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Comparative Dissolution Studies of Marketed Tablets of Telmisartan in Biorelevant Media

Monica RP Rao*[1], Rewathi Shiledar[1], Manjiri Bhosale[1], Mayuresh Garud[1], Ganesh Medhekar[1]

1. AISSMS College of Pharmacy, Kennedy Road, Near RTO,Pune 411 001

ABSTRACT

In vitro dissolution studies constitute the mainstay for evaluation of any oral dosage form and more so for a poorly water soluble drugs. Selection of appropriate dissolution medium is critical for these studies as it could have an impact on *in vitro* - *in vivo* correlations. Biorelevant media simulate the *in vivo* conditions in fasting and fed state and are being investigated as novel dissolution media. Telmisartan is a BCS class II drug exhibiting solubility and dissolution rate limited bioavailability. In the present study 03 marketed brands of TEL tablets were subjected to *in vitro* dissolution studies in biorelevant media. The results were compared with tablets prepared using binary and ternary solid dispersions of TEL with poloxamer 188 and TPGS. The marketed and formulated products displayed widely different release profiles in fasting and fed state simulated intestinal fluid. The results indicated the need to develop dissolution studies and media which will facilitate *in vitro in vivo* correlation studies.

Key Words: Telmisartan, fasting state simulated intestinal fluid, fed state simulated intestinal fluid

*Corresponding Author Email: monicarp_6@hotmail.com

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INTRODUCTION

The design of formulations with relevant oral bioavailability depends on a number of factors including solubility, permeability and metabolic stability. Absorbability is related to the first two factors whose importance has been recognized in the guise of the biopharmaceutical classification system (BCS) [1]. The BCS is a framework for classifying drug substances based on their aqueous solubility and intestinal permeability [2]. This important achievement affected many industrial, regulatory and scientific aspects of drug development and research [3]. The phenomenal progress in the field of high throughput screening and combinatorial chemistry in the last two decades has led to the development of a large number of molecules with excellent therapeutic outcomes but nearly 40% of these molecules exhibit poor water solubility thereby giving erratic or poor absorption profiles. The rate at which a drug goes into solution is an important determinant of drug absorption from the GIT. Factors which influence absorption include physicochemical properties of the drug such as pKa, solubility, crystalline energy and specific surface area as well as the physiological parameters like pH, surface tension, solubilization, buffer capacity and volume of luminal contents[4]. Simulation of GI conditions is essential to adequately predict the *in vivo* behavior of poorly soluble drugs. Simulating small intestinal conditions with biorelevant media such as fasted state simulated intestinal fluid (FaSSIF) and fed state simulated intestinal fluid (FeSSIF) has become standard practice in many laboratories [5-7]. These media have been used to examine the solubility and dissolution characteristics of several classes of drugs including poorly soluble weak bases and lipophilic drugs to assist in predicting *in vivo* absorption behavior [4]. Biorelevant *in vitro* dissolution testing is useful for qualitative forecasting of formulation and food effects on the dissolution and availability of orally administered drugs. Biorelevant dissolution media containing bile salt and lecithin at concentrations appropriate for fed and fasted state are useful when testing oral solid formulations of poorly water-soluble drugs. It has been observed that biorelevant media can provide a more accurate simulation of pharmacokinetic profiles than simulated gastric fluid or simulated intestinal fluid. The use of biorelevant media can have a great impact on the pharmacokinetic studies performed to optimize dosing conditions and product formulation. In addition, biorelevant dissolution testing could be used to assess bioequivalence of post-approval formulation changes in certain kinds of drugs [8].

The aim of the present study was to investigate the dissolution profile of some marketed tablets containing a BCS Class II drug, Telmisartan(TEL) in biorelevant media as well as conventional

dissolution medium. TEL, a benzimidazole derivative, is an antagonist of subtype1 angiotensin II receptors (AT2) intended for the treatment of essential arterial hypertension. Other specific angiotensin II receptor antagonists like losartan, valsartan, irbesartan, eprosartan, and candesartan have already been approved in the European Union. TEL is available in the form of tablets of strength 20, 40 or 80 mg. It is practically insoluble in water (9.9 µg/ml) hence the drug is slowly or incompletely dissolved in the gastro intestinal tract and hence shows low oral bioavailability (42%).

