WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 8, Issue 12, 1121-1129. Research Article ISSN 2277– 7105

FORMULATION AND IN-VITRO EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF TELMISARTAN USING VARIOUS HYDROPHILIC POLYMERS

Hamid Khan*

ISBM University School of Pharmacy, Chhattisgarh, India.

Article Received on
03 Sept. 2019,
Revised on 24 Sept. 2019,
Accepted on 14 Oct. 2019
DOI: 10.20959/wjpr201912-16080

***Corresponding Author**
Dr. Hamid Khan
ISBM University School of Pharmacy, Chhattisgarh, India.

ABSTRACT

The formulation and in-vitro evaluation of matrix tablets containing telmisartan as sustained release using various hydrophilic polymers such as different grades of HPMC and PVP by wet granulation method. The tablets were subjected to in-vitro drug release study in hydrochloric acid buffer of pH 1.2 (0.1N) with 1% w/v SLS using USP paddle apparatus. The drug released at various time intervals were determined by validated UPLC-PDA method. The prepared tablets showed better sustained release effect when compared with marketed tablets. The drug release mechanism from hydrophilic polymers was established. The formulated tablets provided sustained release of telmisartan over a period of 24 h.

KEYWORDS: Telmisartan, HPMC, PVP, Hydrophilic polymer, Sustained release.

INTRODUCTION

Telmisartan (TEL), is an antihypertensive drug, belongs to a group of angiotensin converting enzyme (ACE) inhibitors. It is used for the treatment of hypertension. Telmisartan is poorly water soluble drug with low bioavailability (about 45%). The low bioavailability of Telmisartan is mainly due to extensive first pass hepatic metabolism.[1] Telmisartan has the longest biological half life (24 h) compared to any other ACE inhibitor and dosing frequency once in day makes it an ideal candidate for sustained release dosage form. From the literature survey it was found that the formulation and evaluation of telmisartan immediate release tablets using superdisintegrants such as sodium starch glycollate by applying direct compression method was reported for drug release up to 8 h.[2] Preparation of nanocomposite

of telmisartan with cyclodextrin has also been reported by complexation method which was successfully used to improve the solubility and bioavailability of telmisartan.[3] Drug release of telmisartan through formation of drug-Aminoclay complex has been reported in which the release was dependent on the pH of the medium. From these complexes telmisartan exhibited fast dissolution and enhanced bioavailability at pH 1.2 for all the prepared formulations.[4] Formulation and evaluation of pH modulated solid dispersions has also been reported by applying various processes for solubilization of telmisartan.[5,6] But for the treatment of hypertension, prolonged effect of drug is required which can maintain the concentration of drug in the body for long period of time. The telmisartan tablets available in the market are conventional tablets which provide the drug release only for few hours. Therefore making telmisartan as immediate release is not suitable as it will dissolve quickly and give the fast effect.

Formulation of matrix tablets using hydrophilic polymers is the simplest method for extended release tablet. The HPMC hydrophilic polymer has been widely used because of its excellent stability within wide pH range, pH-independent drug release and suitability of various drugs. HPMC is water swellable polymer and increases the size of the tablet thereby retains in the stomach for the long time and provide the extended action.[7-10] The hydration and gel forming abilities of HPMC makes it use in prolong the drug release of drug. Similarly Polyvinyl Pyrrolidine (PVP) is also water soluble polymer. It is used mainly as binder in tablets. It enhances the bioavailability of drugs by increasing the dissolution rate. They form water soluble complexes with drugs and increase the bioavailability. It acts as hydrophiliser for sustained release tablets.

The aim of the present work is to formulate and evaluate matrix tablets containing telmisartan as sustained release using hydrophilic polymer such as HPMC and PVP polymers in different amounts the by wet granulation method. The prepared tablets were subjected to drug release study by validated UPLC-PDA method.

MATERIALS AND METHODS

Materials

The pure sample of telmisartan was kindly supplied by Systopic Pharmaceuticals Ltd. (New Delhi, India). Various grades of HPMC, polyvinyl pyrrolidone (PVP), talc and magnesium stearate was purchased from S.D. Fine Chemicals Ltd., Mumbai, India. HPLC grade water, methanol, and ammonium acetate were used throughout the analysis. All other chemicals and

reagents were of analytical grade.

