Journal of Pharma Research
Available online through
www.jprinfo.com

Research Article
ISSN: 2319-5622

Formulation and Evaluation of Immediate Release Capsules of Telmisartan

M. Santhosh Aruna*, N. Santhi Priya, D. Charitha, A. Naga Jyothi, N. Rama Rao
Department of Pharmaceutics, Chalapathi Institute of Pharmaceutical Sciences, Lam, Guntur, INDIA.

Received on: 24-11-2015; Revised and Accepted on: 04-11-2015

ABSTRACT

Oral bioavailability of a drug depends on its solubility and/or dissolution rate, and dissolution may be rate determining step for appearance of medicinal effect, therefore efforts to increase dissolution of drug with limited water solubility is often needed. Many methods are available to improve these characteristics, including salt formation, micronization and addition of solvent or surface active agents. The present study was aimed to increase the solubility of the poorly water soluble drug Telmisartan by using sodium starch glycolate (SSG), micro crystalline cellulose (MCC). Solid dispersions were prepared by solvent deposition technique, Saturation solubility studies, in-vitro dissolution of pure drug, physical mixtures and solid dispersions were carried out. All the polymers were found to be effective in increasing the dissolution rate of Telmisartan in solid dispersions when compared to pure drug.

Key Words: *Solvent Deposition, Telmisartan, Solubility, Dissolution, Bioavailability.*

INTRODUCTION

Some drugs classified as low solubility drugs on the basis of *in vitro* measures of aqueous solubility may have acceptable *in vivo* solubility because of either pH dependence or solubility in GI fluids. If these drugs with acceptable *in vivo* solubility are BCS Class II, they would then be expected to have acceptable oral bioavailability from standard solid oral dosage forms [1]. For BCS Class II drugs that are shown to have low bioavailability owing to their poor solubility and inability to dissolve rapidly, the selection of formulation is often of great importance in developing a successful product for oral administration of Class II drugs. The bioavailability of these drugs can be improved by several formulation approaches.

Solvent Deposition Technique:

Reduction of particle size remains the accepted method for increasing dissolution rates. However, upon micronization, hydrophobic drugs have a tendency to clump when exposed to the dissolution medium [2]. Sekiguchi and Obi proposed that the incorporation of a microcrystalline or molecular dispersion of a poorly soluble drug in a solid matrix of water-soluble carrier would increase the dissolution rate and absorption of the drug [3]. Since then, modifications of the technique have been suggested under a variety of names, including solid solutions, eutectics, co-precipitates, and fast-release solid dispersions [4].

This new method was investigated for increasing the dissolution rate of drug by depositing drug in "minuscular form" on the surface of an adsorbent. This technique was termed as solvent deposition. The term "minuscular form" implies that the drug has undergone molecular micronization when it is dispersed on the extensive surface of the micro particulate adsorbents. It is an approach used for increasing the dissolution rates of relatively insoluble powders.

Telmisartan is chemically described as 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H- enzimidazol]-1'-yl) methyl]-[1, 1'-biphenyl]-2-carboxylic acid. Its molecular formula is $C_{33}H_{30}N_4O_2$ with molecular weight of 514.6. It appears as White to slight yellowish crystalline powder. Telmisartan is practically insoluble in water and in the pH range of 3 to 9, sparingly soluble in strong acid (except insoluble in hydrochloric acid), and soluble in strong base. Telmisartan interferes with the binding of angiotensin II to the angiotensin II AT1-receptor by binding reversibly and selectively to the receptors in vascular smooth muscle and the adrenal gland. As angiotensin II is a vasoconstrictor, which also stimulates the synthesis and release of aldosterone, blockage of its effects results in decreases in systemic vascular resistance.

Following oral administration, peak concentrations (Cmax) of telmisartan are reached in 0.5-1 hour after dosing. Food slightly reduces the bioavailability of telmisartan, with a reduction in the area under the plasma concentration time curve (AUC) of about 6% with the 40 mg tablet and about 20% after a 160 mg dose. The absolute bioavailability of telmisartan is dose-dependent. At 40 mg and 160 mg, the bioavailability was 42% and 58%, respectively [6, 7]. So, in order to enhance oral bioavailability, solubility enhancement can be achieved via solid dispersion formation.

The aim of the present study was to in order to achieve increased dissolution rates. Therefore, in the present study, solvent depositions of telmisartan were prepared by solvent evaporation technique using acetone as solvent for dissolving the drug. Acetone was selected as a solvent of choice since the drug has highest solubility in this solvent and acetone could be easily evaporated and recovered because of its low boiling point. Acetone as per ICH guidelines is categorized under class II solvents thus rendering it to be less toxic than other chlorinated solvents.

