

PREPARATION AND EVALUATION OF GASTRORETENTIVE SYSTEMS OF TELMISARTAN**Jamal Ali Ashoor***

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Corresponding Author*Dr. Jamal Ali Ashoor**Pharmaceutics Department,
College of Pharmacy,
Karbala University, Iraq.**ABSTRACT**

Telmisartan (TEL) is a selective angiotensin II receptor blocker used in the management of cardiovascular disorders. It is a class II drug according to biopharmaceutics classification system; with poor solubility and high permeability. Owing to its hydrophobicity, TEL demonstrates low dissolution behavior in gastro-intestinal (GIT) media ensuing deprived absorption, and later poor bioavailability. The subject of the research is to prepare a floating tablet of TEL for oral use, which related to various benefits which can be summarized by improvement in the solubility and increment in the absorption and hence better

bioavailability will be obtained in addition to reduction in its side effects. The Gastroretentive Floating Tablets (GFT) were formulated by means of hydroxy propyl methyl cellulose (HPMC). Six batches were formulated by Direct Compression (DC) and Wet Granulation (WG) method by using different HPMC concentrations. In addition to that, changing the diluent type (avecil 101 and 102) to reach optimal floating and dissolution performance. These prepared formulas were examined for angle of repose, Carr's Index (CI), hardness, Floating Lag Time (FLT), Floating Duration (FD) and dissolution profile. F5 (the favored formula) comprised 120mg HPMC plus 20mg sodium bi carbonate (NaHCO_3) which formulated by DC displays a reasonable characteristics in release profile with FLT of 8 ± 2 second and buoyancy of 6.5 ± 0.5 hours. It was concluded that F5 (the favored formula) represent a hopeful one as a floating of gastroretentive drug delivery systems of Telmisartan.

KEYWORDS: In addition to that, changing the diluent type (avecil 101 and 102) to reach optimal floating and dissolution performance.

1 INTRODUCTION

Different approaches pursued to enhance the retention of orally dosage forms in stomach, involving floated drug delivery systems (FDDS), hydrogel composite system which is characterized by unbendable, expandable, flexible and super-porous dosage form, high-density systems, muco-adhesive systems, and magnetic systems.

FDDS is a one of futuristic and hopeful approach for improving the bioavailability of drugs via floating the tablets instantly upon interacting with gastric fluids. The aim of this approach is to overcome instability of drugs in the intestinal or colonic environment which, as a result, showing low solubility at high pH values and then; consequently, to target drugs within absorption windows in stomach or upper small intestine.^[1] This delivery system is characterized by floating the dosage form in the gastric fluids. It shows this behavior due to it has less bulk density in comparison with gastric fluids with no pronounced effect on the rate of gastric emptying for a prolonged period. The drug in this strategy is released slowly at the required rate from the system.^[2] It would be successful to apply this approach for many drugs such as telmisartan (TEL).

In terms of pharmacotherapy, TEL works by specific inhibiting the binding of angiotensin II through blocking the AT1 receptors in various tissues, for example vascular smooth muscle as well as the adrenal gland; hence, it used in the treatment of hypertension.

In terms of absorption and solubility profile, TEL is a drug with high penetrability, in another words, it has high absorption rate with peak plasma concentrations of 44.7 µg/L. It has a dosage- reliant bioavailability which is ranging between 42% and 58% according to its own doses of 40 mg to 140 mg respectively.^[3] It is practically insoluble in water (7 µg/mL). TEL's solubility in aqueous solutions is potentially depending on pH, with highest solubility showed at high and low pH range i.e. it shows considerably increment in solubility profile above and below the range of pH 3–9.

AIM OF THIS STUDY

This study was conducted to explore new and novel method of formulating telmisartan's oral floating tablet. The advantages of this system is associated with improvement in solubility and absorption profiles. As a result, bioavailability would be enhanced and the side effects of the drug will be minimized.

2 METHODOLOGY

2.1 Materials: The crude of telmisartan was purchased from Hetero drugs limited, India. HPMC (Hydroxypropyl Methyl Cellulose) and Microcrystalline cellulose (Avicel PH 101 and 102) were purchased from Whatman international, England. Polyvinylpyrrolidone (PVP K30) and Sodium bicarbonate were purchased from Riedel De Haen AG Seelze, Honnover, Germany.