MATERIALS AND METHOD:

Telmisartan (TEL) was a gift sample from Unichem Laboratories, Mumbai, India. Tocopherol polyethylene glycol 1000 succinate (TPGS) was a generous gift sample by Isochem, France. All the ingredients and reagents used in the study were of analytical grade and procured locally. The marketed products selected for the study were CRESAR (Cipla Ltd.) (Brand 1), TELMA (Glenmark Pharmaceuticals Ltd.) (Brand 2) and TELISTA (Lupin Pharmaceuticals Inc.) (Brand 3). Each uncoated tablet contained 40 mg of TEL.

Preparation of calibration curve:

The stock solution, containing 100 µg/ml of TEL was prepared in FaSSIF and FeSSIF as well as phosphate buffer pH 7.4. Dilutions in concentration range of 0.5-10 µg/ml were prepared in methanol as Beers-Lambert law was followed in this range and the dilutions were analyzed at 298 nm by UV spectrophotometer. For phosphate buffer the Beers-Lambert law was obeyed in the concentration range of 10-50 µg/ml.

Preparation of solid dispersions of TEL:

The term solid dispersion (SD) refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles[9]. SDs of TEL drug were prepared by using fusion method using poloxamer 188 as a carrier, singly in one formulation (F1) and combination of poloxamer 188 and TPGS in another formulation (F2).Briefly, the components were weighed in the specified ratio (1:1) of drug and poloxamer 188 for F1, while for F2 the ratio was (1:1:0.1) for TEL, poloxamer 188 and TPGS, respectively. For preparing the SDs by fusion method drug and carrier were placed separately in porcelain dish. The carrier(s) was heated up to the melting point (for Poloxamer 188 (45° C) and TPGS (37-41°C) respectively, using controlled heating in a heating mantle. The drug was then dispersed in molten carrier and mixed thoroughly and allowed

to cool with continuous stirring. The solidified masses were kept overnight in vacuum dessicator, triturated and passed through sieve no. 60 for further use.

Preparation of TEL Tablets:

Tablets were prepared using SDs of the drug. SDs equivalent to 40 mg of TEL were mixed with other tablet excipients as given in Table 1. The components were weighed, mixed in geometric proportion and passed through sieve 22. Tablets were then prepared by direct compression, using Mini Press II MT (Make: RIMEK) and 8 mm flat punches. Each tablet weighed ~ 220 mg for both types of formulations and hardness was between 5 ±1kg/cm^2. The tablets were subjected to dissolution study in biorelevant media.

Table 1: Formula of tablets containing binary and ternary solid dispersions

Sr. no.	Ingredient	F1	F2
1.	Solid dispersion	80 mg	84 mg
2.	Micro crystalline cellulose	22 mg	22 mg
3.	Talc	5.5 mg	5.5 mg
4.	Magnesium stearate	5.5 mg	5.5 mg
5.	Sodium starch glycolate	1.1 mg	1.1 mg
	Lactose	q.s.	q.s.

Preparation of biorelevant media and dissolution study:

FaSSIF and FeSSIF media were prepared on the day of the experiment as per the procedure given byZoeller[10] (Table 2).

Table 2: Composition of biorelevant media

Ingredients	FaSSIF	FeSSIF
Sodium taurocholate	15mM	3mM
Lecithin	3mM	0.75mM
NaH_2PO_4	-	3.438g
Acetic acid	8.65g	-
NaCl	11.874g	6.186g
NaOH pellets	4.04g	qs pH6.5
Deionized water	qs 1 liter	qs 1 liter

