.7	11.6	8.3
Hausner's Ratio	1.8	1.1	1.4	1.5	1.2	1.1	1.1
Assay (%)	100.1	99.8	100.1	100.2	99.8	100.2	100.8
Saturation Solubility in Water (mg/mL)	0.08	75.58	68.54	52.54	82.54	72.54	78.85

Table 4: Results of Ex Vivo Permeability Study

Formulations	Amount of Drug Permeated within (MEAN ± SD)				
	30 min	60 min	120 min	240 min	360 min
ALC 34	17.58 ± 0.12	28.89 ± 0.21	35.82 ± 0.22	39.1 ± 0.11	39.16 ± 0.12
Pure drug	8.65 ± 0.21	16.94 ± 0.13	22.10 ± 0.24	24.73 ± 0.34	32.42 ± 0.24
Marketed	14.67 ± 0.34	21.28 ± 0.44	29.99 ± 0.32	32.59 ± 0.21	35.96 ± 0.12

Table 5: Plasma Concentration Profile of Azilsartan Formulations

Time (hours)	Plasma Concentration (ng/mL)		
	APD	AZ	ALC4
0	0.00	0.00	0.00
0.5	63.73	86.77	233.43
1	179.48	184.60	344.35
1.5	348.21	374.87	463.79
2	581.15	604.44	761.30
3	770.80	786.57	893.47
4	984.01	1010.06	1230.01
6	817.38	861.11	1011.88
8	762.13	784.62	950.96
10	717.48	722.08	893.17
12	653.84	672.74	833.27
18	550.19	554.57	692.81
24	446.90	462.91	570.89

Table 6: Pharmacokinetic Parameters of Azilsartan Formulations

Parameter	Unit	APD	AZ	ALC4
K	1/h	0.033	0.031	0.032
t1/2	h	20.82	22.24	21.80
Tmax	h	4	4	4
Cmax	ng/ml	984.01	1010.06	1230.01
AUC 0-t	ng/ml*h	14829.55	15220.82	18744.84
AUC 0-inf_obs	ng/ml*h	28254.77	30079.76	36704.48
AUMC 0-inf_obs	ng/ml*h^2	894295.40	1006141.38	1208952.17
MRT 0-inf_obs	h	31.65	33.44	32.94
Vz/F_obs	Ltrs	0.318	0.320	0.257
Relative BA with APD				129.91
Relative BA with AZ				122.02

