International Journal for Modern Trends in Science and Technology, 8(08): 141-148, 2022

ISSN: 2455-3778 online
DOI: https://doi.org/10.46501/IJMTST0808019
Available online at: http://www.ijmtst.com/vol8issue08.html

Studying the Effect of Gastric Retention on Solubility of Poorly Water Soluble Drug Telmisartan: A Systematic Research

Ashish Purohit, Kshipra Vyas ,Purva Bhandari, Roshan Issarani, Ashwin Singh Chouhan

Lachoo Memorial College of Science and Technology, Jodhpur, Rajasthan

To Cite this Article
Ashish Purohit, Kshipra Vyas ,Purva Bhandari, Roshan Issarani and Ashwin Singh Chouhan. Studying the Effect of Gastric Retention on Solubility of Poorly Water Soluble Drug Telmisartan: A Systematic Research. International Journal for Modern Trends in Science and Technology 2022, 8(08), pp. 141-148. https://doi.org/10.46501/IJMTST0808019

Article Info
Received: 11 July 2022; Accepted: 06 August 2022; Published: 12 August 2022.

ABSTRACT

Gastro retentive drug delivery system for drug telmisartan, a well known AT I receptor blocker, with an oral bioavailability of only 40% were prepared. Hydroxypropyl methyl cellulose (HPMC) of viscosity grade K4M was used as a polymer for enhancing the floating of tablets and Micro crystalline cellulose (MCC) was used as a wicking agent to enhance the dissolution of drug. The tablets were prepared by using the direct compression method. The quantities of HPMC K4M and MCC were optimized to get desired minimum floating lag time and drug release. The formulations were evaluated for physical characterization, hardness, friability and weight variation and data analysis along with presentation was done.

Keywords: Telmisartan, Gastric Retention, Biopharmaceutical Classification System, Bioavailability, Hypertension, Angiotensin Receptor Blocker, release kinetics, data analysis etc

1. INTRODUCTION

Telmisartan (TEL) is a selective angiotensin II receptor blocker used in the management of cardiovascular disorders. It is a class II drug according to Biopharmaceutical Classification System (BCS); with poor solubility and high permeability. Owing to its hydrophobicity, TEL demonstrates low dissolution behavior in gastro-intestinal (GIT) media and thus deprived absorption, and later poor bioavailability.

The aqueous solubility of TEL is strongly pH dependent. Telmisartan is practically insoluble at physiological pH (3 - 7). The maximum solubility of TEL is observed at extremely low and high pH. [11]

Dosage forms that can be retained in stomach are called gastro retentive drug delivery systems (GRDDS). Hydro dynamically controlled systems are a type of low density gastro retentive drug delivery system that have sufficient buoyancy to float over the gastric content and remain buoyant in the stomach thus allowing the drug to solubilize sufficiently in the low pH of gastric fluid (pH of 1-2).

2. MATERIALS AND METHODOLOGY

Materials: TEL was received as a gift sample from Virchow Drugs Limited, Mumbai. HPMC K4M from Ases chemical work, Jodhpur, India. Microcrystalline

cellulose, lactose, magnesium stearate and talc, other ingredients and solvents were of analytical grade.

Drug-excipients interaction study

Attenuated total reflection (ATR) spectroscopy: Attenuated total reflection (ATR) spectroscopy is a useful analytical technique utilized to check the chemical interaction between the drug and excipients used in the formulation. 1:1 mixture of solid fine powder of telmisartan and dry powder of HPMC K4M was prepared in a mortar and mixed well with the help of a spatula. Spectrum measurement was carried out in the wavelength region of 500 cm^{-1} – 4000 cm^{-1} by ATR spectrophotometer. The IR spectrum of the physical mixture was compared with that of the pure drug to check any possible drug-excipient interaction.

Solubility studies: The solubility if telmisartan was determined using shake flask method. Saturated solution of telmisartan was prepared by adding excess amount of drug into 0.1N HCL and allowed to equilibrate for 24 hrs. The solution was filtered, suitably diluted and analyzed spectrophotometrically at 291nm. Same process was repeated for performing the solubility studies with 7.5pH phosphate buffer. The solubility of telmisartan is reported in Table 6.

