Available online on 15.01.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Research Article

In-vitro studies and evaluation of telmisartan marketed tablets

Jayendra Singh Bayas[a], Rameshwar Cheke[b], Prachi Lokhande[c], Santosh Waghmare [d], Shivshankar Gunjegaonkar[e], Sachin Shinde[f]

[a,c,d,e] JSPM's Charak College of Pharmacy and research, Pune 412207, Maharashtra, India.

[b] Department of Pharmaceutical chemistry, Dr. Rajendra gode college of pharmacy, Malkapur,443201, Maharashtra, India.

[f] Department of pharmacology, Shri R D Bhakt college of pharmacy, Jalna, 431203, Maharashtra, India.

ABSTRACT

Tablets or capsules taken orally remain one of the most effective means of treatment available. The effectiveness of such dosage forms relies on the drug dissolving in the fluids of the gastrointestinal tract prior to absorption into the systemic circulation. The present study reveals the evaluation of four marketed sample of Telmisartan tablets. The main aim of the study is to conduct dissolution test on the tablets to determine the compliance with a given official monograph. Four different marketed samples of Telmisartan were purchased from local market. The Telmisartan tablets were evaluated for the various in-vitro tablet properties such as thickness, hardness, friability, weight variation, drug content, disintegration time and dissolution rate. *In-vitro* dissolution test is conducted on four different brands of telmisartan tablets to assess their equivalency. All the four marketed samples of Telmisartan have shown good tablet properties and comply with the pharmacopoeial specification. The *in- vitro* dissolution showed the 80% drug release within one hour from all the four brands which complies with the specification of pharmacopoeia.

Key words: Telmisartan, *In-vitro* Dissolution Profile, hardness, disintegration.

Article Info: Received 20 Nov 2018; Review Completed 26 Dec 2018; Accepted 31 Dec 2018; Available online 15 Jan 2019

Cite this article as:

Bayas JS, Cheke R, Lokhande P, Waghmare S, Gunjegaonkar S, Shinde S, *In-vitro* studies and evaluation of telmisartan marketed tablets, Journal of Drug Delivery and Therapeutics. 2019; 9(1):74-78

DOI: http://dx.doi.org/10.22270/jddt.v9i1.2267

***Address for Correspondence:**

Jayendra Singh Bayas, JSPM's Charak College of Pharmacy and research, Pune 412207, Maharashtra, India.

INTRODUCTION

Seventy-six percent of patients achieve a full response to treatment (Diastolic BP ≤ 90mm Hg or ≥ 10mm Hg reduction) and 22% had an inadequate response to telmisartan therapy (Diastolic BP > 90mm Hg or < 7mm Hg reduction). Overall, heart rate was reduced from 78.0 to73.8 beats/min after 6 months of treatment. The dosage was increased in 24% of patients because of the insufficient BP reduction with the lower dosage Global tolerability was rated as very good, good, moderate or poor in 75%, 22%, 1% and 1% of patients, respectively. There were no significant differences in global tolerability ratings between the patient groups. Telmisartan had only a minor or no effect on serum creatine levels across all patient groups. Serious adverse events were reported in 0.06% of patients and included death in 6 patients. None of the deaths were considered drug-related.[1-4]

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 has low bioavailability increase in dosage, large inter and intra-subject variation in blood drug concentrations under fed versus fasted conditions.[5-7]

A drug may be a substance for diagnosis, cure, mitigation, prevention or treatment of disease in human beings or animals, which act by altering any structure or function of body of human being or animal. Every year number of drugs is introduced into the market. The total drug absorption into the body when administered i.e. *In-vivo* and dissolution tests is used to determine the absorption of drug *In-vitro* i.e. IVIVC absorption of the drug.[9-13]

Drug absorption from a solid dosage form after oral administration depends on the release of the drug substance from the drug product, the dissolution or solubilization of the drug under physiological conditions, and the permeability across the gastrointestinal tract. Because of the critical nature of the first two of these steps, *In-vitro* dissolution may be relevant to the prediction of *In-vivo* performance. Based on this general consideration, *In-vitro* dissolution tests for immediate release solid oral dosage forms, such as tablets and capsules, are used to

1) Assess the lot-to-lot quality of a drug product;

2) Guide development of new formulations;

3) Ensure continuing product quality and performance.