2.2 Instruments: The formulation was examined and evaluated using Fourier transform infrared (FTIR) system, (Shimadzu, Japan) and the scanning range from 4000-600 cm^{-1} , the dissolution apparatus, Copley dissolution 8000, (Copley scientific, UK), Oven (Mammert, Germany), UV-Visible spectrophotometer, Carry win UV, (Varian, Australia) and Tablet hardness tester Stokes, Monsanto Co. Ltd.

2.3 Determination of λ_{max} and calibration curve of TEL

A solution of 400 $\mu\text{g/ml}$ of TEL in a buffer solution ($\text{pH}=1.2$) of 0.1N HCl was made and the λ_{max} of the drug was determined using UV visible spectrophotometer scanner (range: 200-400 nm). A calibration curve of TEL was constructed by preparing serial dilutions of different concentrations (20, 40, 60, 80, 100, 120 and 140 $\mu\text{g/ml}$) of TEL at the λ_{max} of the drug, the absorbance was measured and plotted against the respective concentrations.

2.4 Preparation of TEL Floating tablet

Different formulas of TEL floating tablet were prepared as shown in table (1) using wet granulation and direct compression methods. The drug, polymer(s), and diluent were weighed and mixed in the mortar for dry blending for 5 minutes. Then the powder blend was granulated by continuous addition of binder solution (10% PVP in ethanol) with kneading until positive ball test constancy was achieved. After that, the wet mass was screened with 12 mesh size sieve and drying in a pre-warmed oven at 60 $^{\circ}\text{C}$ for one hour. Magnesium stearate and talc powder were added and mixed for 3-4 minutes then compressed by 9 mm flat face punch tableting machine.

Table 1: Several formulas of Telmisartan's floating tablets:

Formula No.	TEL (mg)	HPMC (mg)	NaHCO ₃ (mg)	Avicel 101(mg)	Avicel 102(mg)	Mg Stearate (mg)	Talc (mg)	PVP
F1	40	30	20	226	-----	2	2	---
F2	40	60	20	196	-----	2	2	---
F3	40	90	20	166	-----	2	2	---

F4	40	120	20	136	-----	2	2	---
F5	40	120	20	-----	136	2	2	---
F6	40	120	20	136	-----	2	2	6.4

***total weight of each tablet is 320 mg**

Direct compression method was used to prepare formulations (1, 2, 3, 4 and 5), in which the drug and other ingredients were mixed for fifteen minutes to obtain a blend of homogenous powder. Then, magnesium stearate and talc powder were mixed for 3-4 minutes. The mixture was compressed using 9 mm flat face punch tableting machine.

2.5 Preformulation Characterization of Powder Blend

The angle of repose of powder blend was calculated according to the equation 2.1, where h and D represent height of the cone and diameter of the heap respectively.

$$\text{Tan } \theta = 2h/D \dots\dots\dots \text{ (Eq.2.1)}$$

Determination of Carr's Index was calculated according to equation 2.2. Where (V_0) and (V_f) represent untapped volume and tapped volume respectively.

$$\text{Carr's Index (\%)} = (V_0 - V_f) / V_0 \cdot 100 \dots\dots\dots \text{ (Eq.2.2)}$$

Monsanto hardness tester was used to measure the hardness of each 5 tablets and the average was taken.

2.6 Determination of Floating Lag Time and Floating Duration

Floating lag time (FLT) can broadly be defined as the duration interval of introducing the tablet into the dissolution media and its floatation to the surface of that media; while, the period up to which the tablet hangs on the surface of dissolution mixture was termed as floating duration (FD). These parameters were calculated by introducing the tablets in a beaker (100 mL) containing 0.1N HCl. The mixture was kept in quiet condition and the temperature was stored at 37 °C.^[4]

2.7 Dissolution Test: The USP type II was used to analyze the in vitro release of each formula using paddle method under sink condition. The speed of the paddle was 50 rpm and 0.1 N HCl solution was used as a dissolution media at 37 °C. Samples of 5 mL were taken regularly and exchanged by fresh media that is maintained at 37 °C ± 0.5. The samples were filtered and measured spectrophotometrically at the TEL λ max. The percentage of the drug release was measured and plotted against time.

3 RESULTS AND DISCUSSION

3.1 Determination of λ_{\max} and calibration curve of TEL

Scanning solutions containing 400 $\mu\text{g/ml}$ of TEL was shown a peak representing the λ_{\max} at 296 nm. This result is in agreement with the reported one.^[5] Both absorbance versus respective concentrations was plotted and represented in a straight line. The obtained calibration curves comply with the Beer's law within the used concentrations range as shown the figure 1.

