Commercial Telmisartan Tablets: A Comparative Evaluation with Innovator Brand Micardis

PRATIKKUMAR A. PATEL AND VANDANA.B.PATRAVALE[1]

Department of Pharmaceutical Sciences and Technology, Institute of Chemical Technology, N.P.Marg, Matunga, Mumbai 400 019, India.

ABSTRACT

Purpose: Telmisartan is an angiotensin II receptor antagonist used in the management of hypertension. The solubility of Telmisartan in aqueous solutions is strongly pH-dependent. Five commercial tablets of telmisartan (40 and 80 mg) were compared with the reference formulation Micardis (Innovator brand of telmisartan molecule). **Experimental**: Dissolution tests were performed by employing USP type apparatus-II (Paddle type) at 75rpm using pH 1.2, 4.5 and 7.5 buffers as the dissolution media. The percentage cumulative release of Telmisartan was measured at 5, 10, 15, 30, 45, and 60 minutes respectively. The factor f2 of the FDA's SUPAC Guide was applied to the qualitative determination of 'similarity' between pairs of dissolution profiles of Micardis and those of each investigated formulation. **Results:**None of the commercial brands were similar to Micardis in dissolution profile at various pH points of testing. This was observed for both the strengths. **Conclusion**: Micardis tablets at both the strengths 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 it would release the drug consistently irrespective of pH.

Key words: Telmisartan, Micardis, F2 Factor, Comparative Dissolution Profile

INTRODUCTION

The pharmacokinetic and pharmacodynamic parameters are the strong predictors of the therapeutic response of the drug. Pharmacodynamics is a link relating dosage forms with pharmacological effects, especially how solid dosage forms are absorbed in vivo. In the process many complicated factors are involved, among which, drug disintegration and dissolution are very important ones [1].

Telmisartan is an angiotensin II receptor antagonist (ARB) used in the management of hypertension. Generally, angiotensin II receptor blockers such as Telmisartan bind to the angiotensin II type 1 (AT1) receptors with high affinity, causing inhibition of the action of angiotensin II on vascular smooth muscle, ultimately leading to a reduction in arterial blood pressure.

The pharmacokinetics of orally administered Telmisartan is nonlinear over the dose range 20-160 mg, with greater than proportional increases of plasma concentrations (C_{max} and AUC) with increasing doses. The solubility of Telmisartan in aqueous solutions is strongly pH-dependent, with maximum solubility observed at high and low pH. In the range of pH 3–9 it is only poorly soluble. Telmisartan is active as such: it is not a prodrug. The Telmisartan molecule is unusually stable [2].

Formulations of different brands have different types and/or amount of diluents, disintegrants, lubricants, or other excipients. They may be also subjected to different compression forces which affect the disintegration and dissolution rate of a given formulation. Apart from this, feedback from doctors that some Telmisartan brands need to be given more than the recommended once daily dose or that doses higher than the recommended 80 mg are required to produce the desirable clinical effects necessitated a study comparing the dissolution profiles and other parameters of these generic Telmisartan brands with that of the innovator brand Micardis.

[1] **For correspondence**
E mail: vbp_muict@yahoo.co.in
Tel No: +91-22-3361-2217; Fax: +91-22-33611020

MATERIALS AND METHODS

Samples

Five commercially available samples were purchased from the local market for the study (see Table no.1)

Name of Company	Code	Brand Name	Strength	Batch Numbers	Manufacturing Date	Expiry Date
Glenmark Pharmaceuticals	GLN 40	Telma	40	349000806	Dec. 2009	Nov. 2011
	GLN 80		80	05901664	Sep. 2009	Aug. 2011
Aristo Pharmaceutical Pvt. Ltd	ART 40	Telvas	40	32502B0	Feb.2010	Jan. 2012
	ART 80		80	34802K9	Oct. 2009	Sep. 2011
Lupin LTD	LUP 40	Telista	40	13129B	Dec.2009	Nov.2011
	LUP 80		80	01010B	Jan. 2010	Dec.2011
Intas Pharmaceutical	INT 40	Sartel	40	DL0411	Feb. 2010	Jan. 2012
	INT 80		80	DL0360	Feb. 2010	Jan. 2012
Dr. Reddy's Laboratory	DRL 40	Telsartan	40	TB91225	Dec.2009	Nov.2011
	DRL 80		80	TC00202	Feb. 2010	Jan. 2012
Boehringer Ingelheim	BI 40	Micardis	40	907851	Sep. 2009	Sep. 2013
	BI 80		80	907224	Aug. 2009	Aug. 2013

Table-I Details of commercially available Telmisartan tablets used in the study

Chemicals

Telmisartan was a kind gift from Boehringer Ingelheim, Germany, potassium dihydrogen phosphate, sodium acetate, concentrated hydrochloric acid, sodium hydroxide pellets, potassium chloride (s.d. fine chemicals, Mumbai) were used as received. Whatman Filter Paper (Ashless, 1440-110, Grade 40 circles, 110 mm) and Distilled water were utilized for studies.
The dissolution media were prepared as per USP procedure

