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## Dissolution studies of telmisartan: Influence of pH on the release of drug from oral formulations

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### ABSTRACT

Telmisartan is Angiotensin II Receptor Antagonist, which is used in the prevention and treatment of Hypertension. Telmisartan belongs to class II drug in BCS classification, i.e. low solubility and high permeability. The dissolution of a drug in specific gastrointestinal fluids is important for absorption into the systemic circulation. Dissolution studies {using USP Apparatus 2 (Paddle Apparatus) at 75 rpm with dissolution media including pH 1.2 hydrochloric acid, and pH 4.5, pH 6.8, pH 7.5 buffers} on various commercial products of Telmisartan were carried out to compare drug release. Statistical methods were used to compare the dissolution profiles. These included Model independent method, i.e. Dissimilarity factor (f1) and the Similarity factor (f2) as recommended by FDA. It was observed that formulation factors significantly affect the solubility of a drug at various pH. The dissolution profile of Tazloc tablets at various pH exhibited significant differences compared to other commercial products. Tazloc tablets showed consistently higher release at pH 4.5 and 7.5, (i.e., pH conditions relevant to the intestine) suggesting its pharmacokinetic activity could be perhaps superior to other marketed brands as higher dissolution leads to better absorption that may lead to better plasma levels and thus better efficacy.



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### INTRODUCTION

Telmisartan is an angiotensin II receptor antagonist used in the treatment of hypertension. It binds to the angiotensin II type 1 (AT1) receptors with high affinity, inhibiting the action of angiotensin II on vascular smooth muscle, thus causing a reduction in arterial blood pressure (Wienen *et al.*, 2000).

The drug release from a formulation and solubility at the site of absorption can significantly predict the therapeutic efficacy of a drug. This is related to the pharmacodynamics, which relates the dosage form and the pharmacological effects of a drug, including the *in vivo* absorption of solid dosage forms. Several complex factors are involved during these processes, with disintegration and dissolution playing a major role (Lee *et al.*, 2002).

According to the Biopharmaceutics Classification System (BCS), aqueous solubility and permeability are the most important variables affecting drug bioavailability. Telmisartan is classified as Class II, that is drugs that have low solubility and high permeability characteristics after oral administration as telmisartan is practically insoluble in water and the pH range of 3 to 9, sparingly soluble in strong acid, and soluble in strong base. Bioavailability of telmisartan is also poor about 45%, which is due to extensive first-pass hepatic metabolism. As the site of absorption is mainly duodenum and jejunum, thus dissolution is very important at the site of absorption (Pang S K 2003).

The difference in formulations of various brands is in the use of excipients such as diluents, disintegrants, lubricants, and variations in their amounts (Pillay *et al.*, 1998; Maggio *et al.*, 2008). During processing, the formulation is subjected to compression forces which alter the disintegration time of the dosage form, as well as its dissolution rate of the formulation. Poor dissolution and absorption and leads to inadequate blood pressure control. Thus increasing aqueous solubility and dissolution of telmisartan at is of therapeutic importance.

Numerous studies have been carried out in order to modify the dissolution kinetics of poorly soluble telmisartan and to improve absorption. Tazloc is a tablet containing telmisartan in a highly soluble form. This highly soluble telmisartan is obtained by using a unique manufacturing process (ODCA - Optimum Dissolution Complete Absorption) wherein telmisartan is solubilized in an alkaline matrix, which will improve the absorption at the right site in the intestine.

Considering these facts, it was considered necessary to carry out a comparative dissolution study of various brands of telmisartan available in retail pharmacies. An ideal dissolution test is expected to give information of product quality as well as some preliminary *in vivo/in-vitro* correlation or bio-relevance (Emami, 2006).

## MATERIALS AND METHODS

### Materials

Three commercially available marketed products were purchased from pharmacies for the study, the details of which are shown in Table 1.