After certain changes, such as changes in the formulation, the manufacturing process, the site of manufacture, and the scale-up of the manufacturing process. Current knowledge about the solubility, permeability, dissolution, and pharmacokinetics of a drug product should be considered in defining dissolution test specifications for the drug approval process. This knowledge should also be used to ensure continued equivalence of the product, as well as to ensure the product's similarity under certain scale-up and post-approval changes.[14-16]

New drug applications (NDAs) submitted to the Food and Drug Administration (FDA) contain bioavailability data and in vitro dissolution data that, together with chemistry, manufacturing and controls (CMC) data, characterize the quality and performance of the drug product. *In-vitro* dissolution data are generally obtained from batches that have been used in pivotal clinical and/or bioavailability studies and from other human studies conducted during product development. Acceptable bioequivalence data and comparable *In-vitro* dissolution and CMC data are required for approval of abbreviated new drug applications (ANDAs). The *In-vitro* specifications for generic products should be established based on a dissolution profile. For new drug applications, as well as generic drug applications, the dissolution specifications should be based on acceptable clinical, bioavailability, and/or bioequivalence batches.[17-22]

MATERIAL AND METHODS

Chemicals and Reagents

Potassium dihydrogen phosphate, concentrated hydrochloric acid, sodium hydroxide were used as received. Whitman 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. Immediate release Telmisartan 40 mg tablets of four different brands were purchased from different local retail pharmacists at shikrapur local market Pune. Products were codified as Brand A, Brand B, Brand C, and Brand D.

The following commercial tablets of Telmisartan 40 mg were taken for the study:

Table 1: Brands of 40 mg Telmisartan Tablets.

Sr. No.	Brand Code	Batch No.	Mfg. date	Exp. date	Price/10 units	Manufacturer
1	A	E4ALNO87	09/2014	08/2016	25.80	Mankind Pharma Ltd.
2	B	B325J064	09/2014	08/2016	45.50	Aristo Pharmaceuticals Pvt. Ltd.
3	C	GETL14004	05/2014	04/2016	77.00	Eris Life sciences Pvt. Ltd.
4	D	GTB14021	07/2014	06/2016	30.10	Emcure Pharmaceuticals Ltd.

Methods

1) Analytical Method Development

For dissolution study, the drug was analyzed by UV Spectroscopy at λmax of 291 nm and standard curves was plotted for respective buffers.

Preparation of Standard Curve

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 2, 4, 6, 8, 10, 12 and 14 µg/ml of Telmisartan. The absorbance of these solutions was measured at 291 nm on UV-Visible spectrophotometer against pH 7.5 buffers as blank. 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.

Evaluation of Marketed Telmisartan Tablet

Thickness: The thickness of the tablets were study by using Vernier Caliper

Drug Content: Weight tablets (5) were powdered using a glass mortar and pestle. An accurately weighed quantity of tablet containing about 250mg of telmisartan is dissolve in methanol and taken in to 100 ml volumetric flask. Then pipette out 10 ml of above solution then diluted up to 50 ml. From this standard solution again , 5 ml is pipette out , diluted to 50 ml with 0.1 N HCL, resulting solution was measured at 296 nm and drug content was calculated against 0.1 N HCL as blank.

Determination of Hardness and Friability

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

About 10 previously weighed tablets were placed in a friability apparatus, which was rotarod at 100 revolution and the tablets were reweighed. The percent friability was calculated using formula.

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.

Dissolution Profile Study OR *In-vitro* release studies

The *In-vitro* dissolution studies of the marketed conventional IR tablets and the developed SR tablets were carried out using USP type II apparatus (Electrolab, Pune, India) at 75 rpm. The dissolution medium consisted of 900 ml of distilled water maintained at 37 ± 0.5°C. The drug release at different time intervals was measured using an UV visible spectrophotometer. It was made clear that none of the ingredients used in the matrix formulations interfered with the absorbance of the drug. The release studies were conducted for three tablets in a batch and the mean values were plotted against time. Dissolution test by USP paddle apparatus. The *In-vitro* dissolution study is carried out using apparatus II (paddle). The dissolution jars are cleaned with a mild detergent and then rinsed with distilled water and dry to room temperature. 900 ml of dissolution medium is transferred into the dissolution jars and are placed in the test assembly which is maintained at 37 °C which is given an

allowance of 0.5 °C. The medium is allowed to attain the set temperature.