Methods

Preparation of Tablets

The wet granulation method was applied for table preparation as per the following procedure. The composition of different formulations for the SR tablets is given in **Table 1.** HPMC polymer was blended with drug and PVP in a planetary mixer for 5 min. The powders were granulated, sieved by 20 mesh screen, dried at 30 ºC for 1 h and mixed with talc and magnesium stearate. Prepared granules were compressed in to 150 mg tablets to an average hardness of 7 Kg/cm^2 using tablet punching machine (Cadmach, Mumbai, India). Tablet formulation was named as F1, F2 and F3.

Table 1: Composition of Various Formulations of Telmisartan Using HPMC and PVP.

Ingredients (mg)	Formulation Code		
	F1	F2	F3
Telmisartan	80	80	80
HPMC K100	20	30	50
Polyvinyl Pyrrolidone	40	30	10
Talc	5	5	5
Magnesium Stearate	5	5	5
Total weight	150	150	150

Evaluation of Physical Properties of Tablets

The tablets were evaluated for various quality control tests. The weight variation was carried out on 20 tablets using an electronic balance. 10 tablets were used for friability test in a Roche friabilator at the speed of 25 rpm for 5 min. Similarly 10 tablets were used for hardness testing with the help of Mosanto tester. The thickness was measured on 10 tablets by Vernier caliper.

Drug Content Studies

Twenty tablets were weighed, powdered and equivalent amount of 80 mg of telmisartan was taken in a 50 mL volumetric flask. The powder was dissolved with 25 mL of methanol, sonicated and final volume was made up with methanol. Solution was filtered by 0.45 mm membrane filter to remove all the excipients. The resultant filtrate was further diluted with methanol: water (50:50, v/v) to give a sample solution containing 800 ng/mL of telmisartan. Solutions were again filtered by 0.20 mm syringe filter and injected in to the UPLC/PDA system for analysis. The amount of telmisartan in tablets was determined by calibration

equations obtained from the calibration curve.

UPLC Conditions

The ultra performance liquid chromatography (UPLC) with PDA detector was employed for drug release study. The Waters Acquity UPLC system (Waters Corporation, MA, USA) with a binary solvent manager, auto-sampler, and column manager was used for analysis. Chromatographic separation was performed on a Waters Acquity UPLC BEH C_{18} (100.0×2.1 mm, 1.7 mm) column. The detection was carried out at 295 nm. For isocratic separation the mobile phase was acetonitrile-2 mM ammonium acetate (50:50, v/v), sonicated and filtered through 0.45 mm membrane filter. The flow rate of the mobile phase was kept at 0.20 mL/min and the total chromatographic run time was 2.0 min.

Validation of the Method

The developed method was validated according to ICH validation guidelines.[11] For the determination of linearity and range, different standard concentrations of the drug ranging from 1-1000 ng/mL were prepared separately in methanol: water (50:50, v/v). Solutions filtered by 0.20 mm syringe filter and injected in to the UPLC-PDA system for analysis. Average peak area at each concentration level was subjected to linear regression analysis for making linear graph. The other parameters which were evaluated are limit of detection (LOD) and limit of quantitation (LOQ), precision and accuracy.

Drug Release Studies

Drug release studies from the tablet were performed using USP paddle apparatus, Veego VDR-8DR (Veego Instruments, Mumbai, India). The dissolution medium consisted hydrochloric acid buffer of pH 1.2 (0.1N) with 1% w/v sodium lauryl sulfate (SLS) as solubiliser maintained at 37ºC with a rotation speed of 100 rpm. One tablet was added to each vessel filled with dissolution medium. Ever hour 5 mL of samples were taken and equivalent amount of medium was added to the dissolution vessel. The solutions were filtered by 0.45 mm membrane filter to remove all the excipients. The filtrates were further diluted with methanol: water (50:50, v/v) to get the sample solution containing required concentration of drug. The samples were again filtered by 0.20 mm syringe filter and injected in to the UPLC-PDA system for analysis. The amount of the drug dissolved in different time intervals was calculated from the peak areas and finally the release profile of drug in terms of percentage was calculated.