The dissolution test for each formulation (F1, F2) and marketed tablets (Brand 1, 2, 3) was performed in triplicate using USP Type II dissolution test apparatus (Electrolab TDT-08L. USP standard) at 75 rpm and 37 ± 0.5°C. The test was carried out by using 500 ml of FaSSIF and 1000 ml of FeSSIF as dissolution medium. Aliquots of 5 ml were periodically withdrawn and the volume was replaced with fresh dissolution medium. The aliquots (1ml) were further diluted with methanol upto 10 ml and analyzed using UV spectrophotometer (Jasco V-550, Japan) at 298 nm, using methanol as blank. Cumulative percentage of labeled amount of drug released at

each time point was then calculated. Dissolution studies were also carried out in phosphate buffer pH 7.5 in a similar way, as per the guidelines of US FDA.[11]

RESULTS AND DISCUSSIONS:

Drug dissolution is an important physicochemical factor affecting the drug absorption and hence bioavailability. For drug to be absorbed from gastrointestinal (GI) tract to systemic circulation, it must be released from the product and dissolved in aqueous based GI fluid. In general, without dissolution in aqueous based medium, absorption of the drug in the body may not occur. Absorption of hydrophobic, poorly water soluble drugs is often said to be dissolution rate limited.

The best way of assessing therapeutic efficacy of drugs with slow dissolution rate is *in vivo* determination of bioavailability which is usually done whenever a new formulation is to be introduced into market. However, monitoring batch to batch consistency through use of such *in vivo* testing is extremely costly, tedious and time consuming besides exposing healthy subject to hazards of drugs. It would therefore be always desirable to substitute the *in vivo* bioavailability test with inexpensive *in vitro* methods. *In vitro* dissolution testing is a prognostic tool which can quantitatively assure the biological availability of drug from its formulation. For the *in vitro* assessment of *in vivo* behavior of a drug formulation, the dissolution test is most often used, both for development purposes and for quality control. Physical and chemical data for the drug substance and dosage unit need to be determined before selecting the dissolution medium. Two key properties of the drug are the solubility and solution state stability of the drug as a function of the pH value. When selecting the composition of the medium, the influence of buffers, pH value and surfactants on the solubility and stability of the drug need to be evaluated .The dissolution characteristics of an oral formulation should be evaluated in the physiologic pH range of 1.2 to 6.8 (1.2 to 7.5 for modified-release formulations). Typical media for dissolution may include dilute hydrochloric acid, buffers in the physiologic pH range of 1.2 to 7.5, simulated gastric or intestinal fluid (with or without enzymes), water, and surfactants (with or without acids or buffers) such as polysorbate 80, sodium lauryl sulfate and bile salts[12]. Ampiphilic bile components including bile salts and lecithin, the concentration of which increase following a meal [13], have been shown to increase the *in vitro* dissolution rate for numerous poorly soluble compounds [14-15] either by an increase in solubility via micellar solubilization (at concentrations above the critical micelle concentration) and/or by improved wettability of the compound. In case of TEL, the US FDA recommends phosphate buffer pH 7.4 as the media for studying the *in*

vitro dissolution profile. All the brands under study showed profoundly different dissolution profiles in the three media.

Figure 1 shows cumulative percentage release of labeled amount of drug in FaSSIF media. Brand 1 showed an initial burst release of about 6.51% in the first 60 min followed by a release of 28.38% in 8h whereas Brand 2 showed a release of 99.47% in 8 h. Brand 3 showed complete release in 2 h. While F1 showed initial release of 35.85% followed by a release of 94.45% at the end of 8 h, F2 showed a release of 99 % in 8h.