MATERIALS AND METHODS

Telmisartan a gift sample of Hetero drugs, Hyderabad, Acetone (qualigens), Croscarmellose sodium (CCS) and sodium starch glycolate (SSG). All other materials used in the study were of analytical or pharmaceutical grade.

Analytical Methods:

Telmisartan (10 mg) was accurately weighed, dissolved in methanol and volume was made to 100 ml to obtain a stock solution (100 µg/ml). Different aliquots of this solution were diluted suitably with pH 7.5 buffers to give solutions containing 2 - 10 µg/mL of Telmisartan. The absorbance of these solutions was measured at 296 nm on UV-Visible spectrophotometer against pH 7.5 buffer as a blank.

Phase Solubility Studies:

Phase solubility studies were carried out according to the method of Higuchi and Connors. An excess amount of drug was added to 15 ml of aqueous solution containing SSG, MCC in various molar ratio concentrations (0, 3.0, 6.0, 9.0, 12.0, 15.0 mM) and

***Corresponding author:**
M. Santhosh Aruna
Department of Pharmaceutics,
Chalapathi Institute of Pharmaceutical Sciences,
Lam, Guntur, INDIA.
**E-Mail: santhosharuna.kathi@gmail.com*

placed on a rotatory shaker and agitated at room temperature for 48 hours. After equilibrium, the solutions were carefully filtered through Whatman No.41 filter paper and after appropriate dilution; solutions were analyzed at 296 nm by using UV- visible spectrophotometry.

Preparation of Pure drug Capsules of telmisartan:

10mg of telmisartan was accurately weighed and transferred manually in to hard gelatin capsules. They were coded as gelatin capsules.

Preparation of Solvent Deposited Systems of telmisartan:

Required amount of telmisartan was dissolved in 10 ml of acetone. Accurately weighed carrier corresponding to different drug: carrier ratio by weight was dispersed in drug solution. The solvent was allowed to evaporate on water bath under occasional stirring at temperature of 40-42°C in a protected environmental condition containing an exhaust system. The dried mass was pulverized and was passed through a #60-mesh sieve. The powder was subsequently dried at 40°C for 3 hours in a tray drier. The dried powder was triturated thoroughly and powder equivalent to 50 mg of irbesartan was filled into capsules manually. These capsules were subjected to assay and dissolution studies.

Preparation of Physical Mixtures

Physical mixtures (PM) of telmisartan, CCS and SSG were prepared by geometric dilution method using a mortar and pestle then, powder equivalent to 10mg of telmisartan was filled into capsules manually. These capsules were subjected to assay and dissolution studies. The formulae of the various capsule formulations are given in Table No.1.

Table No. 1: Coding Data of Irbesartan Formulations

DRUG	CARRIER& METHOD	CODE	RATIO
Telmisartan	Nil	A	pure
	Cross caramellose sodium	B	1:1
	Solvent deposition	C	1:2
	Sodium starch glycolate	D	1:1
	Solvent deposition	E	1:2
	Cross caramellose sodium Physical mixture	F	1:1
	Sodium starch glycolate Physical mixture	G	1:1
	Marketed	H	-

Characterization:

1. Percent yield:

Percent yield was determined by following formula:

$$Yield = \left(\frac{a}{b+c}\right) \times 100$$

Where,
a is the weight of solid dispersion sifted through a # 60 sieve,
b is the weight of irbesartan taken for solid dispersion preparation,
c is the weight of polymer taken for solid dispersion preparation.

2. Assay of Capsules:

The contents and the shells of one capsule were taken in a 100 ml volumetric flask, 20 ml ethanol and 20 ml of pH 7.5 buffer was added and the contents were sonicated for 10 min. Later it was made up to the mark with pH 7.5 buffer. This solution was filtered and suitably diluted with pH 7.5 buffer and was assayed at 296 nm for irbesartan.

3. FT-IR Studies:

Structural changes and lack of a crystal structure can lead to changes in bonding between functional groups which can be detected by infrared spectroscopy. The FT-IR spectra was obtained by using an FT-IR spectrometer-430(JASCO, Japan).The samples (Pure drug, PMs and SDs) were previously ground and mixed thoroughly with potassium bromide at 1:100(sample: KBr) ratio, respectively. The scanning range was 4000- 400 cm-1.

4. Dissolution Rate Studies:

The dissolution rate testing of different telmisartan capsule formulations was studied using USP XX1 dissolution rate testing apparatus, (basket type) (LAB INDIA DISSO 2000). The basket was rotated at a speed of 50rpm and the dissolution fluid (1000 ml pH 7.5 buffer) was maintained at a temperature of 37.5^0± 0.5 ^{0}C. At specific time intervals, a 5 ml aliquot of dissolved medium was withdrawn and was replaced with fresh quantity of dissolution medium. The samples were suitably diluted with dissolution medium and assayed for telmisartan content by measuring the absorbance at 296 nm using U.V Spectrophotometer (ELICO SL 159).