Apparatus/Instruments

- **Dissolution Test Apparatus**
  USP type II apparatus (Paddle) Electrolab Tablet Dissolution Tester USP TDT-06
- **UV Visible Spectrophotometer**
  Shimadzu UV-1560
- **Monsanto Hardness Tester**
  Model: EI 66 Expo
- **Disintegration Test Apparatus**
  Electrolab tablet disintegration tester USP, ED-22

EXPERIMENTAL

All samples were coded as shown in Table 1 and given to the investigator for analysis.
All products tested were stored within specified conditions and were within their shelf life.

I. Analytical Method Development

For dissolution study, the drug was analysed by UV Spectroscopy at λ_{max} of 296 nm and standard curves was plotted for respective buffers.

Preparation of Standard Curve

a) Standard Curve at pH 1.2

Telmisartan 10 mg was accurately weighed. The drug was dissolved in pH 1.2 buffer and volume was made to 100 mL to obtain a stock solution of 100 µg/mL. Different aliquots of this solution were diluted suitably to give solutions containing 3, 6, 9, 12 and 15 µg/mL of Telmisartan. The absorbance of these solutions was measured at 296 nm on UV-Visible spectrophotometer against pH 1.2 buffer as blank. The standard curve was performed in triplicate. The linearity was established over the entire concentration range by plotting graph of absorbance versus corresponding concentrations. The data were statistically evaluated using linear regression analysis.

b) Standard Curve at pH 4.5

Telmisartan 10 mg was accurately weighed. The drug was dissolved in methanol and volume was made to 100 mL to obtain a stock solution of 100 µg/mL. Different aliquots of this solution were diluted suitably with pH 4.5 buffer to give solutions containing 3, 6, 9, 12 and 15 µg/mL of Telmisartan. The absorbance of these solutions was measured at 296 nm on UV-Visible spectrophotometer against pH 4.5 buffer as blank. The standard curve was performed in triplicate. The linearity was established over the entire concentration range by plotting graph of absorbance versus corresponding concentrations. The data were statistically evaluated using linear regression analysis.

c) Standard Curve at pH 7.5

Telmisartan 10 mg was accurately weighed. The drug was dissolved in methanol and volume was made to 100 mL to obtain a stock solution of 100 µg/mL. Different aliquots of this solution were diluted suitably with pH 7.5 buffer to give solutions containing 3, 6, 9, 12, 15 and 18 µg/mL of Telmisartan. The absorbance of these solutions was measured at 296 nm on UV-Visible spectrophotometer against pH 7.5 buffer as blank. The standard curve was performed in triplicate. The linearity was established over the entire concentration range by plotting graph of absorbance versus corresponding concentrations. The data was statistically evaluated using linear regression analysis.

d) Standard Curve in Methanol

The standard curve in methanol was prepared to analyze the drug content in the commercially available products.

Telmisartan 5 mg was accurately weighed. The drug was dissolved in methanol and volume was made to 50 mL to obtain a stock solution of 100 µg/mL. Different aliquots of this solution were diluted suitably with methanol to give solutions containing 3, 6, 9, 12, 15 and 18 µg/mL of Telmisartan. The absorbance of these solutions was measured at 296 nm on UV-Visible spectrophotometer against methanol as blank. The standard curve was performed in triplicate. The linearity was established over the entire concentration range by plotting graph of absorbance versus corresponding concentrations. The data was statistically using linear regression analysis.

II. Evaluation of Hardness

Hardness of the tablets was determined using a Monsanto Hardness Tester.

III. Drug content Determination

Telmisartan content in the tablets was estimated in triplicate using the UV method. Drug content was assessed for six randomly selected tablets. The tablets were crushed and total content of the six tablets was mixed thoroughly. The powder weighed for 40 mg and 80 mg tablets was 50 mg and 25 mg respectively and dissolved in sufficient

quantity (25 mL) of methanol. The solution was sonicated for 10 mins for extraction of the drug in methanol and volume was made up to 25 ml to obtain stock solution I. Stock solution I was filtered and suitably diluted to obtain solution A. The absorbance of solution A was read at 296 nm on UV- Visible Spectrophotometer. The same procedure was followed for all tablets. Due consideration was given to weight of individual commercial samples. The concentration of Telmisartan in tablets was calculated from the standard curve.

IV. Determination of Disintegration Time

The tablets were placed in each of the six tubes of the basket of the disintegration apparatus using water as the immersion fluid. The test was carried out for 30 minutes. The disintegration time was noted when no residue of the unit, except fragments of insoluble coating, remained on the screen of the apparatus.