### Chemicals

Telmisartan was obtained from Vedant Life SciPvt. Ltd, A.P. (India), potassium dihydrogen phosphate, potassium chloride were purchased from Merck Life Sciences Pvt. Ltd Mumbai, concentrated hydrochloric acid purchased from Loba Chemie, Mumbai, sodium hydroxide pellets, sodium acetate, Glacial acetic acid were purchased from-Chemdyes, Gujarat. Whatman filter paper (Grade 42, Ashless). Distilled water was used to prepare aqueous solutions. The USP method was used to prepare the required dissolution media.

### Apparatus and instruments

#### ➤ Dissolution Test Apparatus

USP Apparatus 2 (Paddle Apparatus) : Electrolab Tablet Dissolution Tester USP-8

#### ➤ UV Visible Spectrophotometer (Jasco UV-630)

## EXPERIMENTAL

Table.1. Gives the details of the various Telmisartan tablets used in the study.

### Analytical method development

#### Standard plot of Telmisartan: pH 1.2 Hydrochloric acid

10 mg of accurately weighed Telmisartan was dissolved in pH 1.2 HCl in a 100ml volumetric flask and the volume was made up to thus giving a stock solution (100 µg/ml). Suitable aliquots were diluted to obtain solutions with 2, 4, 6, 8, 10, 12, 14 and 16 µg/ml of Telmisartan. A UV-Vis spectrophotometer was used to measure the absorbance at 291 nm. A graph of absorbance versus concentrations was plotted to obtain the standard plot and the results were evaluated using linear regression analysis.

#### Standard plot of Telmisartan: pH 4.5 buffer

10 mg of accurately weighed Telmisartan was dissolved in pH 4.5 buffer in a 100ml volumetric flask and the volume was made up to thus giving a stock solution (100 µg/ml). Suitable aliquots were diluted to obtain solutions with 2, 4, 6, 8, 10, 12, 14 and 16 µg/ml of Telmisartan. A UV-Vis spectrophotometer was used to measure the absorbance at 296 nm. A graph of absorbance versus concentrations was plotted to obtain the standard plot and the results were evaluated using linear regression analysis.

#### Standard plot of Telmisartan: pH 6.8 buffer

10 mg of accurately weighed Telmisartan was dissolved in pH 6.8 buffer in a 100ml volumetric flask and the volume was made up to thus giving a stock solution (100 µg/ml). Suitable aliquots were diluted to obtain solutions with 2, 4, 6, 8, 10, 12, 14 and 16 µg/ml of Telmisartan. A UV-Vis spectrophotometer was used to measure the absorbance at 296 nm. A graph of absorbance versus concentrations was plotted to obtain the standard plot and the results were evaluated using linear regression analysis.

#### Standard plot of Telmisartan: pH 7.5 buffer

10 mg of accurately weighed Telmisartan was dissolved in pH 7.5 buffer in a 100ml volumetric flask and the volume was made up to thus giving a stock solution (100 µg/ml). Suitable aliquots were diluted to obtain solutions with 2, 4, 6, 8, 10, 12, 14 and 16 µg/ml of Telmisartan. A UV-Vis spectrophotometer was used to measure the absorbance at 296 nm. A graph of absorbance versus concentrations was plotted to obtain the standard plot and the results were evaluated using linear regression analysis.

### Dissolution studies

Dissolution studies of Telmisartan tablets were carried out as per the protocol is given in Table.2. The drug in the aliquots withdrawn was analysed by UV Spectroscopy at a wavelength of 296 nm.

### Comparison with Tazloc (USVPvt.Ltd.)

The reference product was Telmisartan (40mg) tablets marketed by USV Pvt. Ltd.  $f_1$  and  $f_2$  factors of SUPAC (Scale-up and Post Approval Change), as given by the Food & Drug Administration, was used to compare the samples. A value of  $f_2$  greater than 50 and difference factor ( $f_1$ ) between 0-15 (in the dissolution profiles) indicates similarity between the reference and samples.