Formulation of gastro retentive tablets of telmisartan by direct compression method:

Gastro retentive tablets of telmisartan were prepared by direct compression method. HPMC K4M and MCC were used as a floating and wicking agent respectively. The quantities of the above ingredients were optimized as shown in below table-1 on the basis of trial preparation of the tablets. All the ingredients were weighed accurately. The drug was mixed with the polymers and other excipients, except magnesium stearate and talc. The powder mix was blended for 20 min to have uniform distribution of drug in the formulation. Then, magnesium stearate and talc were added and mixed for not more than 1 min (to ensure good lubrication.) About 250 mg of the powder mix was weighed accurately and fed into the die of single punch machinery and compressed using 8mm punches. The hardness of the tablets was adjusted at 2-4kg/cm2 using a Pfizer hardness tester.

Evaluation of Gastro Retentive Tablets of Telmisartan:

Pre Compression Parameters: The powder blend is evaluated for various pre compression parameters such as bulk density, tapped density, angle of repose, hausner's ratio, compressibility index to determine the flow properties of the powdered blend.

Post compression parameters:

Thickness: Vernier calipers was used for the measurement of tablet thickness, the tablet was placed in between the movable jaw and the stationary jaw. Then the screw was rotated, so as to fit the tablet in between the jaws and values are noted.

Tablet hardness: Hardness of the tablet of each formulation was determined by using Pfizer Hardness tester.

The formulation Table used for preparing the gastro retentive tablets of telmisartan is shown below in Table 01.

Friability: Roche friabilator was used to determine the friability by following procedure. Pre weighed tablets are placed in the friabilator. Friabilator consist of a plastic chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each revolution. The tablets were rotated in the friabilator for at least 4 minutes. At the end of test tablets were dusted and reweighed; the loss in the weight of tablet is the measure of friability and is expressed in percentage as Formula,

Friability [%] = (Initial weight - Final weight)/ Initial weight x 100

Table 01: Formulation Table for Gastro Retentive Tablets of Telmisartan

Batch code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Telmisartan (mg)	40	40	40	40	40	40	40	40	40
HPMC K4M (mg)	75	75	75	85	85	85	95	95	95
Microcrystalline cellulose (mg)	50	60	70	50	60	70	50	60	70
Talc (mg)	2	2	2	2	2	2	2	2	2
Magnesium strearate (mg)	2	2	2	2	2	2	2	2	2
Lactose (mg)	81	71	61	71	61	51	61	51	41
Total weight	250	250	250	250	250	250	250	250	250

Weight variation: Twenty tablets were individually weighed and average weight was calculated. The individual weight was compared to the average weight.

Buoyancy lag time determination and Total floating time: The in-vitro buoyancy was determined by the floating lag time. The tablets were placed in a 100 ml beaker containing 0.1N HCL. The time required for the tablet to rise to the surface for floating was determined as the floating lag time and further floating duration of all tablets was determined by visual observation.

Drug release: Release of telmisartan from the Tablets was studied in 0.1 N HCL (900 ml) using a USP type II dissolution apparatus i.e. paddle type at 75 rpm and 37± 0.5°C.

06 tablets of each formulation were taken for dissolution study. Samples (5 ml) were withdrawn at Interval of 5, 10, 15 and 30 minutes and same volume (5 ml) of the dissolution medium was replenished after each sampling.

The samples withdrawn were filtered and analyzed for drug content released spectrophotometerically at 291 nm.

Check point formulation and model validation: The observed results of the check point formulation can then be compared to the predicted value to test the generated regression equation/ model. In this a formulation was prepared with X1 (Conc. Of HPMC K4M) = 80 mg and X2 (Conc. Of Micro crystalline cellulose) as 65 mg.

%Bias = Predicted value-Actual value/ Predicted value X 10.

3. RESULTS AND DISCUSSION:

The transmittance peaks exhibited in the spectrum of telmisartan sample were found to be similar with functional group present in the structure.

The spectrum of physical mixture as on day 0 and day 14, were compared with the peaks of telmisartan. It was found that there was no change/ disappearance of peaks nor there was appearance of any new peak. It indicates chemical compatibility of the telmisartan with the polymers.