V. Dissolution Profile Study

The protocol followed for the dissolution study of Telmisartan tablets was as depicted in Table no.2

Table -II Protocol for dissolution studies

Apparatus	Six station USP Type II Dissolution Testing Apparatus (Paddle)
Speed	75 rpm
No. of tablets	6 units
Dissolution media	pH Buffer 1.2, 4.5 and 7.5 (900 ml)
Sampling interval	5,10,15,30,45 and 60 min
Sampling volume	5 ml
Replenishing fluid	pH Buffer 1.2, 4.5 and 7.5 respectively
Temperature	37°C ± 0.5°C
Analytical Method	UV Spectrophotometry (λ_{max} =296 nm)

VI. Comparison with Reference Standard

Micardis tablet containing Telmisartan (40 and 80 mg), supplied by Boehringer Ingelheim, Germany was used as the reference product. References was compared with the samples via f2 factor of SUPAC (Scale-up and Postapproval Change) suggested by FDA. Dissolution profiles of control and samples would be considered similar when f2 is larger than 50.

$$f_2 = 50 \log\left\{\left[1 + \frac{1}{T}\sum_{t=1}^{T}(X_t - Y_t)^2\right]^{-0.5} X100\right\}$$

X*t* is dissolution percentage of reference at time *t* and Y*t* is dissolution percentage of samples at time *t*.

RESULTS AND DISCUSSION

I. Analytical Method Development

Standard plots of Telmisartan and their respective equations relating the concentrations and absorbances were plotted. The method was found to be linear in the range of 3-15 µg/mL with a regression coefficient closed 0.999. The slope of equation was found to be consistent in all the developed methods.

II. Determination of Hardness

Hardness of commercial samples was variable. It varied from 2.0-11.12kg/cm^2.Generally low hardness tablets disintegrate fast but would be more friable and cause problems whilst shipping. Also, additional cost in packaging may be incurred. The values for hardness are provided in the Table no.3.

Code	Strength	Hardness[a] (Kg/cm^2)	DT[b] (Min)	Drug Content[c]	
				Amount (mg)	Percentage (%)
GLN	40	04.87± 0.25	07.10-8.08	40.87 ± 0.94	102.17
	80	06.8 ± 0.62	08.25-9 .00	75.40 ± 2.87	94.25
ART	40	04.46± 0.45	03.08-3.45	39.01 ± 2.06	97.52
	80	11.12 ± 1.03	10.00-1.28	79.87 ± 3.21	99.83
LUP	40	03.75± 0.28	06 .01- 7.10	39.51 ± 3.03	98.77
	80	03.25 ± 1.19	06.05- 6.58	82.49 ± 0.95	103.11
INT	40	05± 0.81	08.06 -8.27	38.21 ± 1.69	95.52
	80	04.8 ± 0.25	09.30-10.21	81.90 ± 1.50	102.37
DRL	40	02± 0.40	05.30 -6.00	38.61 ± 2.10	96.52
	80	07.25 ± 0.86	07.35-8.00	82.12 ± 4.73	102.65
BI	40	08.62± 0.75	08.50 -9.00	39.51 ± 0.87	98.77
	80	07.87 ± 3.56	11.0-12.41	82.70 ± 1.24	103.37

Table-III. The Hardness, DT and drug content of Telmisartan tablets

[a] Data is expressed as mean ± S.D., (n = 4); [b] Data is expressed as mean ± S.D., (n = 6)
[c] Data is expressed as mean ± S.D., (n = 6);DT: Disintragration Time

III. Drug content Determination

The content of active ingredient was determined as described earlier. The concentration of the drug in the tablets analyzed was found to be in the range of 95-103 %. The values for content of Telmisartan are provided in the Table no.3.

IV. Determination of Disintegration Time

From Table no. 3 it is clear that all the commercial brands were within limits as per the pharmacopoeia. ART 80 and BI 80 showed a longer disintegration time as compared to other brands, as hardness of the products was higher. No correlation between hardness and disintegration was seen in rest of generic samples.

V. Dissolution Profile Study

At pH 1.2

The results are indicated in Fig. I. All the samples except BI 40 and GLN 40 gave more than 80% release in 60min.