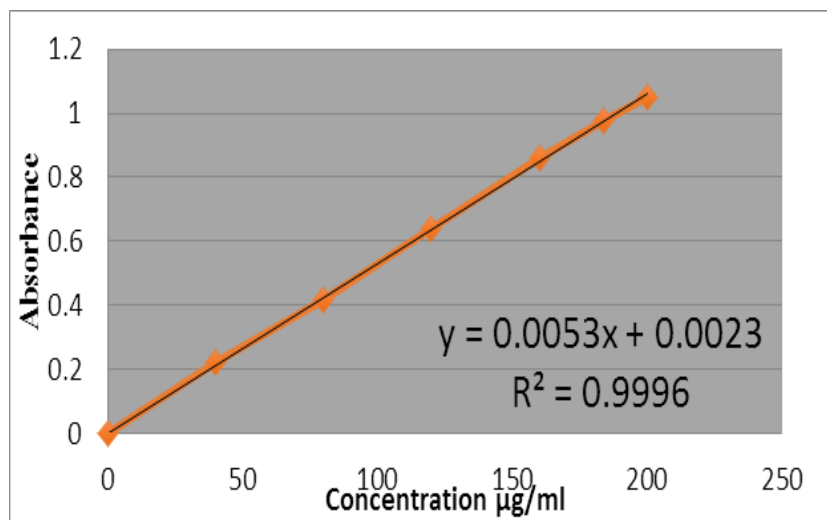


Figure 1: TEL's calibration curve in 0.1N HCl (pH 1.2)

3.2 Preformulation Characterization of Powder Blend

The FTIR spectra of the pure TEL, physical mixture of TEL and polymer at equal ratio (1:1), and the selected TEL floating formula is shown in figure (2). The reported and observed FTIR peaks of pure TEL is shown in table (2).^[6,7] No result of chemical incompatibility was showed between the drug and the polymer. All the typical peaks of pure drug were also showed up in the spectra of the physical mixture of TEL and polymer.

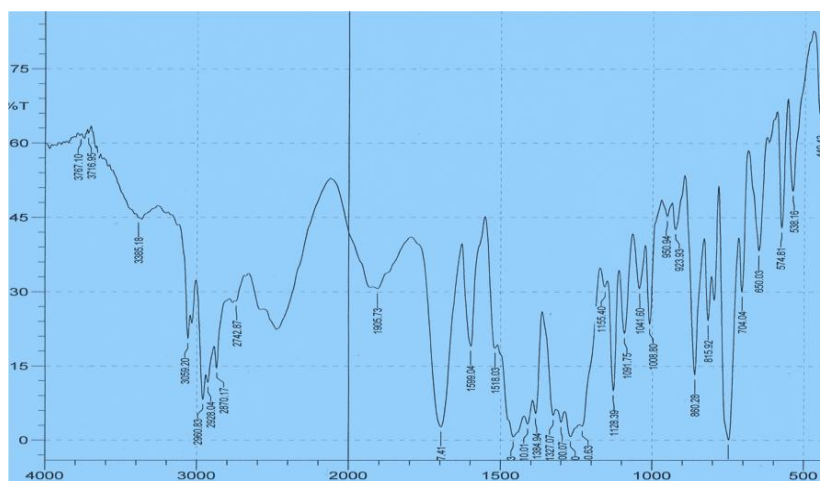


Figure 2: The FTIR spectrum of pure TEL

Table 2: The Reported and Observed FTIR Peaks of pure TEL

Reported Peaks of pure TEL (cm ⁻¹)	Observed Peaks of pure TEL (cm ⁻¹)	Functional Group Assignment
3400	3385	O-H stretching of carboxylic acid
2960	2960	(C-H) Stretching of aromatic
1697	1697	C=O stretching of carboxylic acid
1599	1599	Aromatic(C=C) bending and stretching
1458	1460	Aromatic (C-H) bending
1384	1384	hydroxyl bending and carbonyl stretching of carboxylic acid
1268	1268	Carboxylic acid bending
755	757	1,2-disubstitued benzene ring

The angle of repose of formulation (F5) was the best ($32 \pm 2.5^\circ$) and it displayed a considerable ($p < 0.05$) improvement in the flowability because the diluent used in this formulation was AVECIL pH 102 which has larger particle size than AVECIL pH 101 that was used in the all other formulations and the results of Carr's index were improved as well by using AVECIL pH 102 in formulation (F5) and for the same previous reason. Wet granulation method (F6) has the advantages of increasing bulk density of powders and improving the flow properties of the mixture.^[8] These results are within the pharmacopeia prescribed limits^[9] and revealed that the granules have a good flow properties. The values are shown in table (3).