Theoretical Release from Tablets

Telmisartan dose from a once daily SR tablet was determined by Rawlins equation[12-14] and taking the pharmacokinetic data on telmisartan mentioned in the literature. The Higuchi's equation ($Q = k_H t^{1/2}$) was applied to study the mechanism of telmisartan release from the matrix tablets, where, Q is the amount of the drug release at time t, and k_H is the Higuchi's diffusion constant. If the release of drug from the matrix tablet is by diffusion mechanism then the plotted graph will be linear $D_{Total}=Dose_{IR}$ $(1+0.693\times t/t_{1/2})$. Where, D_{Total} = Total drug dose, $Dose_{IR}$ = Dose of IR part, t = Time (h) desired for SR (24 h), and $t_{1/2}$= Half life of drug (24 h).

$Dose_{IR}$ $(1+0.693\times 24/24) = 80$; $Dose_{IR}$= 47.25 mg. Hence theoretical drug release from tablets should be 47.25 mg in 1 h and thereafter, 1.423 mg per hr up to 24 h.

RESULTS AND DISCUSSION

Physical Properties of Tablets

The tablets formulations were tested for various quality control tests such as weight variation, thickness, hardness, friability, and drug content studies. The results of evaluation tests are given **Table 2.** Tablets were passed all the tests in accordance with the specification limits of United States Pharmacopoeia (USP, 2002) that is less than 1% all for weight variation, thickness, hardness, friability and 98% drug content studies.[15] The developed analytical method was applied to study the drug content from prepared tablets containing 80 mg of telmisartan. The telmisartan content from tablets was 98.12-99.10%.

Table 2: Physical Properties of the Tablets.

Formulation Code	Weight Variation (%)[b]	Thickness (mm)[a]	Hardness (Kg/cm^2)[a]	Friability (% w/w)[a]	Drug Contents (%)[b]
F1	1.45 ± 0.42	7.00 ± 0.01	7.10 ± 0.11	0.44 ± 0.35	98.12 ± 0.75
F2	1.57 ± 0.45	7.10 ± 0.02	7.20 ± 0.10	0.64 ± 0.28	98.24 ± 0.92
F3	1.20 ± 0.25	7.00 ± 0.04	7.00 ± 0.21	0.24 ± 0.22	99.10 ± 0.55

[a]Values are represented as *M* ± *SE*, (n=10); [b]Values are represented as *M* ± *SE*, (n=20)

Validation of the Method

The retention time (R_t) of telmisartan was 2.25 min with the total chromatographic run time of 3 min. For telmisartan calibration curve was linear in the concentration range of 1-1000 ng/mL with correlation coefficient was more than 0.999. The LOD of the drug was 1 ng/mL. The obtained results indicated that higher sensitivity of the method. Hence the method was suitable for drug content studies and in-vitro drug release studies.

Drug Release Studies

Dissolution study was carried out by validated UPLC-PDA method. HPMC of poorly water soluble drug telmisartan. The drug solubility study was carried out using the various grades of HPMC polymer such as HPMC K100, HPMC K4M, HPMC K15M, and HPMC K100M which were selected as per their increasing viscosity at 25ºC, respectively. The study showed that formulation with low viscosity HPMC polymer (HPMC K100) provided the best effect of drug release as compared to other grades of HPMC. Due to lowest viscosity of polymer, faster rate of polymer hydration and gel formation occurs within the tablet matrix. Simultaneously erosion of the polymer from gel layer is fast which provide the extended drug release. Hence from all the studied HPMC grades, HPMC K100 was selected for final three trial formulations of telmisartan sustained release. The mechanism of drug release from hydrophilic polymer is proposed in the **Figure 1**. From the study it was observed that when the content of HPMC K100 polymer increases in the formulation, it dissolves slowly in the medium resulting provide the sustained release effect over the extended period of time. At the same time amount of PVP also decreases which give the additional sustained effect in tablets. Formulation F3 was found to release telmisartan in sustained manner up to 24 h.

Theoretical Release from Tablets

The theoretical release profile was calculated by the Rawlins equation described earlier. The release rates of drug were established for different time intervals. According to the theoretical release pattern, a once daily telmisartan SR tablet should release 47.25 mg in 1 h and thereafter, 1.423 mg per h up to 24 h.