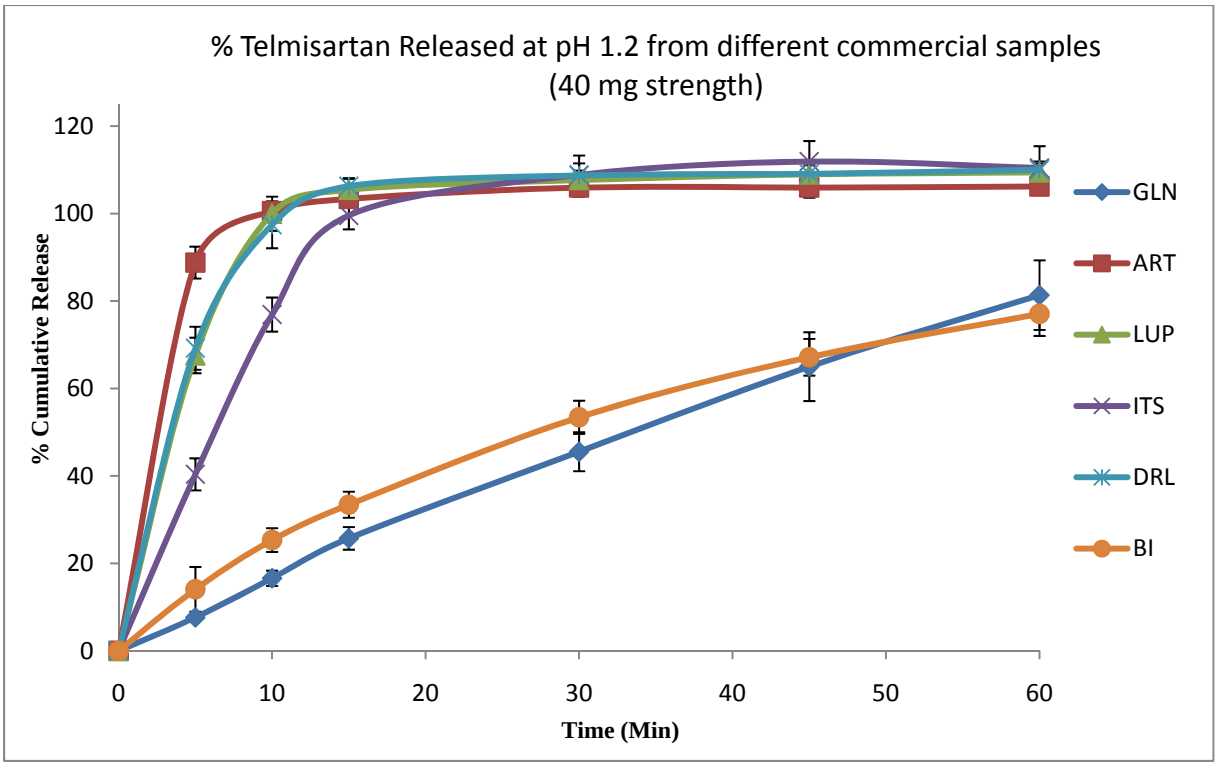

Fig. I. Graph of % Telmisartan released at pH 1.2 from different commercial samples (40 mg strength)

The results are indicated in fig. II. All the samples except GLN 80 and BI 80 gave almost 100% release in 60 min.