A measure of the relative error between two dissolution curves is  $f_1$  (difference factor) :

$$f_1 = \left\{ \frac{\sum_{t=1}^n |R_t - T_t|}{\sum_{t=1}^n R_t} \right\} \cdot 100$$

where  $n$  = number of time points in the study,  $R_t$  = dissolution value of the reference (pre-change) at time  $t$ , and  $T_t$  = dissolution value of the test (post-change) at a given time  $t$ .

It gives the percent difference between the two curves at each time of withdrawal of aliquot.

The similarity factor ( $f_2$ ) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves (FDA, 1997; Simionato *et al.*, 2018).

The factor  $f_2$  is given by:

$$f_2 = 50 \cdot \log \left\{ \left[ 1 + \frac{1}{n} \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} \right\} \cdot 100$$

where  $n$  = number of time points in the study,  $R_t$  = dissolution value of the reference (pre-change) at time  $t$ , and  $T_t$  = dissolution value of the test (post-change) at a given time  $t$ .

## RESULTS AND DISCUSSION

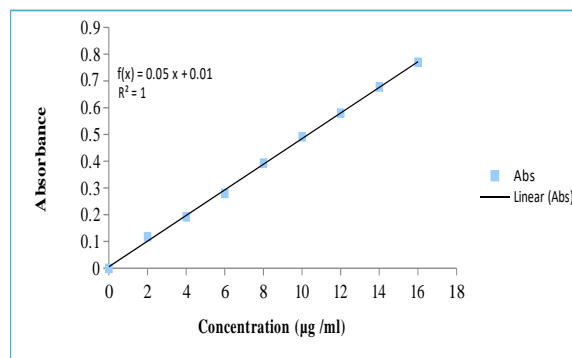
### The standard curve of Telmisartan

Calibration curve of telmisartan was obtained in pH 1.2 HCl, pH 4.5 sodium acetate buffer, pH 6.8 phosphate buffer and pH 7.5 phosphate buffer. The plot was linear in the concentration range of 2-16  $\mu$ /ml. The respective coefficient of regression values  $R^2$  is as given in Table.3 and fig.1, 2, 3 and 4.

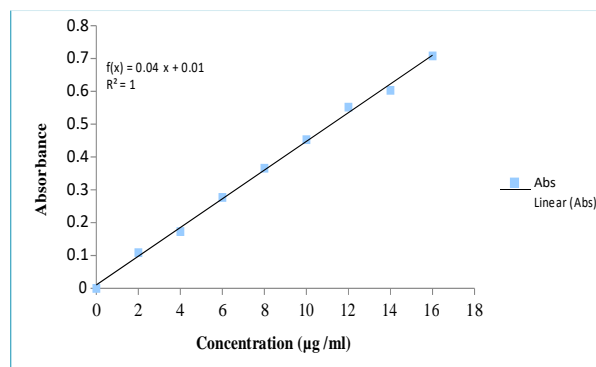
### Dissolution studies (*In vitro* drug release)

#### pH 1.2 hydrochloric acid

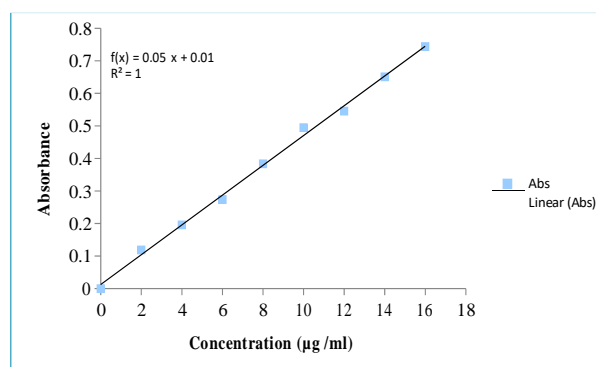
The *in vitro* release patterns of Telmisartan tablets are shown in fig.5. Tazloc showed 83.6 % maximum drug release in 1hr when compared with Brand A and Brand B. The Indian Pharmacopoeia (2010) states that not less than 70 % of the drug must be released in 60 mins. These criteria are fulfilled by only Tazloc which was 83.6 % (IP, 2010; USP, 2012).