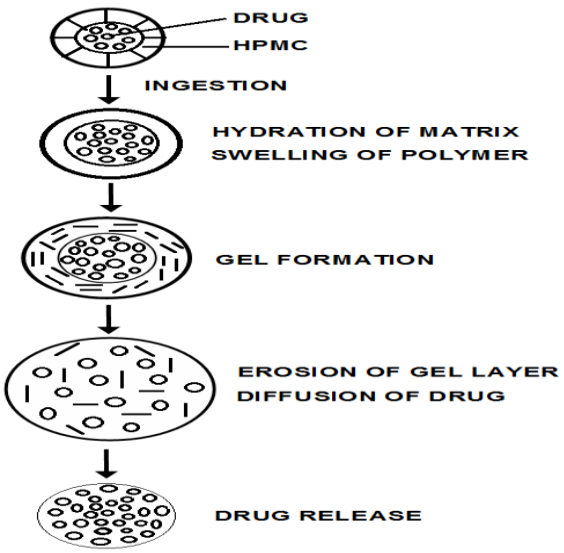

Figure 1: Mechanism of Drug Release from HPMC Hydrophilic Matrix Tablets.

The in-vitro release profile of telmisartan release from matrix tablets in F1, F2 and F3 is shown in **Figure 2.** Hence formulation F3 was selected the optimum formulation and compared with the telmisartan marketed tablets. The optimized tablets showed the better sustained release of telmisartan (98.95%) up to 24 h when compared to the marketed tablets (92.72%) for 1 h as shown in **Figure 3**.

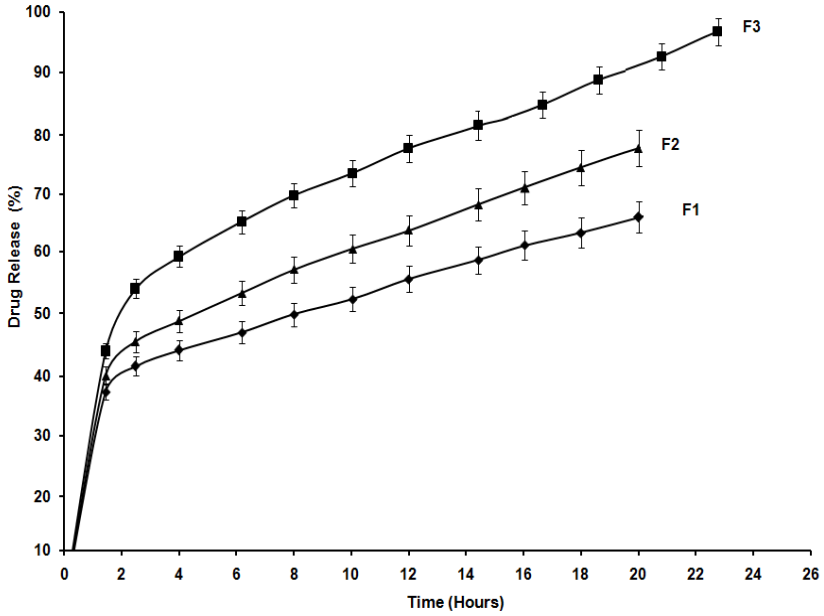

Figure 2: The In-vitro Release Profile of Telmisartan Release from Matrix Tablets in F1, F2 and F3.

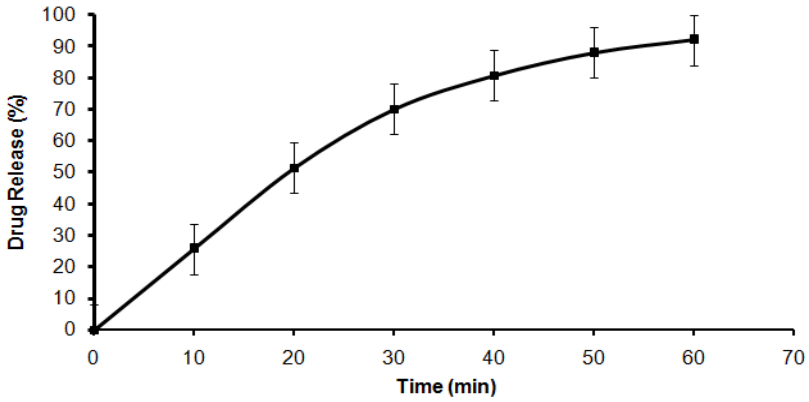

Figure 3: In-vitro Release Profile of Telmisartan Release from Marketed Tablets (Bars ± *SD* [n=3]).