The rpm is set to 75. The test sample is introduced inside the dissolution jar and the test assembly is brought down to the Static position and the medium is stirred at 100rpm. 10 ml of the samples are withdrawn at various time intervals such as 0 minutes, 10 minutes, 20 minutes, 30 minutes, 40 minutes, and 50 minutes using a graduated pipette and transfer it immediately to clean, dried and labeled test tubes. The equal volume of fresh dissolution medium is replaced after each sampling and maintained at the correct temperature. The sample withdrawn is diluted 10 by buffer and the absorbance is measured at 291nm for 0.1N HCl and 294 nm for phosphate buffer at pH 7.5. 10 ml of sample is withdrawn at the end of 30 minutes from each of the test jar, using a graduated pipette and it is filtered if necessary.

It is then transferred to a cleaned, dried and labeled test tube. The sample is diluted by buffer and the absorbance is measured at 291nm for 0.1N HCl and 294 nm for phosphate buffer at pH 7.5. The cumulative percentage of released is calculated using the formula.

$$\text{Cumulative \% release } \frac{\text{Volume of sample withdraw (ml)}}{\text{Bath volume (v)}} \times P\,(t-1) + Pt$$

Where,

Pt = Percentage release at time t'

P (t – 1) = Percentage release previous to't'.

Table 2: Protocol for Dissolution Studies

Apparatus Parameters	Six station USP Type II Dissolution Testing Apparatus (Paddle)
Speed	75 rpm
No. of tablets	4 units
Dissolution media	pH 7.5 Phosphate Buffer (900 ml) 0.1N HCl Buffer (900 ml)
Sampling interval	10,20,30,40 and 50 min
Sampling volume	5 ml
Replenishing fluid	pH 7.5 Phosphate Buffer 0.1N HCl Buffer
Temperature	37°C ± 0.5°C
Analytical Method	UV Spectrophotometry (λmax =291nm)

Comparison of Different Brands of Telmisartan Tablet

Tablets containing Telmisartan (40 mg), was used and compared with the each other suggested by FDA. Dissolution profiles of the four different brands of Telmisartan containing 40 mg of the drug would be compared. These dissolution profiles are studied in presence of 7.5 pH phosphate buffer and the percentage release which is calculated by absorbance.

Formula for determination of percentage of release of drug Telmisartan from *In-vitro* dissolution testing:

Concentration of drug (µg/ml) = (slope × absorbance) ± intercept

$$\text{Amount of drug released (mg/ml)} = \frac{\text{Concentration x dissolution x dilution factor}}{1000}$$