5. Mechanism of drug release:

Mechanism of drug release was obtained by applying the release data to various models like zero order, first order, Higuchi.

Table No. 2: Mechanism of drug release

MODEL	EQUATION	PLOT OF GRAPH	PARAMETER
Zero order	F= Ko t	% drug release Vs time	Ko- release rate constant
First order	Log (100-F)=Kt	log % drug remaining Vs time	K- release rate constant
Higuchi release	F= K_1 t1/2	% drug release Vs square root of time	K1- release rate constant

RESULTS AND DISCUSSION

1. Percentage yield:

Percentage yield was calculated according to the formula and results are given in Table 3

2. In vitro dissolution studies:

Dissolution data of solvent depositions on excipients were reported in Fig 2, all the prepared solid dispersion showed an enhancement in the dissolution rate of the drug compared to plain drug. Solvent depositions prepared by using sodium starch glycolate showed enhanced dissolution rate when compared to other carriers. Solvent depositions of telmisartan were prepared with various carrier concentrations and the effect of increasing carrier concentration on dissolution rate was determined.

3. Mechanism of drug release:

To determine the kinetics of release, the drug release data was treated and rate constants for zero order, first order and Higuchi model was obtained and reported in Table 5. The release of drug from solvent depositions followed first order kinetics as seen from R2 value.

Table No. 3: % Yield & Assay of various formulations of Telmisartan solvent depositions

CODE	D:C RATIO	% YIELD	ASSAY
B	1:1	94.25	97.89±0.5
C	1:2	97.65	98.25±0.2

D	1:1	91.58	95.88±0.6
E	1:2	93.55	97.54±0.5
F	1:1	95.64	96.99±0.4
G	1:1	96.57	98.62±0.8

Table No. 4: Comparison studies of Dissolution profiles in pH 7.5 buffer (n=3)

CODE	D:C RATIO	T5	T20	T30	T45	T60	T90
A	PURE	4.52	10.21	14.62	19.95	25.82	32.22
B	1:1	10.22	16.46	25.29	32.54	45.95	65.89
C	1:2	25.21	35.48	45.21	58.55	62.84	82.78
D	1:1	19.87	42.22	54.35	69.86	72.54	89.95
E	1:2	29.89	52.62	65.98	74.86	84.52	92.54
F	1:1	7.52	14.56	26.31	31.57	39.78	52.55
G	1:1	12.24	38.47	41.53	52.21	59.67	75.68
H	MARKETED	10.58	24.85	36.86	54.22	65.14	79.96