Drug Release Kinetics

Drug release mechanism of SR telmisartan from matrix tablet, the data was fitted to Higuchi's equation. Telmisartan release kinetic parameters from the tablets (F1 to F3)

showed good linearity (R^2: 0.994-0.999). Formulation F3 was found to release telmisartan in sustained manner up to 24 h.

CONCLUSIONS

Matrix tablets containing telmisartan as sustained release have been prepared by selecting various grades of HPMC along with PVP. The study showed that the optimized formulation (F3) allowed its sustained erosion and can be used in extended release dosage forms. In-vitro drug release from prepared tablets showed better effect when compared with marketed tablets. Tablets thus formulated provided sustained release of telmisartan over a period of 24 h.

ACKNOWLEDGEMENTS

The author is grateful to Systopic Pharmaceuticals Ltd., New Delhi, India, for providing gift sample of telmisartan. Author is also thankful to In-charge of Instrumentation Facilities, Faculty of Pharmacy, Hamdard University, New Delhi, India, for providing opportunities to work on UPLC-PDA system.

REFERENCES

1. Merck Index: An Encyclopedia of Chemicals, Drugs and Biologicals, 14th edition, Merck Research Laboratories, Merck and Co., Inc., White House Station, NJ, USA, 2006; 1569.
2. Ashutoshkumar S, Arunachalam A, Karthikeyan M, Manidipa1 S, Ravishankar V, Senthilraj R, Design and evaluation of sustained release tablet of telmisartan. Int J Pharm Sci., 2010; 8(1): 595-603.
3. Sangwai M, Vavia P. Amorphous ternary cyclodextrin nanocomposites of telmisartan: Improved solubility and reduced pharmacokinetic variability. Int J Pharm, 2013; 453(2): 423-432.
4. Young L, Shao Y, Han H. Improved pH dependent drug release of telmisartan a poorly soluble drug through formation of drug-Aminoclay complex. Int J Pharm, 2014; 471(1-2): 258-263.
5. Marasini M, Tran TH, Poudel BK, Cho HJ, Choi YK, Chi SC, Choi HG, Yong CS, Kim JO. Fabrication and evaluation of pH modulated solid dispersions for telmisartan by spray drying technique. Int J Pharm, 2013; 441(1-2): 424-432.
6. Park J, Cho W, Cha KH, Ahn J, Han K, Hwang SJ. Solubilization of the poorly water soluble drug telmisartan by SAS process. Int J Pharm, 2013; 441(1-2): 50-55.
7. Hogan JE. Hydroxypropyl methylcellulose sustained release technology. Drug Dev Ind

Pharm, 1989; 15(6-7): 975-999.

8. Rajabi-Siahboomi, A.; Jordan, M. P. Slow release HPMC matrix systems. Eur. Pharm. Rev., 2000; 5(4): 21-23.
9. Li CL, Martini LG, Ford JL, Roberts M. The use of hypromellose in oral drug delivery. J Pharm Pharmacol, 2005; 57(5): 533-546.
10. Veeran Gowda Kadajji and Guru V. Betageri, Water Soluble Polymers for Pharmaceutical Applications, Polymers, 2011; 3: 1972-2009.
11. International Conference on Harmonization, ICH Q2 (R1), Validation of Analytical Procedures: Text and methodology, Geneva, 2005.
12. Rawlins EA. Bentley's Textbook of Pharmaceutics; All India Traveller Book Seller: Delhi, India, 2004; 641-665.
13. Higuchi WI. Analysis of data on the medicament release from ointments. J Pharm Sci., 1962; 51(8): 802-804.
14. Subrahmanyam, C.V.S. Textbook of Physical Pharmaceutics; Vallabh Publication: Delhi, India, 2001; 123-125.
15. United States Pharmacopoeia. United States Pharmacopoeia-national formulary (USP24/NF 19): United States Pharmacopoeial Convention, Rockville, MD, 2002; 16.