ATR spectroscopy

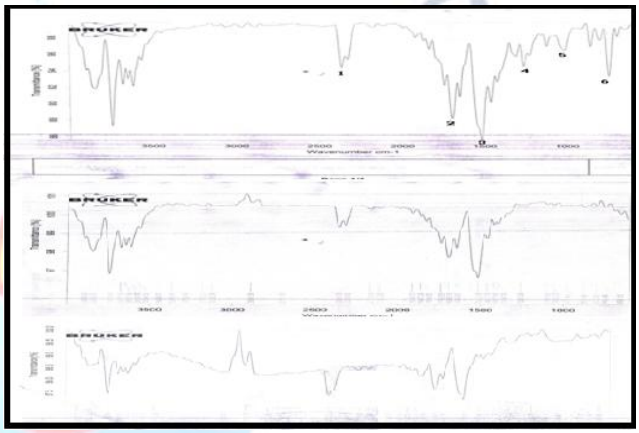

Figure 01: a) Recorded IR spectrum of telmisartan and b) Reference IR spectrum of telmisartan.

Table 2: Position of characteristic peaks in telmisartan

Peak No.	Wave no. (cm^{-1})	Band width range (cm^{-1})	Characteristic functional group/ vibration
1	3059.10	3000-3700	O-H Stretching
2	1693.50	1600-1900	C= Stretching
3	1278.81	1180-1360	C-N Stretching
4	1342.46	1300-1500	CH_3 Bending

Table 3: Solubility studies of telmisartan with different solvents

Solvent	Solubility (mg/ml)	Volume of solvent required to dissolve single dose (40 mg) of drug (ml)	Part of solvent required to dissolve 1 part of the drug
Water	0.087	460	11,500
Phosphate buffer 7.5 pH	1.604	24	624
0.1N HCL	1.533	27	653

Telmisartan was found to be practically insoluble in water (>10,000 parts of solvent required for one part of solute) and soluble in 0.1N HCL (10 to 30 parts of solvent required for one part of solute) as volume of solution required to dissolve telmisartan equivalent to its single dose was found to be 27.0 in 0.1N HCL. This shows that 0.1N HCL is not a limiting factor for testing the solubility of telmisartan.

It was found to be soluble in 7.5 pH phosphate buffer (10-30 parts of solvent required to dissolve 1 part of solute) as volume of solution required to dissolve telmisartan equivalent to its single dose was found to be 24 in 7.5 pH phosphate buffer. However, telmisartan used with strong alkanizers disrupt and degenerate duodenal and ieiunal mucosal tissues at that pH.

Evaluation of pre-compression parameters of gastro retentive tablets of Telmisartan:

Table 4: Data for pre-compression parameters of tablet formulations (F1-F9)

Formulation code	Bulk density (g/cc)	Tapped density (g/cc)	Carr's Index	Hausner Ratio	Angle of repose (θ)
F1	0.54±0.04	0.59±0.08	8.47±0.16	1.09±0.05	32.02±0.28
F2	0.57±0.06	0.62±0.06	8.06±0.08	1.08±0.08	31.40±0.03
F3	0.56±0.02	0.62±0.10	9.67±0.0	1.10±0.01	33.4±0.45
F4	0.58±0.02	063±0.08	11.11±0.48	1.12±0.02	32.35±0.48
F5	0.48±0.01	0.54±0.05	14.28±0.86	1.12±0.04	33.08±0.64
F6	0.45±0.05	0.52±0.16	13.46±0.24	1.15±0.02	31.37±0.53
F7	0.46±0.01	0.58±0.12	11.53±0.18	1.13±0.04	32.68±0.23
F8	0.47±0.18	0.54±0.05	12.96±0.38	1.14±0.08	34.04±0.18
F9	0.43±0.02	0.50±0.14	14.00±0.64	1.16±0.03	34.50±0.48

All the formulations were evaluated for bulk density, tapped density, % compressibility, hausner's ratio and angle of repose. The results of % compressibility, hausner's ratio and angle of repose were found to be <16, <1.25 and <30 respectively. These results show that the formulations have very good flow properties.