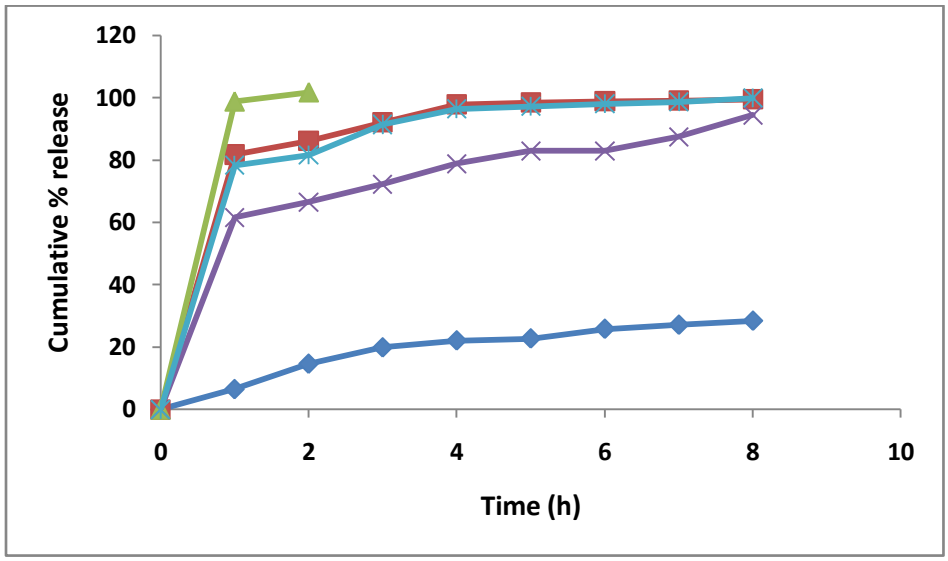

Figure 1: Comparative Dissolution Profile of TEL in FaSSIF

Each of the marketed tablets showed widely different dissolution profiles in FaSSIF. In F2 presence of TPGS as surfactant contributed to enhanced release from the tablets. This could be attributed to improved wettability of TEL obviously leading to improved dissolution and release form the dosage form.

Figure 2 shows cumulative percentage release of labeled amount of drug in FeSSIF media. Brand 1 showed an initial burst release of about 42.72% in the first 60 min followed by a release of 58.98% in 5h whereas Brand 2 showed a release of 66.72% in 5 h. Brand 3 released 63.62 % after 8h in FeSSIF media. Each brand under study showed varying dissolution profiles in FeSSIF as compared to FaSSIF. While F1 showed initial release of 40.54 % followed by a release of 53.72% at the end of 8h and F2 showed a release of 62.40% after 8h.No similarities were found between the release profiles of the products under study in the biorelevant media. No specific trend was evident and this could have undesirable ramifications if one product is substituted with the other or if appropriate directions for intake of the tablet are not clearly provided.