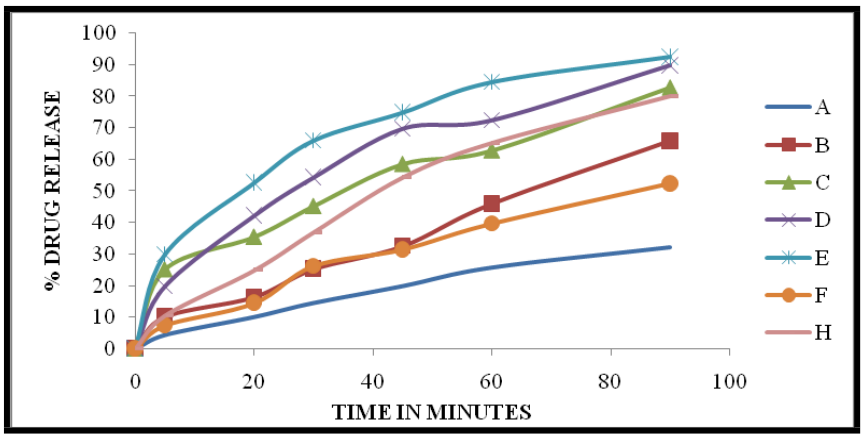

Fig. 2: Dissolution profiles of different formulation in pH 7.5 buffer

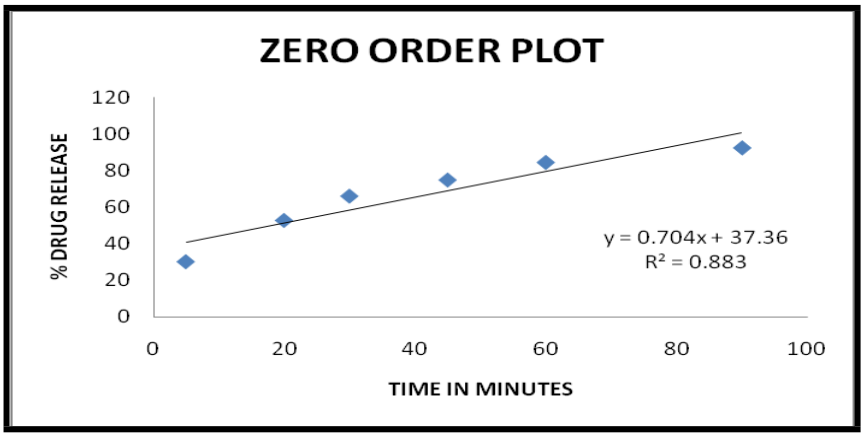

Fig. 3: Formulation E Zero Order Plot

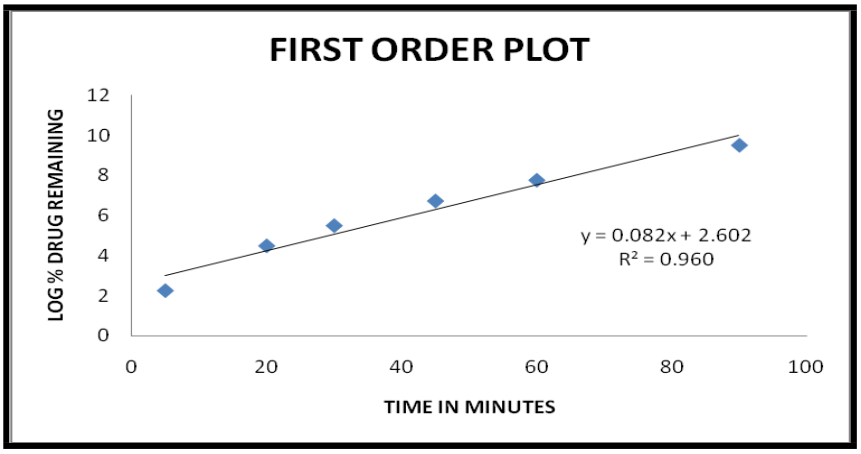

Fig. 4: Formulation E First Order Plot

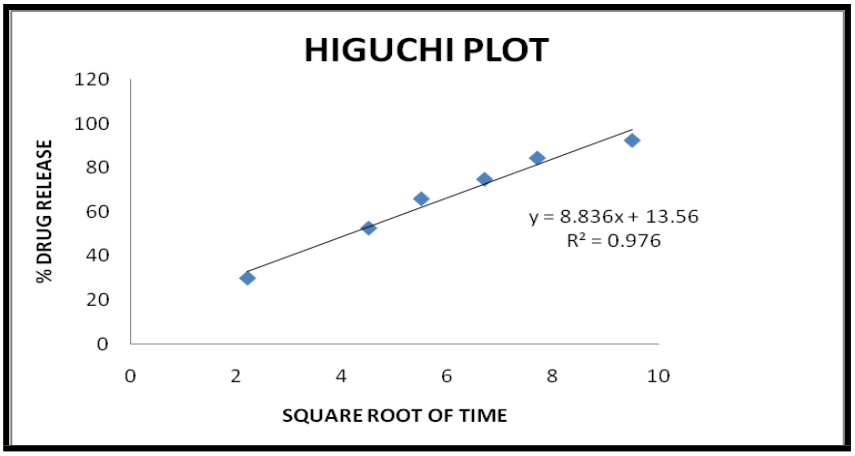

Fig. 5: Formulation E Higuchi Plot

Table No. 5: Drug release and Rate constants for zero order, first order and Higuchi model

CODE	PARAMETER	ZERO ORDER	FIRST ORDER	HIGUCHI
E	K	0.704	-0.082	8.836
	r^2	0.883	0.960	0.976

CONCLUSION

The solubility and dissolution profile of Telmisartan which is a poorly water soluble drug was significantly improved by preparing solvent depositions by using Croscarmellose sodium and sodium starch glycolate as carriers. Compatibility studies revealed that there is no interaction between the drug and carrier. The mode of drug release is following first order kinetics, the release of drug is expected as erosion of polymer from the solid dispersions.

ACKNOWLEDGEMENTS

We would like to sincerely thank the Management of Chalapathi educational society and Principal of Chalapathi institute of pharmaceutical sciences, Guntur, for letting us avail the facilities of the College.

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How to cite this article:

M. Santhosh Aruna, et al.,: Formulation and Evaluation of Immediate Release Capsules of Telmisartan, J. Pharm. Res., 2015; 4(11): 379-382.

Conflict of interest: The authors have declared that no conflict of interest exists.

Source of support: Nil