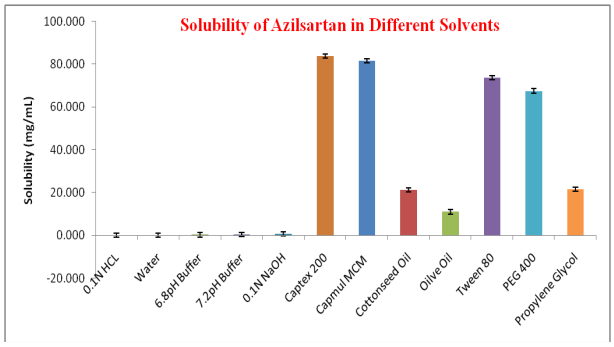

Figure 1: Solubility of Azilsartan in different non volatile liquids

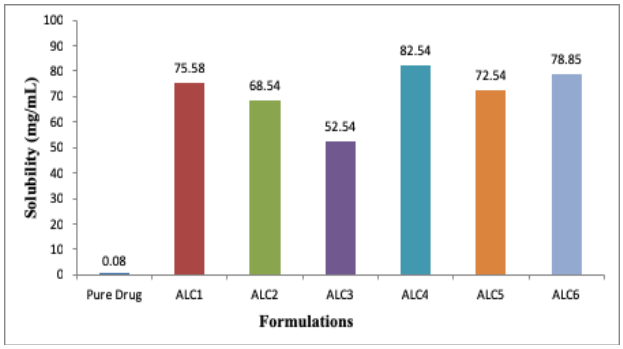

Figure 2: Saturation Solubility results of Liquisolid formulations in water

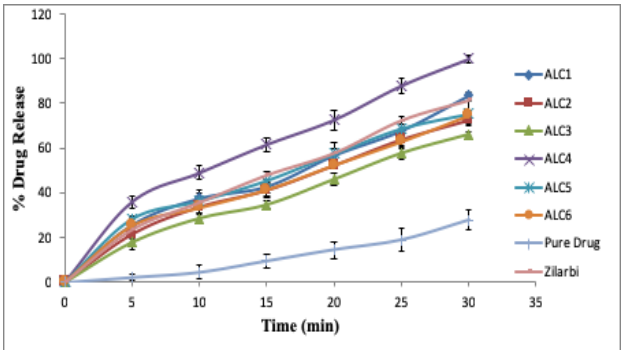

Figure 3: Dissolution Profile of Lipid Based Liquisolid Formulations

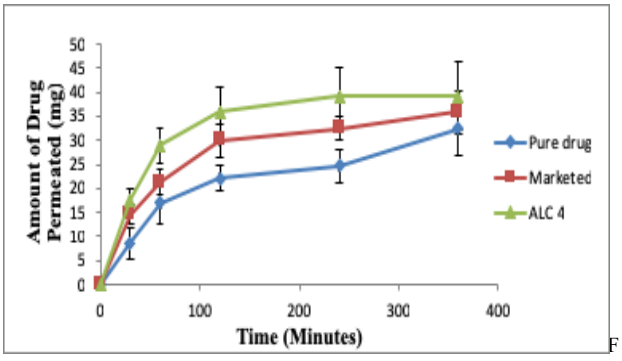

Figure 4: Ex Vivo Permeability results of azilsartan formulations

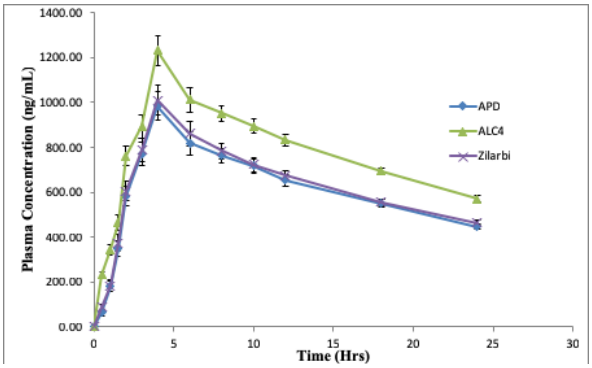

Figure 5: Comparative Plasma Concentration- Time Profile of Different Formulations of Azilsartan

RESULTS AND DISCUSSION

Saturation Solubility Studies

Saturation solubility data of drug Azilsartan medoxomil in various liquid vehicles is shown in Figure 1. Azilsartan appears to be more soluble in Capmul MCM and Captex 200 than other vehicles. The solubility is an important factor in liquisolid systems, as higher solubility of drug in liquid vehicle can lead to higher dissolution rates since the drug will be more molecularly dispersed and more surface of drug will be exposed to the dissolution media. Hence, these two vehicles were selected for liquisolid formulations.

Evaluation of Liquisolid Formulations

Micromeritics Parameters

Good flow is required and is crucial for content uniformity. The results of various flow parameters are shown in Table 3. All the formulations have shown good and improved flow compared to pure drug. This could be probably due to the presence of silica.

Content Uniformity

All the prepared formulations were found to uniform in their drug content

Saturation Solubility studies

Results of saturation solubility studies are shown in figure 2. It was observed that all the prepared formulations has shown improved solubility in water and the formulation prepared with Capmul MCM as non volatile liquid vehicle and Pearlitol SD 200 as carrier (ALC4) has comparatively higher solubility than other formulations.

In Vitro Dissolution Studies

The dissolution profiles of the pure drug, marketed formulation and liquisolid formulations are shown in Figures 3. It was observed that the dissolution rate has been increased significantly compared to the pure drug formulation and marketed formulation. Formulation ALC4 has shown complete drug release in 30 minutes. Improved drug dissolution might be due to the high intrinsic solubility of drug in Capmul MCM, presence of this liquid in the formulation and hydrophilic coat formation of Pearlitol SD200 surrounding the drug.

Ex vivo Permeability Study

Ex vivo permeation studies were conducted for 6 hrs using goat intestinal membrane for the optimized formulation, pure drug and marketed formulations. Amount of drug diffused at various time intervals was calculated and the results obtained are given in the Tables 4. Graph was plotted by taking amount of drug permeated on Y-Axis and time on X-axis and shown in Fig. 4. From the results it was noticed that optimized formulations have shown greater amount of drug permeation through membrane than the marketed and pure drug at each time interval.

In Vivo Pharmacokinetic Study

In vivo studies revealed that the bioavailability of optimized formulation is high compared to pure drug and marketed product. The plasma concentration data was given in table 5. The pharmacokinetic parameters were calculated and listed in table 6. Plasma concentration time profile is shown in figure 5. It was observed that the oral bioavailability of optimized formulation is increased by 1.29 times and 1.22 times when compared to pure drug and marketed formulation respectively.

CONCLUSION

In the present study, the potential of lipid based liquisolid systems to improve the dissolution and permeability properties of BCS Class IV drug Azilsartan Medoxomil was investigated. The results showed that saturation solubility, dissolution, permeability and in vivo bioavailability has been increased to greater extent. Thus lipid based liquisolid technology shall be used to improve the dissolution release and permeability rate of BCS Class IV drugs that will make the dosage form will be more bioavailable and cost effective.

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