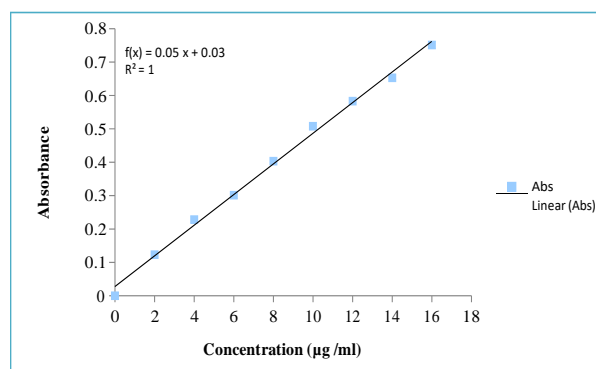
**Figure 1: Standard Plot of Telmisartan: pH 1.2 Hydrochloric acid**



**Figure 2: Standard Plot of Telmisartan: pH 4.5 Acetate buffer**



**Figure 3: Standard Plot of Telmisartan: pH 6.8 Phosphate buffer**



**Figure 4: Standard Plot of Telmisartan: pH 7.5 Phosphate buffer**

**Table 1: Marketed brands of Telmisartan tablets**

Brand Name	Strength (mg)	Batch Number	Manufacturing Date	Expiry Date
Brand A	40	E4ALQ090	July 2017	June 2019
Brand B	40	18170560	May 2017	April 2019
Tazloc	40	48008960	May 2017	April 2019

**Table 2: Dissolution studies: Protocol**

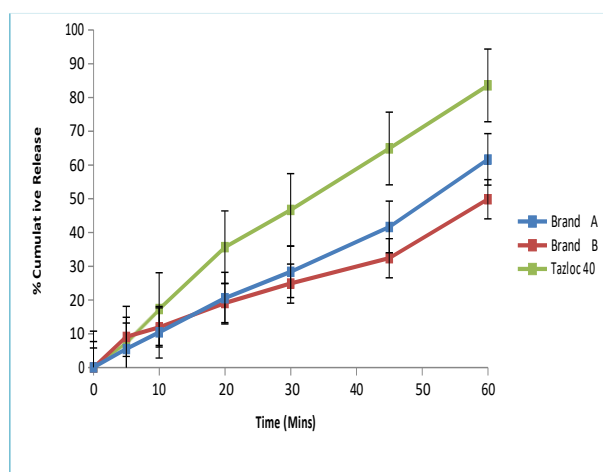
Factors	Details
Apparatus	USP Apparatus 2 (Paddle Apparatus)
Dissolution Media	pH 1.2 Hydrochloric acid, pH 4.5 Acetate buffer, pH 6.8 Phosphate buffer and pH 7.5 Phosphate buffer
Volume of Dissolution Medium	900 ml
Speed	75 RPM
Sampling time	5,10, 20,30, 45 and 60 mins
Aliquot withdrawn	5 ml
Temperature	37°C ± 0.5°C
Method of analysis	UV Spectrophotometry pH 1.2 Hydrochloric acid:λmax= 291 nm and for other buffers λmax =296 nm
No. of Tablets	6

**Table 3: Standard plot of Telmisartan in various media**

Buffers (pH)	Straight line equation	R <sup>2</sup>
1.2 Hydrochloric acid	Y= 0.0479X + 0.006	0.998
4.5 Acetate buffer	Y=0.0437X + 0.010	0.997
6.8 Phosphate buffer	Y= 0.0458X+0.012	0.997
7.5 Phosphate buffer	Y=0.0459X+0.027	0.996