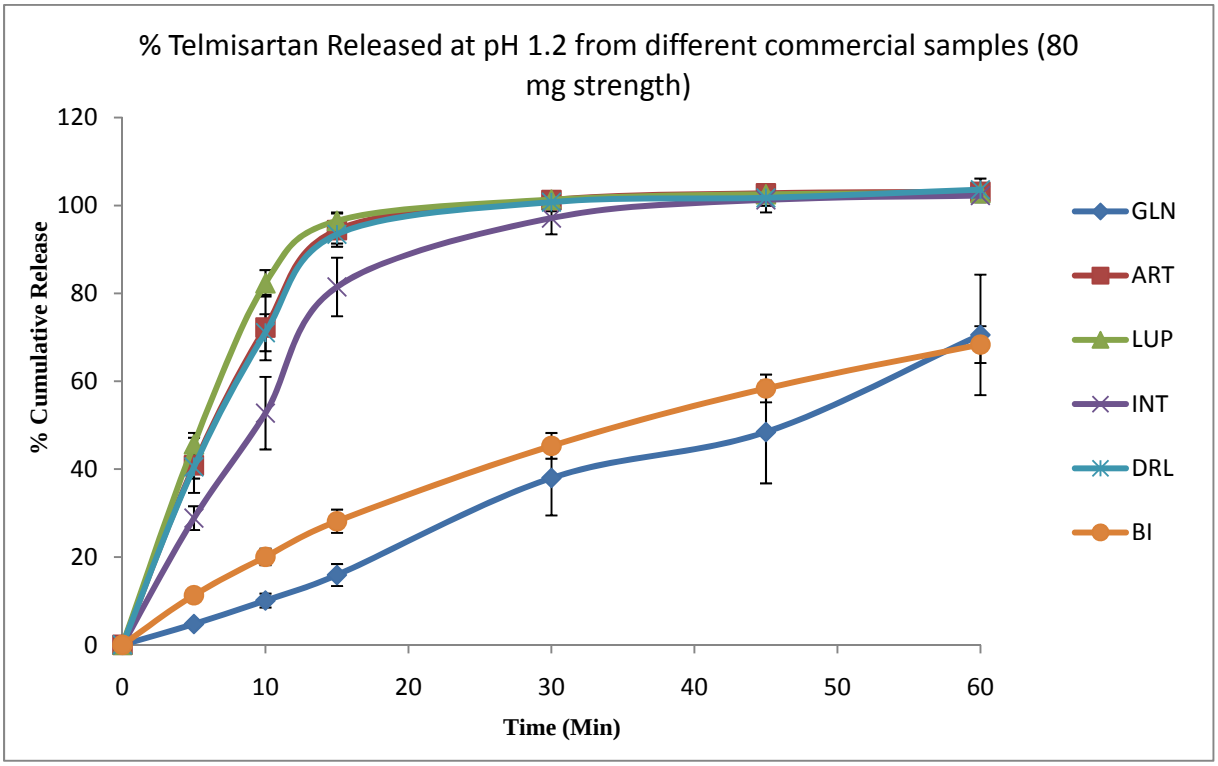

Fig. II. % Telmisartan released at pH 1.2 from different commercial samples (80 mg strength)

At pH 4.5

The only sample which gave more than 50% release in 60min was BI 40. This may be due to formulation characteristics of the product. The drug by itself has low solubility in this buffer as indicated earlier suggesting superiority of BI 40 formulation over others.

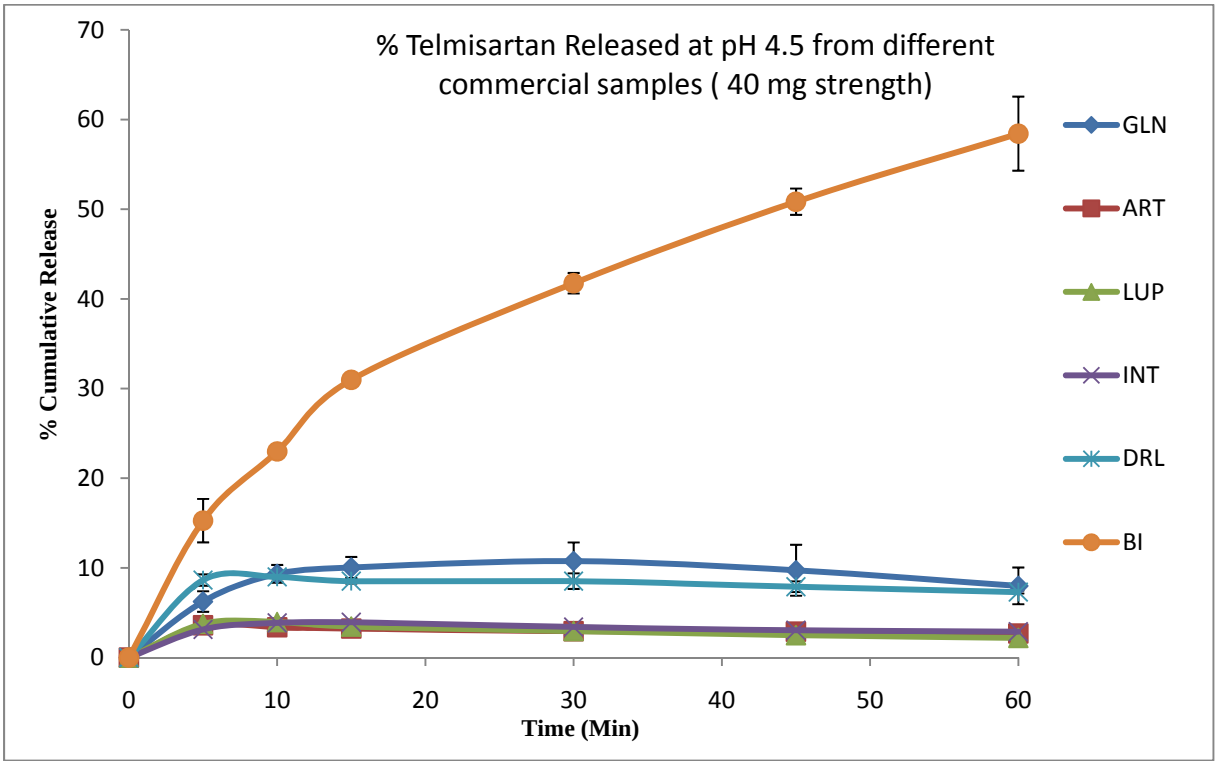

Fig. III. % Telmisartan released at pH 4.5 from different commercial samples (40 mg strength)