Evaluation of post-compression parameters of floating tablets of Telmisartan:

Table 5: Data for post compression parameters of tablet formulations (F1-F9)

Formulation code	Weight Variation (mg)	Thickness (mm)	Hardness (kg/cm2)	Friability (%)	Floating lag time(sec)	% Drug released (at 30 min.)
F1	250±8.75	5.2 ±0.2	3.0±0.4	0.23 ±0.01	04±0.2	7.27±0.18
F2	250±7.34	5.4±0.4	3.2±0.2	0.19 ±0.03	06±0.4	5.42±0.17
F3	250±8.13	5.2±0.2	3.2±0.4	0.60±0.08	05±0.6	5.38±0.32
F4	250± 8.24	5.2±0.2	3.6±0.8	0.34±0.04	03±0.4	6.45±0.29
F5	250±8.15	5.8±0.6	3.3±0.4	0.48±0.02	03±0.5	9.34±0.29

Formulation code	Weight Variation (mg)	Thickness (mm)	Hardness (kg/cm2)	Friability (%)	Floating lag time(sec)	% Drug released (at 30 min.)
F5	250± 8.18	5.6±0.4	3.2±0.2	0.50±0.08	04±0.4	7.68±0.64
F6	250± 7.65	5.4±0.2	3.2±0.2	0.43±0.04	03±0.2	7.49±0.38
F7	250± 7.38	5.6±0.2	3.4±0.4	0.46±0.06	05±0.4	7.34±0.36
F8	250± 8.65	5.8±0.4	3.4±0.8	0.47±0.01	04±0.4	7.86±0.27
F9	250± 8.18	5.6±0.4	3.2±0.2	0.50±0.08	04±0.4	7.68±0.64

The tablets were evaluated for weight variation, thickness, hardness, friability, floating lag time and in-vitro drug release study. All the formulations passed the evaluation tests and showed comparable satisfactory results. The thickness of all tablets was found to be in the range of 3.1-3.6 mm and hardness was found to be in the range of 2-3 kg/cm2 in all the formulations, the MCC and HPMC K4M together showed good binding properties. In all the formulations, the %friability was (0.37-0.72) below 1% as per USP. The average weight was found to be 248-252 mg which will be within the given limits.

The dissolution of the different formulation was as follows in the decreasing order i.e. F5>F9>F6>F7>F8>F1>F4>F3>F2 as shown in Figure 02.

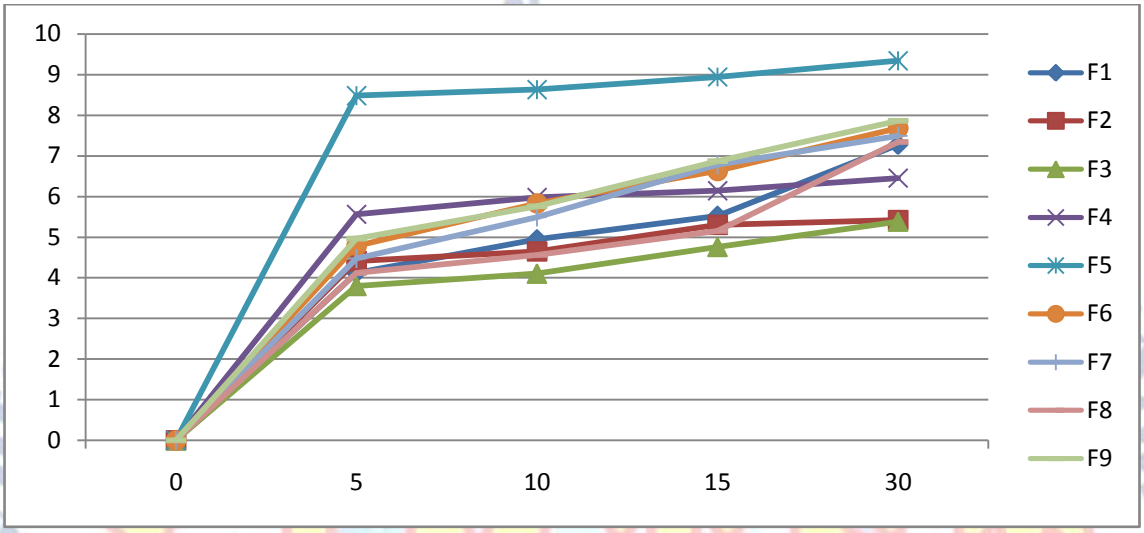

Figure 02: Dissolution profile of formulations F1-F9.