The tablet hardness of all formulations were kept above 3Kg (table 3) which is considered satisfactory values that do not affect floating ability of the tablets.

Table 3: The preformulation characteristics of granules and hardness of TEL floating tablet formulations.

Formulations	Angle of Repose	Carr's Index	Hardness (kg)
F1	43±3.5	40±4	6±0.3
F2	45±3.7	50±5	5±0.2
F3	57±4	45±4.2	4.5±0.2
F4	45±3	42±3.1	3±0.1
F5	32±2.5	38±3	5.1±0.2
F6	36±2.9	26±2.7	4.5±0.2

*SD (±) for N=5.

3.3 Determination of the Floating Lag Time and Floating Duration

Floating lag time (FLT) and floating duration (FD) for all the prepared formulas are shown in table (4).

The acceptance (FLT) of the prepared formulas was due to the presence of the agent of generating gas in the acidic dissolution media (0.1N HCl). It generates CO₂ gas that would be embedded through the gelling layer of the lipophobic polymer. It is also due to the top swelling of hydrocolloid particle after exposure to the aqueous fluids of the gastric, which in turn results in an increment in bulk volume with an internal void space in the dry center of tablet.^[10]

3.4 The Effect of Polymer Concentration: Formulations 1, 2, 3 and 4 which contain 30, 60, 90 and 120 mg HPMC respectively, F1 floated after (5) seconds but it stayed buoyant for one hour and half only and lost its integrity briefly after putting in the dissolution medium with disintegration. This indicates the inability of the polymer (at this concentration) to form the desired coherent gel layer that is able to entrap the liberated CO₂ gas.

However, for formulas 2, 3 and 4 there is a direct relationship between polymer concentration with the FLT and FD, where FLT was 4 seconds for F2 and 3 seconds for F3 and 2 seconds for F4, while FD was 3 hours for F2 and 6 hours for F3 and F4, this can be explained by the fact that high concentration of polymer would increase the tablet integrity by forming a stronger gel that retains CO₂ gas for longer time.^[11]

Table 4: Floating Lag Time and Total Floating Duration

Formulation No.	(FLT) (seconds)	FD (hours)
F1	5±1	1.5±0.2 (Bad integrity)
F2	4±1	3±0.25
F3	3±1	6±0.5

F4	2±1	6±0.9
F5	8±2	6.5±0.5
F6	9±3	7.5±0.6

*SD (±) for N=5.

3.5 The Effect of Diluent Type: All formulations employed microcrystalline cellulose (Avecil pH 101) as a diluent, except formulation 5 which employed the Avecil pH 102. Formulation 5 demonstrated a high FD and the FLT was increased from 2 to 8 sec which are non-significant ($p>0.05$) result. These results demonstrated that Avecil pH 101 is the best diluent type used in this study.

3.6 Dissolution Test: T50%, which is the required time to release 50 per cent of drug, and T80%, which is the necessary time to release 80% of the drug, were 95 and 135 min. respectively for F4, while for F5 they were 92 and 123 min. and for F6 they were 80 and 118 min. respectively.

Burst release means where the large amount of the drug is released immediately upon insertion in the releasing medium and before releasing rate is reaching to a stable profile.^[12] It is one of the important disadvantages of direct compression preparation procedure and can be solved by the use of a rapidly hydrating polymer or high polymer concentration.^[13]

The release of formulations that prepared by direct compression showed a potential reduction in the total releasing profile of drug in a comparison with the method of wet granulation ($p<0.05$) as shown in figure 3. In addition, the burst release was more pronounced due to the hydrophilic nature of PVP-K30, which is take in water quickly and dissolve without forming gelling nature. This would facilitates the medium penetration into the matrix easily with more rapid release of the drug from the designed formula.^[14]

Panna thapa et. al. found that both integrity and release of the prepared ibuprofen tablets by wet granulation procedure would not be maintained more than 70% of the drug through 1 hour. However, 65% of drug after only 10 hours was released from the same tablets that manufactured by direct compression.^[15]

Moreover, burst release was lower with wet granulation technique than that for the direct compression method. This could be explained by that the matrix contains a highly

hydrophilic compound which produces an extra osmotic gradient, resulting in a quicker swelling rate in the polymer and a large increase in thickness of the gel.^[16]