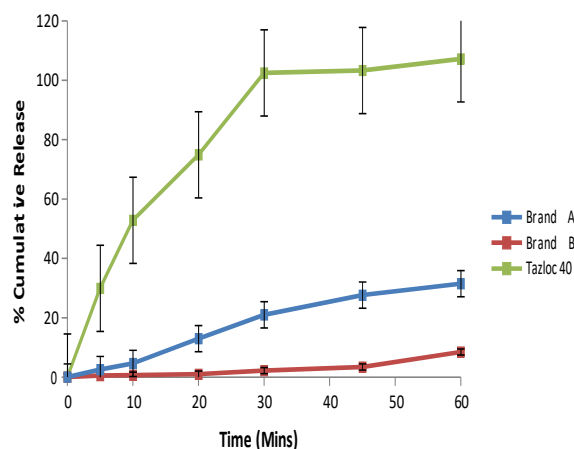
**Table 4: Summary of Dissolution Profile of various brands of Commercial Telmisartan**

Brands	pH 1.2 Hydrochloric acid		pH 4.5 Acetate Buffer		pH 6.8 Phosphate Buffer		pH 7.5 Phosphate Buffer	
	f1	f2	f1	f2	f1	f2	f1	f2
Brand A	26.26	37.23	71.72	17.6	25.92	32.66	25.01	34.21
Brand B	67.67	23.56	92.42	14.756	0.88	100.5	9.62	52.02

**Figure 5: In vitro drug release from Telmisartan tablets: pH 1.2 Hydrochloric acid (Brand A, Brand B, Tazloc)****pH 4.5 Sodium acetate buffer**

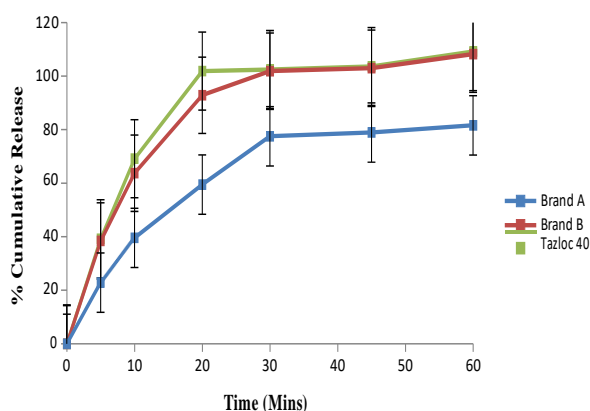
*In vitro* release of Telmisartan tablets are shown in fig. 6. The USV Pvt. Ltd. brand Tazloc exhibited maximum drug release (107.17%) as compared to Brand A and Brand B (less than 40%) in 60 min.

This can be attributed to the effective formulation factors of the product. Telmisartan alone has low solubility in pH 4.5 Sodium acetate buffer as indicated earlier suggesting the release of Telmisartan from Tazloc tablets over a wider range of pH.

**Figure 6: In vitro drug release from Telmisartan tablets: pH 4.5 Sodium Acetate buffer (Brand A, Brand B, Tazloc)**

### pH 6.8 Phosphate buffer

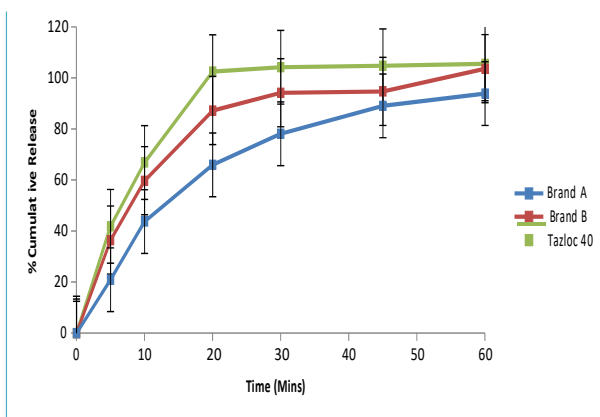
*In vitro* release pattern of Telmisartan tablets are shown in fig.7. Brand A, Brand B and Tazloc showed 81.63, 108.23, 109.2 %, respectively of drug release in 60 mins.