Data analysis and presentation:

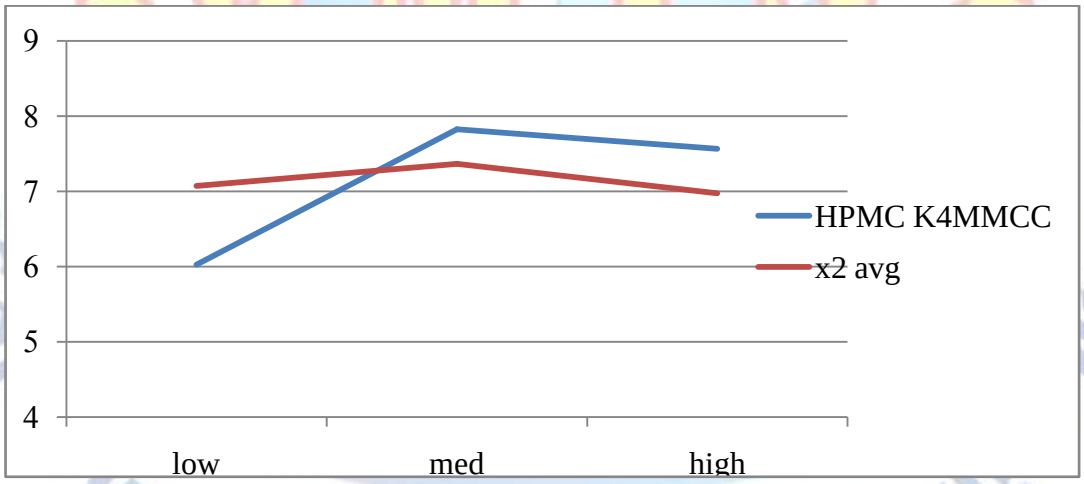

Figure 03: a) Average effect of independent variables (Conc. Of HPMC K4M and Micro crystalline cellulose) on dissolution of floating tablet of telmisartan.

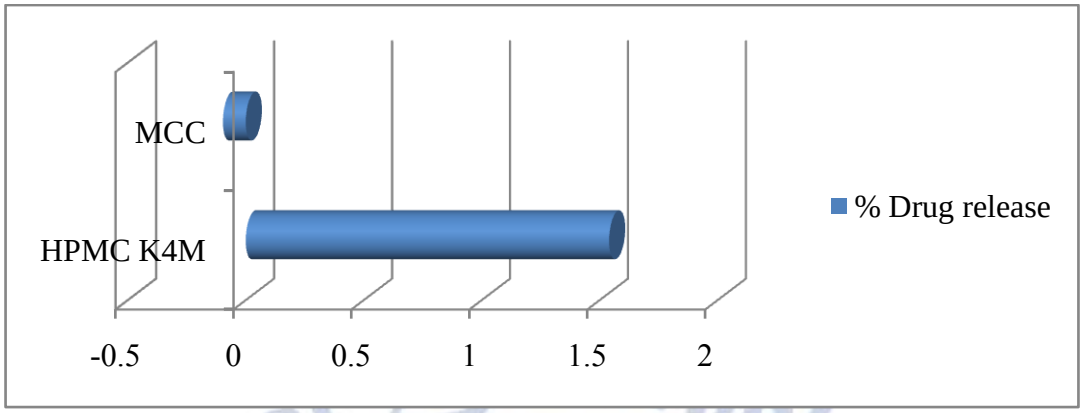

Figure 04: Main effect of independent variables (Conc. Of HPMC K4M and Micro crystalline cellulose) on dissolution of floating tablet of telmisartan

Model for drug release kinetics: $Y = -9.667X_1 - 10.1006X_2 + 0.0494\ X1^2 + 0.020755\ X_2^2 + 0.209\ X_1xX_2 - 0.00099\ X_1^2xX_2 - 0.0029\ X_1XX_2^2 + 456.7233$ and the R value was found to be 0.91.