RESULT AND DISCUSSION

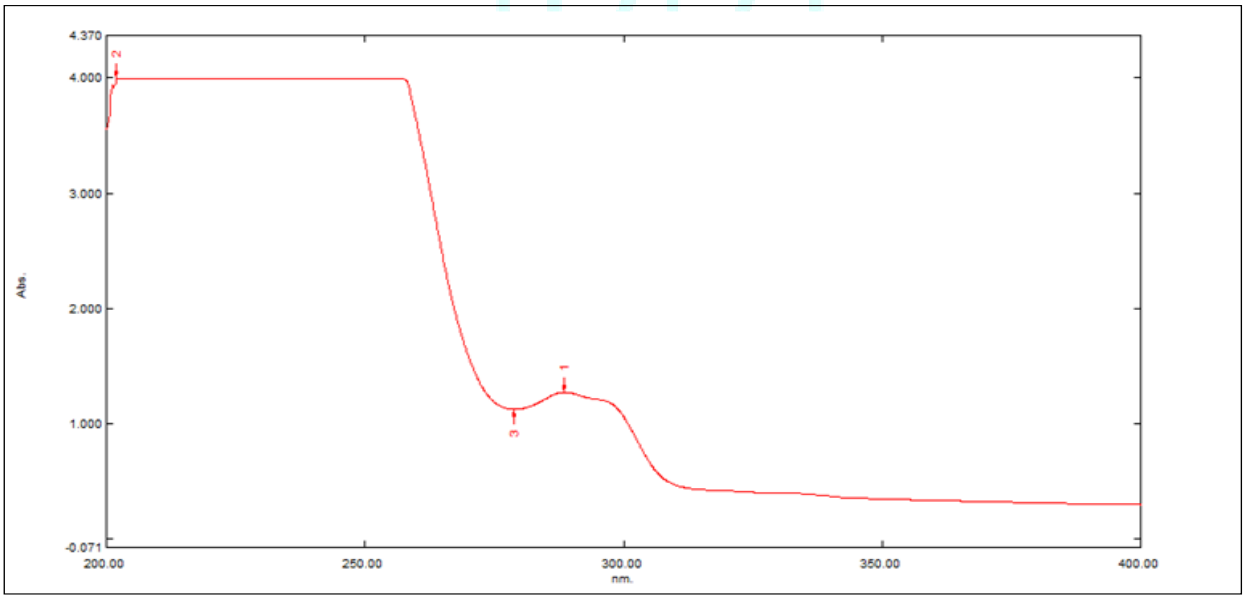

Figure 1: Absorption spectra of Telmisartan in pH 7.5 Phosphate Buffer

Linearity

The Telmisartan drug shows maximum absorbance at 291 nm in the concentration range of 2-14 µg/ml. as shown in **(Table no.3)**

Table 3: Data for calibration curve of Telmisartan

Concentration (µg/ml)	Absorbance (291nm)
0	0
2	0.132
4	0.257
6	0.376
8	0.502
10	0.627
12	0.745
14	0.867

The linearity was observed in concentration range of 2-14 µg/ml. concentration versus respective absorbance at 291 nm was plotted. The regression coefficient was found to be 0.9998. as shown in **(Fig.2)**.

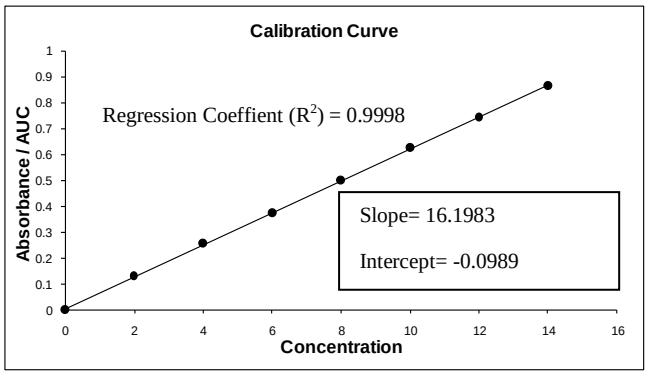

Figure 2: Calibration curve of Telmisartan.

Evaluation Parameter

All the tablet formulations showed acceptable pharmacotechnical properties and complied with the range specified by US Pharmacopoeia for Disintegration, weight variation, friability, hardness.

Table 4: Evaluation Parameter of the Telmisartan Tablets

Parameters	A	B	C	D
Thickness	3.0 mm	3.1 mm	3.00 mm	3.0 mm
Drug Content	99.85	99.50	99.00	99.00
Avg. wt. of 10 tablets(mg)	250.50	250.00	250.20	250.10
Friability	0.12%	0.27%	0.19%	0.22%
Hardness(kp)	8	5.5	5	6
Disintegration Time	8 min 10 sec	11 min 10 sec	min	min 25 sec

Table 5: Absorbance of Telmisartan

Time (min)	Absorbance of Telmisartan			
	A	B	C	D
10	0.3901	0.3987	0.3875	0.3802
20	0.4383	0.4401	0.4120	0.3941
30	0.4487	0.4598	0.4370	0.4208
40	0.4669	0.4701	0.4578	0.4516
50	0.4897	0.4951	0.4775	0.4601

Dissolution Test

The *In-vitro* drug release characteristics of the developed marketed tablets were studied. Dissolution data for all the experiments were highly reproducible and hence only the average values were plotted. The dissolution of the marketed tablets indicated that more than 80% of the drug is released within 1 h, which complies with the pharmacopoeial specifications. In all the batches, we observed that as the polymer concentration increases, the drug release rate decreases.