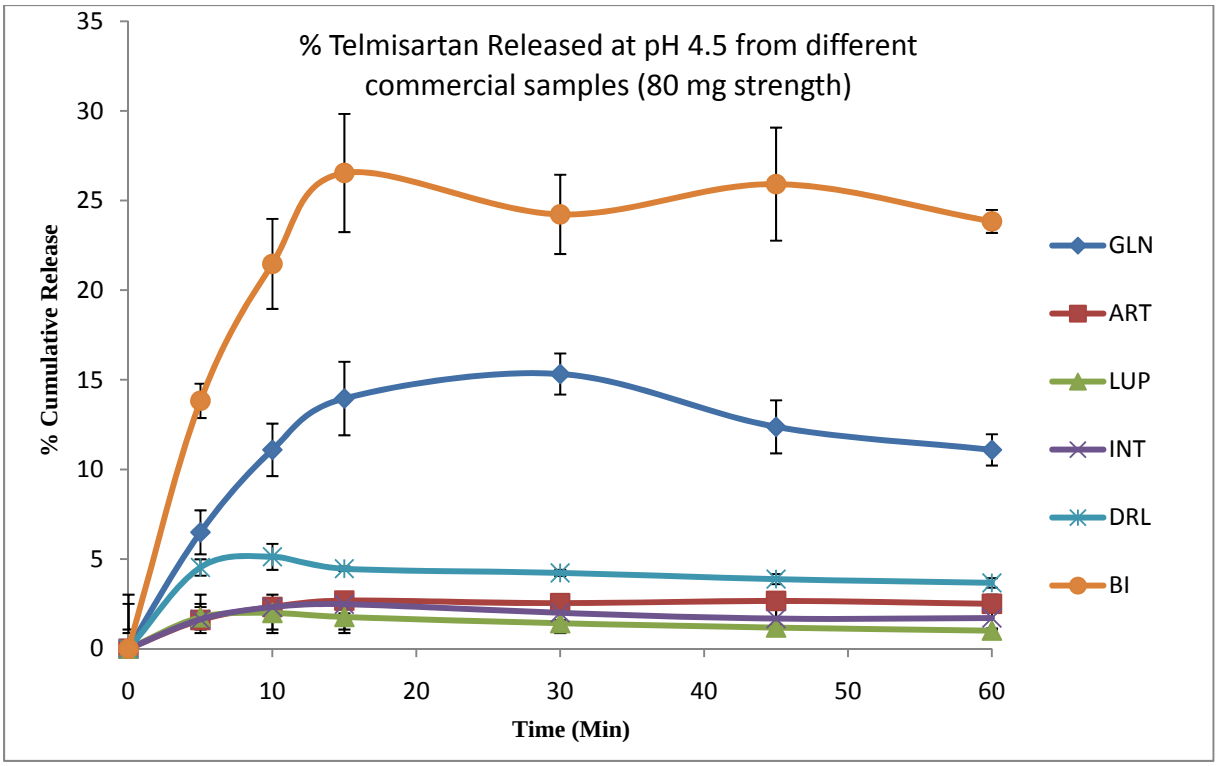

Fig. IV. % Telmisartan released at pH 4.5 from different commercial samples (80 mg strength)

The release of drug from all the formulations was relatively lower than 40mg strength. All dissolution curves obtained did not show further release from 15 min onwards. This may be caused by the limited solubility of Telmisartan at pH 4.5. The only formulation which gave more than 20% in 10min was BI 80 indicating superiority of this formulation for dissolution under these conditions over others.

At pH 7.4

The fig. V indicates that GLN 40, ART 40, LUP 40, INT 40 and DRL 40 gave 39, 23, 19, 19 and 18 % release respectively in 60 min. In fact, this is the media suggested for dissolution studies and profile should match with the innovator [3].