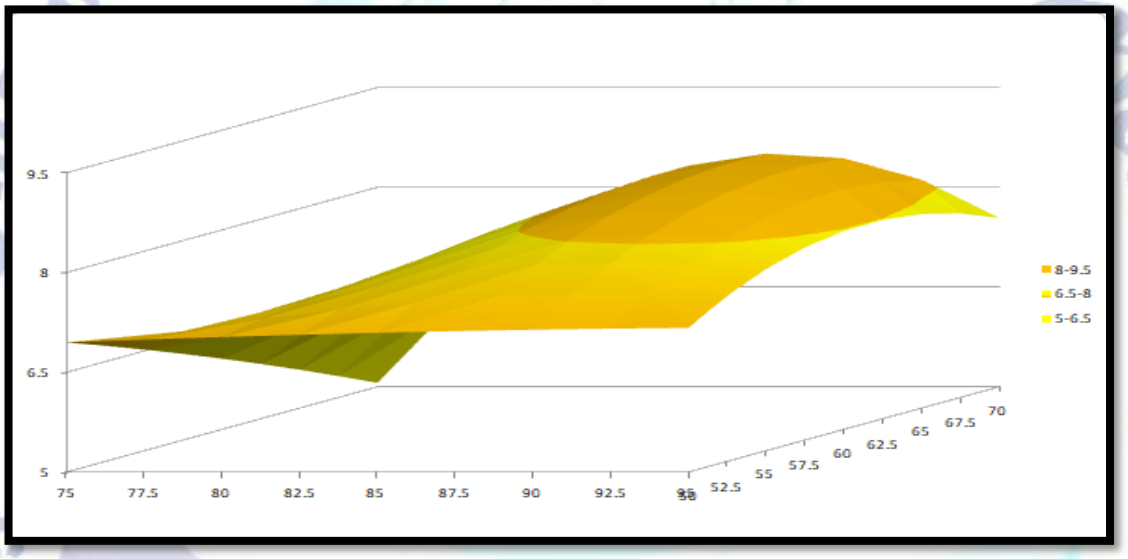

Figure 05: Three dimensional response surface plot showing effect of concentration of HPMC K4M and Micro crystalline cellulose on cumulative % drug release.

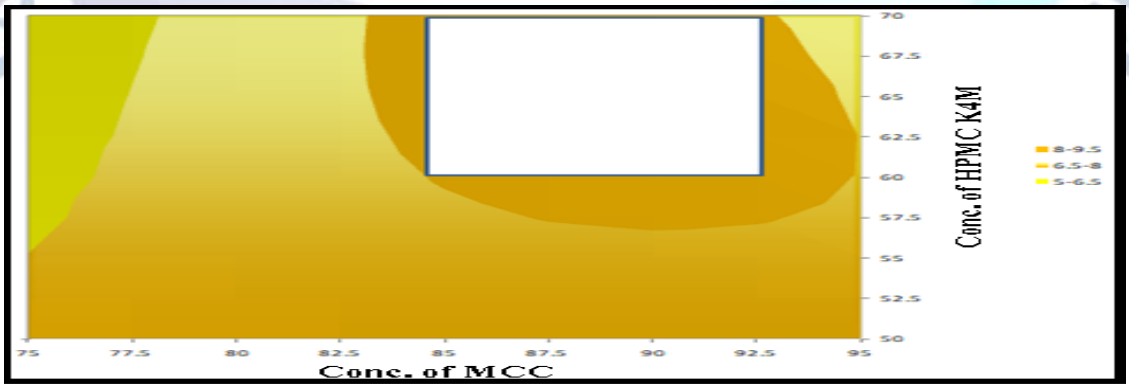

Figure 06: Contour plot showing effect of concentration of HPMC K4M and Micro crystalline cellulose on % drug release.

Design space: The design space of the overlap region of ranges for floating lag time and percentage drug release is presented in Table 06.