Table 6: % Drug Release of Telmisartan

Time (mins)	% Drug Release of Telmisartan			
	A	B	C	D
10	79.703	81.475	79.168	77.66
20	90.073	90.454	84.654	80.95
30	92.713	95.011	90.271	86.90
40	96.972	97.655	95.051	93.72
50	102.198	103.339	99.629	95.99

The percentage releases of the all brands are plotted against the time. Which is shows in **(Fig.3).**

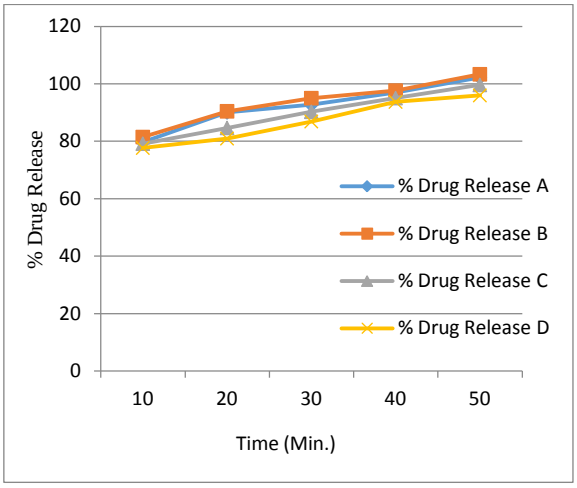

Figure 3: Dissolution profile of all brands in 7.5 pH phosphate buffer, 900ml, paddle, 75 rpm

Dissolution of the all Brands:

Brand B > Brand A > Brand C > Brand D

The entire test i.e. Thickness, drug content, Weigh variation, Hardness, Friability, Disintegrations was passes the tests as per Indian pharmacopoeia. And the dissolution shows that the brand B i.e. Telvas 40 manufactured by ARISTO Pharmaceuticals Pvt. Ltd have the greater absorption in short time as compare to the others.

CONCLUSION

In vitro dissolution methods are developed to evaluate the potential in vivo performance of a solid oral dosage form, and as quality control tests demonstrating the appropriate performance of drugs products.

The in vitro drug release characteristics of the developed marketed tablets were studied. Dissolution data for all the experiments were highly reproducible. The dissolution of the marketed tablets indicated that more than 80% of the drug is released within 1 h, which complies with the pharmacopoeial specifications. All the selected brands of Marketed Telmisartan tablets were found be equivalents in their dissolution and there is no variation the between the tablets of all brand.