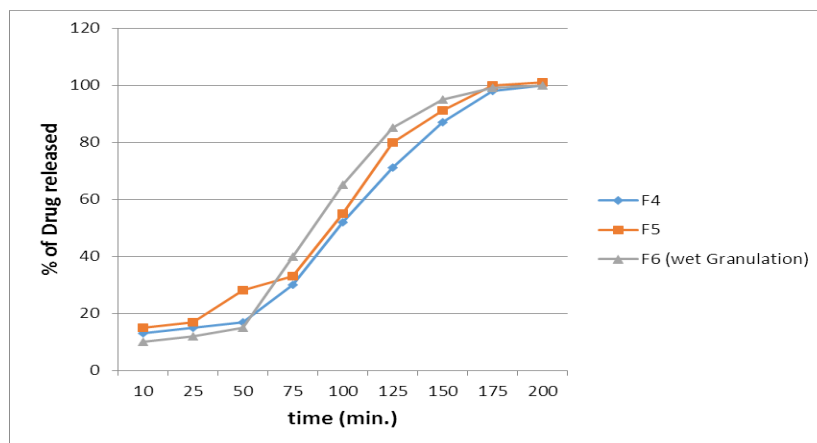


Figure (3) the release profile of selected formulations

4 CONCLUSION

Formulation of TEL as floating tablet improves its solubility and bioavailability by extending the gastric residence time. The floating properties of the formulations and its concentration has a potential effect on the type of the polymer used in the preparation. Preparation method of tablet has also a pronounced effect to enhance the floating tablet the formulations.

REFERENCES

1. Karkhile VG, Karmarkar RR, Sontakke MA, Badgujar SD, Nemade LS. Formulation and evaluation of floating tablets of furosemide. *International Journal of Pharma Research and Development* 2010; 1(12).
2. KAVITHA K, PUNEETH K, MANI TT., Development and evaluation of rosiglitazone maleate floating tablets. *International Journal of Applied Pharmaceutics* 2010; 2(2): 6-10.
3. Muthu A., Sankala R., Prasad A., Kumar D., Manavalan R. Simultaneous Estimation of Telmisartan and Amlodipine By UV Spectrophotometric Method Using Multi Component Mode of Analysis. *IRJP* 2011; 2(5): 175-180.
4. Ajay B, Dinesh K, Pradeep S. Studies on formulation and evaluation of floating tablets of ciprofloxacin HCl. *International Journal of Clinical Practice* 2010; 1(5): 1-4.
5. USP 36- NF 31 (The United States pharmacopoeia), Electronic Edition, 2013.
6. Murthy T., Purna T., Vijayakumar G. Studies on Dissolution Rate Enhancement of Telmisartan with Hydroxy Propyl B Cyclodextrin Complexes. *AJPSR*. 2011; 1(2): 73-85.

7. Hyma P., Laharika A. Formulation and Characterization of Novel Microemulsions of Telmisartan. IJPBS. 2013; 3(3): 162-171.
8. Rajesh A, Yadav N. Pharmaceutical Processing – A Review on Wet Granulation Technology. International Journal of Pharmaceutical Frontier Research April-June 2011; 1(1): 65-83.
9. British Pharmacopeia (BP), 2010.
10. Narang N. AN UPDATED REVIEW ON: Floating drug delivery system (FDDS). Int. J. App. Pharm. 2011; 3(1).
11. Shishu, Gupta N, Aggarwal N. A gastro-retentive floating delivery system for 5-fluorouracil. Asian Journal of Pharmaceutical Sciences 2007; 2(4): 143-149.
12. Xiao H, Christopher S. Review on the importance and mechanisms of burst release in matrix-controlled drug delivery systems. Journal of Controlled Release, 2001; 73: 121–136.
13. Inéz Jiménez M, Tomás QB, Leopoldo VR. Sustained delivery of captopril from floating matrix tablets. International Journal of Pharmaceutics, 2008; 362: 37–43.
14. Ebube NK, Ousu A, Adeyeye CM. Preformulation studies and characterization of the physicochemical properties of amorphous polymers using artificial neural networks. Int. J. Pharm. 2000; 196: 27-35.
15. Panna T, Manish G, Mullen AB, Howard NE. Controlled release oral delivery system containing water insoluble drug. Kathmandu university journal of science, engineering and technology, 2005; 1(1).
16. Enayatifard R, Saedi M, Akbari J, Haeri YT. Effect of hydroxypropyl methylcellulose and ethylcellulose content on release profile and kinetics of diltiazem HCl from matrices. Tropical Journal of Pharmaceutical Research 2009; 8(5): 425-432.