**Figure 7: In vitro drug release from Telmisartan tablets: pH 6.8 Phosphate buffer (Brand A, Brand B, Tazloc)**

### pH 7.5 Phosphate buffer

*In vitro* release pattern of Telmisartan tablets are shown in fig.8. In both the Indian Pharmacopoeia and the United States Pharmacopoeia. Both the IP (2014, 2018) and USP state that not less than 75% of the drug must be released in 30 mins. We observed a cumulative release (CR) of 78.14%, 94.19% and 104.21% for Brand A, Brand B and Tazloc, respectively.

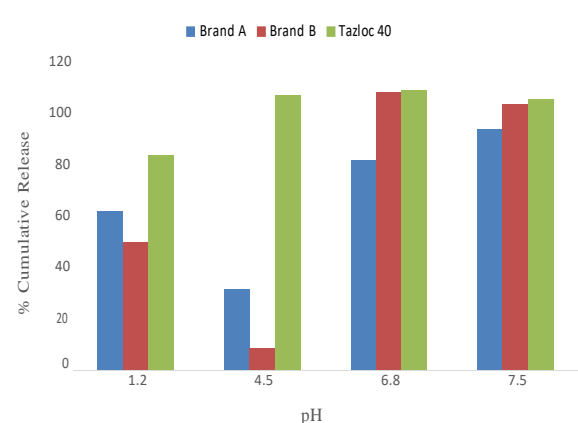


**Figure 8: In vitro drug release from Telmisartan tablets: pH 7.5 Phosphate buffer (Brand A, Brand B, Tazloc)**

### Comparison of *in vitro* release profile of different brands in different Dissolution Media

A comparison of the *in vitro* release profiles of various brands of Telmisartan tablets is shown in fig.9. Although the brands fulfilled the specifications of the dissolution test which is specified in the IP and USP, significant differences were observed between *in vitro* dissolution profiles of

Telmisartan tablets of different commercial products.



**Figure 9: A comparison of in vitro drug release profiles of various brands of Telmisartan tablets in various media (pH 1.2 Hydrochloric acid, pH 4.5 Acetate buffer, pH 6.8 and pH 7.5 Phosphate buffer (Brand A, Brand B, Tazloc) )**

### Comparison with Tazloc (USVPvt. Ltd.)

$f_1$  and  $f_2$  values for dissolution data of other brands and Tazloc were determined to check dissolution dissimilarity and similarity using the two factors. The results are shown in Table 4.

The results revealed that similarity and dissimilarity with the Tazloc were observed with Brand B only in dissolution media pH 6.8 and 7.5 phosphate buffers. Also, none of the commercial brands displayed similarity and dissimilarity with Tazloc in various dissolution media. Variation in solubility and rate of dissolution amongst the formulations studied is mainly due to the incorporation of different excipients for the same purpose or use of particular excipients in an altered concentration. The excipients used in tablet formulations include bulking agents, disintegrants, and manufacturing additives such as lubricants. The disintegration of a tablet occurs before the dissolution of the drug. Therefore the disintegrating agent selected, its optimum concentration, mechanism of action, existence in the tablet: intra or inter-granular, are important factors to be considered. Also, a hydrophobic lubricant can significantly hamper disintegration and dissolution of a drug. Further, the processing method: direct compression or granulation and the force of compression may aid or hamper dissolution.

### CONCLUSION

The rate of dissolution directly affects the therapeutic efficacy of a drug. The rate of drug absorption, the extent to which a drug is absorbed, the onset time can be altered due to poor release and dissolution of the drug from a formulation. The results of dissolution studies for commercial products were found to be quite different from Tazloc; thus

the obtained results proved that the dissolution tests are formulation dependent. It is observed from this dissolution study that Tazloc has higher drug release in all the buffers. Considering the necessary requirement that an orally administered drug must dissolve to be absorbed and thus produce a therapeutic response, it can be predicted that the absorption profile of Tazloc at the site of absorption) (pH 4.5 is better than other brands thus providing better clinical management of the underlying condition.

### Acknowledgement

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