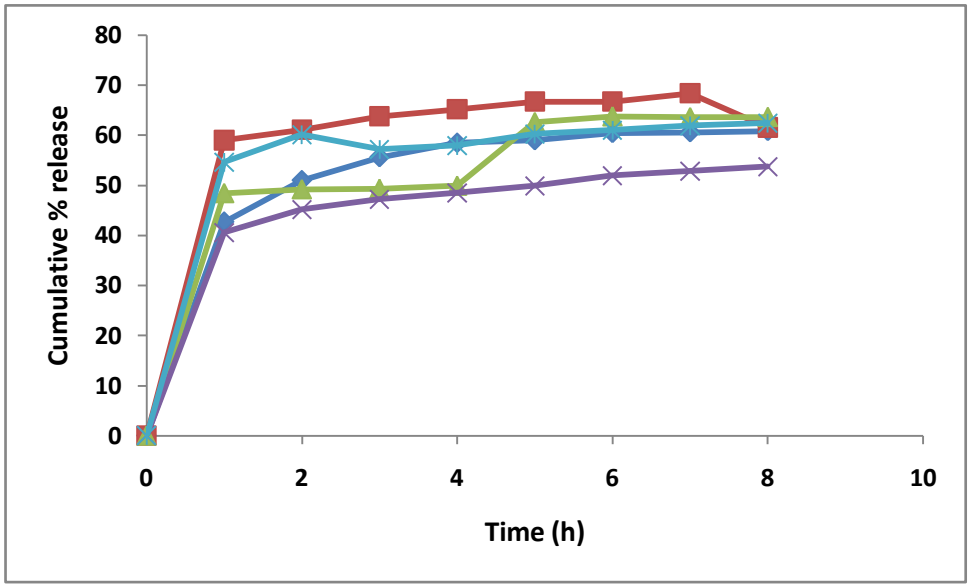

Figure 2: Comparative Dissolution Profile of TEL in FeSSIF

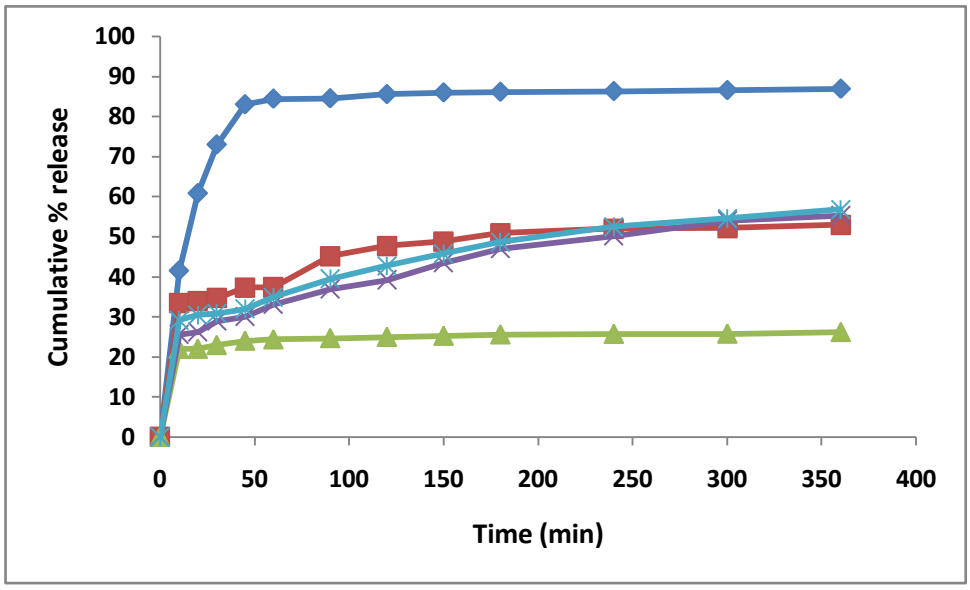

Figure 3: Comparative dissolution profile of TEL in phosphate buffer pH 7.4

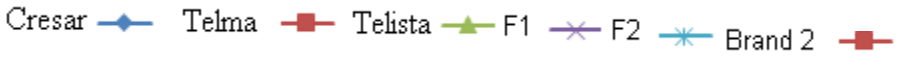

Figure 3 shows cumulative percentage release of labeled amount of drug in phosphate buffer pH 7.4, which is recommended as the dissolution media as per USP specifications. Again no similarities were observed between the dissolution profiles in phosphate buffer and in the biorelevant media. There were also intra-brand differences thereby further stressing the need and importance of selection of appropriate dissolution media. Brand 1showed an initial burst release of about 41.48% in the first 10 min followed by a release of 86.15% in 3h whereas Brand 2

showed a release of 52.97% in 6 h. Brand 3 released only 22-26% drug in phosphate buffer in the span of 6h. F1 showed a initial burst release of 25.51% followed by a release of 46.97% in 3h and F2 showed a release of 56.77% at the end of 6h.The enhancement in dissolution for all five products in FeSSIF indicates that the higher bile salt and lecithin concentration combined with the lower pH have significant impact on the dissolution rate. All the formulations exhibited significantly slower release in biorelevant media as compared to pH 7.4 buffer. Intra-brand differences were also evident in different dissolution media. Brand 1 showed better release in FeSSIF than in FaSSIF whereas tablets of brand 2 and brand 3 displayed a significantly faster release in FaSSIF than in FeSSIF. Formulations F1 and F2 containing binary and ternary SDs of TEL with poloxamer 188 and TPGS also displayed higher release in FaSSIF than in FeSSIF. Presence of TPGS led to a marginal increase in cumulative release in both biorelevant media.

CONCLUSION:

Biorelevant media are useful for forecasting the effect of food and other physiological conditions on the fate of drug *in vivo*. This is particularly critical for BCS class II and IV drugs which show erratic dissolution profiles and it is difficult to produce *in vitro-in vivo* co relations for such drugs. Selection of suitable biorelevant media which can mimic *in vivo* conditions can go a long way in helping the formulation scientists at the formulation development stage and also help the innovator to ensure rational drug therapy to the patients.

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