REFERENCES

1. Patel PKA, et. al., Int J Pharma (IJPSR). 2010; 1(8):282-292.
2. Bhise S. et al., Int J Pharma (IJPL). 2011; 2(8):970-975.
3. Vatsal A. P. Optimization and evaluation of a formulation Containing Low Soluble Antihypertensive agent, Marathwada mitra mandal's college of pharmacy, Off Kalewadi Phata-Pimpri Road, Thergaon Kalewadi, Pune 2012(4); 37-41.
4. Benson SC, Pershadsingh HA, Ho CI, Chittiboyina A, Desai P, Pravenec M, Qi N, Wang J, Avery MA, Kurtz TW. Identification of telmisartan as a unique angiotensin II receptor antagonist with selective PPARγ–modulating activity. Hypertension. 2004; 43(5):993-1002.
5. Schupp M, Janke J, Clasen R, Unger T, Kintscher U. Angiotensin type 1 receptor blockers induce peroxisome proliferator–activated receptor-γ activity. Circulation. 2004; 109(17):2054-7.
6. Fujimoto M, Masuzaki H, Tanaka T, Yasue S, Tomita T, Okazawa K, Fujikura J, Chusho H, Ebihara K, Hayashi T, Hosoda K. An angiotensin II AT1 receptor antagonist, telmisartan augments glucose uptake and GLUT4 protein expression in 3T3-L1 adipocytes. FEBS letters. 2004; 576(3):492-7.
7. Qi N, Pravenec M, Ho CI, Benson SC, Pershadsingh HA, Sugimoto K, Ogihara T, Kurtz TW. Telmisartan is a dual ARB and PPAR gamma activator that limits weight gain, body fat accumulation, and adipocyte size in rats fed high fat, high carbohydrate diets. Hypertension. 2004; 44(4):506.
8. Pershadsingh HA, Kurtz TW. Insulin-sensitizing effects of telmisartan: implications for treating insulin-resistant hypertension and cardiovascular disease. Diabetes care. 2004; 27(4):1015-.
9. Michel MC, Bohner H, Köster J, Schäfers R, Heemann U. Safety of telmisartan in patients with arterial hypertension. Drug Safety. 2004; 27(5):335-44.
10. Derosa G, D RAGONESI P, Mugellini A, Ciccarelli L, Fogari R. Effects of telmisartan compared with eprosartan on blood pressure control, glucose metabolism and lipid profile in hypertensive, type 2 diabetic patients: a randomized, double-blind, placebo-controlled 12-month study. Hypertension Research. 2004; 27(7):457-64.
11. Derosa G., Cicero A.F., Bertone G., Piccinni M.N., Fogari E., Ciccarelli L. and Fogari R. Comparison of the effects of telmisartan and nifedipine gastrointestinal therapeutic system on blood pressure control, glucose metabolism, and the lipid profile in patients with type 2 diabetes mellitus and mild hypertension: a 12-month, randomized, double-blind study. *Clinical therapeutics*, 2004; *26*(8):1228-1236.
12. Rosano GM, Vitale C, Castiglioni C, Cornoldi A, Fini M, Mercuro G. Comparative effect of telmisartan and losartan on glucose metabolism in hypertensive patients with the metabolic syndrome. InCirculation 2004; 110(17): 606-606).
13. Miura Y, Yamamoto N, Tsunekawa S, Taguchi S, Eguchi Y, Ozaki N, Oiso Y. Replacement of valsartan and candesartan by telmisartan in hypertensive patients with type 2 diabetes: metabolic and antiatherogenic consequences. Diabetes Care. 2005; 28(3):757-8.
14. Bloch MJ, Basile JN. Analysis of Recent Papers in Hypertension Jan N. Basile, MD, Senior Editor. The Journal of Clinical Hypertension. 2004; 6(6):342-6.
15. Doggrell SA. Telmisartan–killing two birds with one stone. Expert opinion on pharmacotherapy. 20041; 5(11):2397-400.
16. Hisato Takagi , Hirotaka Yamamoto, Kotaro Iwata, Shin-nosuke Goto, Takuya Umemoto and ALICE (All-Literature Investigation of Cardiovascular Evidence) Group, Effects of telmisartan on proteinuria or albuminuria: A metaanalysis of randomized trials, International Journal of Cardiology, 14730; 1-7.
17. Amr A. Fouad , Iyad Jresat , Protective effect of telmisartan against cadmium-induced nephrotoxicity in mice, Life Sciences, 2011; 89:29-35.
18. Sameer Goyal , Sachin Arora , Rajan Mittal , Sujata Joshi , Tapas C. Nag c, Ruma Ray , Santosh Kumari , Dharamvir Singh Arya , Myocardial salvaging effect of telmisartan in experimental model of myocardial infarction, European Journal of Pharmacology, 2009; 619:75–84.
19. Tetsuya Kakumaa, Koro Gotoha, Takayuki Masakia, Emi Itateyamad, Nobuyuki Abee, Hironobu Yoshimatsu, Telmisartan reduced abdominal circumference and body weight with decreasing triglyceride level in patients with type 2 diabetes and metabolic syndrome, Obesity Research & Clinical Practice, 2010; 4, e145—e152.
20. David H.G. Smith, Treatment of Hypertension with an Angiotensin II-Receptor Antagonist Compared with an Angiotensin-Converting Enzyme Inhibitor: A Review of Clinical Studies of Telmisartan and Enalapril, Clinical Therapeutics 2002; 24, NO. IO.
21. Singh A, Jha KK, Mittal A, Kumar A, A Review on: Telmisartan, Journal of scientific & innovative RESEARCH 2013; 2(1):1-16
22. EMEA 2005, the initial scientific discussion and scientific discussion on procedures, which have been finalised before 1 June 2002; module 8B; 1-18.