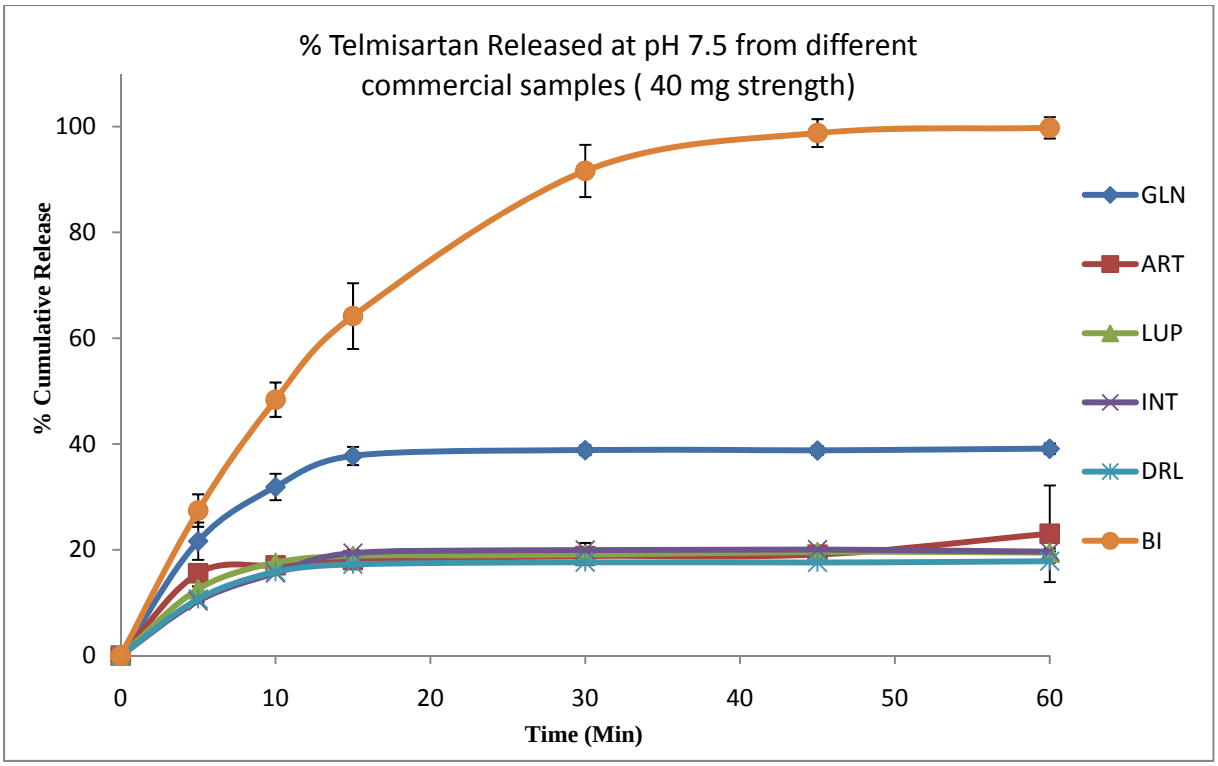

Fig. V. % Telmisartan released at pH 7.5 from different commercial samples (40 mg strength)

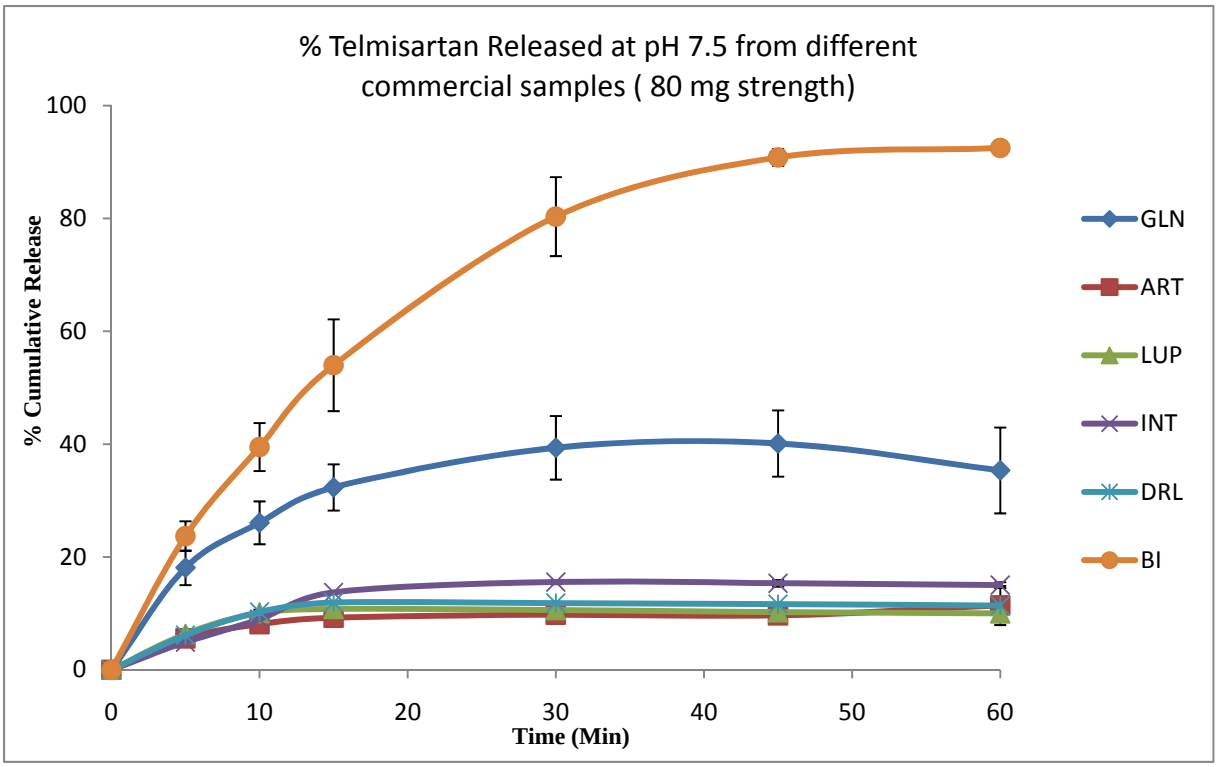

Fig. VI. % Telmisartan released at pH 7.5 from different commercial samples (80 mg strength)

GLN 80, ART 80, LUP 80, INT 80 and DRL 80 gave less than 35 % release in 60 min.