Table 08: Proposed design space

CQA	Process design space (Non linear multivariate	Product

	PAR)		Design Space
	X1/ HPMC K4M (mg)	X2 MCC (mg)	
Q30	85 to 92.5	60 to 70	8-9.2%

PAR: Proven Acceptable Range

Table 6: Results of evaluation of the check point formulation

Parameter	Predicted Response (P)	Actual Response (A)	Residuals (P-A)	%Residuals
In-Vitro release at 360 min.	88.20%	87.86%	0.34	3.4%

Table 7: Model fitting for release kinetics of check point formulation

Formulation code	Zero order	First order	Higuchi Matrix	Hixon-Crowell	Korsmeyer-Peppas			Best Fit model
	R	R	r	r	r	n	K	
Check point	0.994	0.946	0.971	0.980	0.995	0.001	0.014	Peppas

The check point formulation showed % Residuals in acceptance range of proposed design space. The 'n' Value obtained

from the Peppas equation was less than 0.5, which indicates that the formulation showed drug release by Fickian diffusion mechanism.

4.FUTURE ASPECT & CONCLUSION:

In this study, gastro retentive tablets of drug telmisartan were prepared using HPMC K4M and Micro Crystalline Cellulose (MCC) to investigate the effect of gastric retention on the solubility of the drug. Formulated tablets showed satisfactory results for various Post compression evaluation parameters like: tablet thickness, hardness, weight variation, floating lag time, total floating time, content uniformity and in vitro drug release. Formulation F5 gave better % drug release and floating properties in comparison to the other formulations.

The influence of polymers like HPMC K4M and MCC was also studied and the study suggested that the % drug release increased on increasing the concentration of HPMC from 75 to 95 while the % drug release decreased on increasing the concentration of MCC from 50 to 70.

Finally a check point formulation was made to validate the model and also the model fitting done for the same suggested that the drug release mechanism follows a fickian diffusion suggesting that the release occurs because of swelling nature of the polymers used.

From the dissolution data of all formulations developed, solubility of Telmisartan, was enhanced by targeting its release in extreme pH of gastric fluid (1-2) and thus it may be concluded that the gastro retentive floating tablets using a combination of HPMC K4M and MCC in optimized concentrations can be used to increase the solubility of the poorly soluble drugs in gastric fluid by increasing their gastric residence time (GRT).

Acknowledgment

My grateful thanks to all the sincere and extremely helping friends for their support and help for the completion of work. Last but not the least, I am thankful to all those who cooperated and helped me directly or indirectly to carry out this work.

Ethical Approval: - Ethical approval was not required for this letter. All data used is publicly accessible.

Funding: - There were no external sources of funding for this research.

Financial Support and Sponsorship: Nil.

Conflict of interest statement

Authors declare that they do not have any conflict of interest.

REFERENCES

[1] Sharma S, Prashar M, Sahu R, "Floating Drug Delivery System: Incredible revolution", Pharmacology Online, 2011, 3:1039-1054.

[2] Narang N, "An Updated Review on: Floating Drug Delivery System (FDDS)", International Journal of Applied pharmaceutics, 2011, 3(1): 975-1058.

[3] Sharma N, Agarwal D, Gupta M, khinchi M, "A Comprehensive Review on Floating Drug Delivery System"", International

Journal of Research in Pharmaceutical and Biomedical Sciences, 2012, (2):2229-3701.
[4] http://en.wikipedia.org/wiki/telmisartan, accessed on: 02/1/22.
[5] Battershill A, Scott L, "Telmisartan: A Review of its Use in the Management of Hypertension", International Journal of Pharmaceutical Sciences, 2006, 66(1):51-83.
[6] Kunam V, Garikapati D, Suryadevara V, Mandava V, "Solubility And Dissolution Rate Enhancement of Telmisartan by Solid Dispersion and Pelletization Techniques Using Soluplus As Carrier, "International Journal of Applied Pharmaceutics", 2019, 12(1): 50-58.
[7] Kundu S, Kumari N, Soni S, Ranjan S, Kumar R, Sharon A et al "Enhanced Solubility of Telmisartan Phthalic Acid Cocrystals Within the pH Range of a Systemic Absorption Site", ACS Omega, 2018, 3(11):15 380-15388.
[8] Chowdary K, Prasad R, "Optimization of Telmisartan Tablet formulation by 23 Factorial Design By Employing βCD, Primojel And Tween 80", International Journal of Pharmaceutical Sciences And Research", 2017;8(3): 1178- 1182.
[9] Ashoor J.A, "Preparation and Evaluation of Gastroretentive Systems of Telmisartan", World Journal of Pharmacy and Pharmaceutical Sciences, 2017, 208–217.
[10] Aparna C, Srinivas P, Patnaik R, "Enhanced Transdermal Permeability of Telmisartan By A Novel Nano emulsion Gel", International Journal of Pharmacy and Pharmaceutical Sciences, 2015, 7(4): 335-42.
[11] Ajmeera T, Gera S, Reddy P, "Enhancement of Dissolution and Bioavailability of Poorly Soluble Telmisartan: Designing Modified Cyclodextrin Inclusion Complexes", Journal of Chemical and Pharmaceutical Research, 2015, 7(10):164-174
[12] Hyma P, Laharika A, "Formulation and Characterization of Novel Micro emulsions of Telmisartan", IJPBS, 2013, 3(3): 162-171.
[13] Kausalya J, Suresh K and Padmapriya S "Solubility and Dissolution Enhancement Profile of Telmisartan Using Various Techniques" International Journal of PharmTech Research, 2011, 3(3):1737-1749.
[14] Rao M, Karanjkar P, "Formulation And Development of Gastroretentive Drug Delivery System of Efavirenz", International Journal of Pharmaceutical Sciences and Drug Research, 2019, 11(05): 231-239.
[15] Bijumol C et al, "Formulation and Evaluation of Floating Tablets of Theophylline Hygeia", journal for drugs and medicines, 2013, 5(1): 23-31.
[16] Nanjwade B, Adichwal S, Sutar K, "Development And Evaluation of Glipizide Floating Tablet", Journal of Drug Delivery Science and Technology, 2012, 22(4): 327-333.
[17] Padmavathy J. et al, "Formulation and Evaualtion of Ofloxacin Floating Tablets using HPMC" International Journal of Pharmacy and Pharmaceutical Sciences, 2011, 3(1): 170-173.
[18] Satishbabu B, Ravi R, Sandeep V & Shrutinag R, "Formulation and Evaluation of Floating Drug Delivery System of Famotidine" Indian Journal of Pharmaceutical Sciences, 2010, 72(6), 736-738.
[19] Jagdale S, Agavekar A, Pandya S, Kuchekar B, Chabukswar A. Formulation and Evaluation of Gastroretentive Drug Delivery System of Propranolol Hydrochloride. AAPS PharmSciTech. 2009;10(3).
[20] Niharika M, Krishnamoorthy K and Akkala M, "Overview on Floating Drug Delivery System", International Journal of Applied Pharmaceutics, 10(6), 65.
[21] Srusi O.L, Fabio S, Bettini R, Santi P, Colombo G, "Module Assemblage Technology for Floating Systems; In-Vitro Flotation and In-Vivo Gastro Retention", Journal of Controlled Release 2008, 129(2):123-125.
[22] Siepmann J, Peppas NA, "Modeling of Drug Release from Delivery Systems Based on hydroxypropyl methylcellulose", Advanced Drug Delivery Reviews 2001, 48: 139-157.
[23] Pare A et al: "Formulation and Evaluation of Effervescent Floating Tablet of Amlodipine Besylate" Research J. Pharm. And Tech, 2008, 1(4): 974-3701.
[24] https://globalresearchonline.net/journalcontents/v17-2/04.pdf
[25] Ashoor J. A, "Formulation and Evaluation of Non-Effervescent Floating Tablets of Losartan Potassium", World journal of pharmacy and pharmaceutical sciences, 2017
[26] Harshal S, Chetan G, Surbhi U and Sujit P "Development and In-Vitro Evaluation of An Oral floating Tablet of Metronidazole" Journal of Drug Delivery Ther, 2018; 8:83-6.
[27] Bhise S, Mathure D, Patil MVK and Patankar RD, Solubility enhancement of antihypertensive agent by solid dispersion technique, International Journal of Pharmacy & Life Sciences, 2011; 2(8):970-995.