In all the media, irrespective of buffer pH, release of the BI innovator product was significantly more than other commercial brands.

VI. Comparison with Reference Standard

f2 value for dissolution profiles of commercial samples and reference was determined to check profile similarity. Detailed results and relative f2 values are listed in Table IV.

Table-IV. Summary of dissolution profile of commercial tablets

Sample	Label Amount Mg/Tablet	Results					
		pH 1.2 buffer		pH 4.5 buffer		pH 7.5 buffer	
		F2 Value	Similarity	F2 Value	Similarity	F2 Value	Similarity
GLN	40	58.74	**YES**	25.17	NO	18.34	NO
	80	53.01	**YES**	47.56	NO	21.60	NO
ART	40	11.26	NO	21.59	NO	11.50	NO
	80	15.56	NO	34.25	NO	11.16	NO
LUP	40	12.27	NO	21.52	NO	11.28	NO
	80	14.34	NO	33.28	NO	11.28	NO
INT	40	15.86	NO	21.75	NO	11.32	NO
	80	19.55	NO	33.78	NO	11.59	NO
DRL	40	12.22	NO	24.45	NO	10.73	NO
	80	15.86	NO	36.19	NO	11.67	NO

Results indicate that similarity with the reference formulation (Micardis) was observed for Telma (Glenmark) tablets, 40 mg as well as 80 mg strength, in dissolution media pH 1.2 only.

However, none of the commercial samples showed similarity with Micardis in all the buffers. This was observed for both the strengths.

CONCLUSION

When a tablet is ingested it undergoes disintegration, deaggregation and dissolution before being absorbed, the rate and extent of which into the systemic circulation determines its bioavailability. The solubility/dissolution behavior of a drug is key determinant to its oral bioavailability, being the rate-limiting step to absorption of drugs from the gastrointestinal tract. Consequently poor solubility results in low bioavailability increase in the dosage, large inter- and intra-subject variation and large variations in blood drug concentrations under fed versus fasted conditions. If the drug does not dissolve readily or cannot penetrate the epithelial membrane (e.g., if it is highly ionized and polar), time at the absorption site may be insufficient. In such cases, bioavailability tends to be highly variable as well as low. Moreover it has been observed that slow release formulations have poorer bioavailability than the others [4, 5, 6].

Micardis (40 mg and 80 mg) was compared with five commercial brands with respect to *in vitro* parameters. The results indicate that none of the commercial brands were similar to Micardis (Boehringer Ingelheim) in dissolution profile at various pH points of testing. A high variability was seen in hardness as well as disintegration study. No correlation could be established between hardness and disintegration time. Similar study is also being conducted in USA.

Further, none of the commercial samples matched dissolution profile of the Micardis in all the dissolution media (pH 1.2, 4.5 and 7.5). Micardis tablets at both the strengths 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 it would release the drug consistently irrespective of pH and therefore reiterating that absorption may be same in fasted as well as fed state as indicated in the leaflet of Micardis.

It is tempting to speculate that this may translate into better pharmacodynamic effects at the site of action. However this has not been demonstrated so far. Further PK/PD studies are required to confirm these findings in hypertensive patients

Till then one may safely advise that patients controlled on an anti-hypertensive should not be switched only because of economic considerations. In the long run one may end up paying much more in terms of managing the consequences of uncontrolled hypertension.

ACKNOWLEDGEMENT

The study was supported by an unrestricted educational grant from Boehringer Ingelheim India.

REFERENCES

[1] M. Lee, C. Huang, S. Huang, Y. Chen, C. Chen and K. Wen, A Comparative Study on the Dissolution Profiles of Commercial Hydrochlorothiazide Tablets., Journal of Food and Drug Analysis., 2002,10(1):18-24.

[2] W. Wienen, M. Entzeroth, A. Jacobus, J. Stangier, U. Busch, T. Ebner, J. Schmid, H. Lehmann, K. Matzek, J. Kempthorne-Rawson, V Gladigau, and N. Hauel ; A Review on Telmisartan : A Novel, Long-Acting Angiotensin II-Receptor Antagonist ; Cardiovascular Drug Reviews, 2000, 18(2): 127–154

[3] U.S. F.D.A in Dissolution Methods For Drug Products

[4] S. Patro, K. Himasankar, A. Choudhury and M. Rao; Effect of some hydrophilicpolymers on dissolution rate of roxitromycin; Indian Journal of Phamaceutical Science., 2005, 67(3): 334-341.

[5] A. Omaima, A. Mohammed, A. Nagia and S. Ahmed; Formulation and optimization of mouth dissolve tablets containing rofecoxib solid dispersions; AAPS PharmSciTech., 2006., 7(2): E1-E9

[6] S. Torrado, R. Cadorniga, J. Torrado ; Effect of drug release rate on bioavailability of different aspirin tablets; International Journal of Pharmaceutics., 1996., 133: 65-70