

FORMULATION AND EVALUATION OF OLMESARTAN MEDOXOMIL FLOATING TABLETS

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ABSTRACT

Objective: The objective of the present study was to formulate a controlled release floating tablet of Olmesartan Medoxomil.

Methods: Floating tablets of Olmesartan Medoxomil were prepared by direct compression method using both natural (sodium alginate and carrageenan) and semi synthetic polymers (HPMC K4M, HPMC K100LV and HPMC E50LV). Sodium bicarbonate and calcium carbonate were used as gas generating agents.

The floating tablets were evaluated for their hardness, friability, drug content, invitro buoyancy, invitro dissolution, swelling and stability studies. Effect of different polymers and gas forming agents on the drug release from the tablet was studied.

Result: The optimized formulation F3 with HPMC K4M and sodium bicarbonate showed good physical properties and short floating lag time (55.8 sec).

Conclusion: The drug release from the tablet was sustained and non-fickian transport of drug from the tablet was confirmed.

Keywords: Olmesartan Medoxomil, floating tablet, *In vitro* buoyancy, Gas forming agents.

INTRODUCTION

Olmesartan Medoxomil is a non peptide angiotensin II receptor antagonist use in the treatment of mild –moderate hypertension. This drug is weakly basic, lipophilic and having very less oral bioavailability of about 26%. Olmesartan Medoxomil inhibits type I angiotensin II receptor in the rennin angiotensin system, there by producing best antihypertensive action [1,2].

Gastro retentive delivery systems (GRDS) are suitable for the drugs which are (1) locally active on the stomach (antacids) (2) having narrow absorption window in GIT (L-dopa) (3) less soluble or degraded in intestinal pH GRDSs are useful for these drugs which having low bioavailability and low therapeutic efficacy. Natural or semi synthetic polymers are commonly used for the preparation of floating drug delivery system [3].

Cellulose derivatives have been commonly used in the formulation of hydro gel matrices for controlled drug delivery. They are safe, nonionic and minimize interaction problems when used in acidic, basic, or other electrolytic system. They are suitable for preparing formulations with soluble or insoluble drugs and at high or low dosage levels Hydration of polymers results in the formation of a gel layer that controls the release rate of drug [4].

The objective of the present study is to formulate and evaluate the floating tablet of Olmesartan Medoxomil, which will help to retain the dosage form in stomach resulting prolonged gastric drug delivery and improved oral bioavailability using gel forming polymers such as hydroxyl propyl methyl cellulose (HPMC K4M, HPMC K100LV and HPMC E50LV), sodium alginate and carrageenan. The influence of different polymers on the drug release were also evaluated.

MATERIALS AND METHODS**Materials**

Olmesartan Medoxomil, HPMC K4M and carrageenan were purchased from yarrow chemicals Mumbai. Sodium alginate and microcrystalline cellulose were purchased from Loba chemie pvt. Ltd Mumbai. Sodium bicarbonate, calcium carbonate and citric acid anhydrous were purchased from Spectrum reagents and chemicals, Kochi. Purified talc and lactose were purchased from Merck Mumbai. Magnesium stearate and methanol were purchased from Nice chemicals Kochi.

Methodology**Preparation of floating tablets of Olmesartan Medoxomil**

The composition of different formulations of Olmesartan Medoxomil floating tablets is shown in table 1. Direct compression method had been employed to prepare floating tablets of Olmesartan Medoxomil with hydroxyl propyl methyl cellulose (HPMC K4M, HPMC K100LV & HPMC E50LV), sodium alginate and carrageenan. All ingredients were weighed accurately and passed through mesh #60. In order to mix thoroughly polymer and drug blended geometrically in a motor and pestle for 15 minutes then sodium bicarbonate, citric acid anhydrous, calcium carbonate, magnesium stearate, talc and lactose were mixed one by one. After thoroughly mixing these ingredients the powder blend was passed through mesh # 44 . The tablets were compressed on single punch tablet machine Kambert, Ahmadabad.

Table 1: composition of floating tablets Olmesartan Medoxomil.

Ingredients(mg)	F1	F2	F3	F4	F5	F6
OLM	50	50	50	50	50	50
HPMC E50LV	80					
HPMC K100 LV		80				
HPMC K4M			80			80
SA				80		
CAR					80	
NaHCO ₃	70	70	70	70	70	
CaCO ₃						70
Citric acid	35	35	35	35	35	35
Mg stearate	8	8	8	8	8	8
Talc	7	7	7	7	7	7
Lactose	50	50	50	50	50	50

OLM-olmesartan medoxomil, SA-sodium alginate, CAR – carrageenan

Pre compression properties

Flow properties of the final blend can be characterised by angle of repose, bulk density, Carr's index, Hausner's ratio [5].

Evaluation of floating tablet

The prepared floating tablets were evaluated for their hardness (Monsanto hardness tester, for 10 tablets), friability (Roche friabilator for 10 tablets) and thickness (vernier callipers for 10 tablets) [6].

To determine the drug content the 10 tablets were triturated in the mortar .10mg of the powdered tablet dissolved in 10ml 0.1 N HCl.The drug sample was analysed in UV spectro photometer at 257nm.

FTIR Analysis

Drug –excipient compatibility can be determined by IR spectroscopic methods. The KBr pellet method was used in this study.

Scanning electron microscopic analysis (SEM)

The SEM images of drug and the optimised formulation was carried out using Joel jsm-6490la analytical SE instrument.

Dose calculation for sustained release tablet of Olmesartan Medoxomil

Total dose of Olmesartan for once daily sustained release formulation was calculated by the following equation using available pharmacokinetic data.

The amount of drug needed to be sustained = $0.693 / T_{1/2}$

Tablet density

Density of the tablet is important in the case of floating delivery system. The tablet will float if its density is less than that of gastric fluid (1.004).density of the tablet can be calculated using the formula

$d = m/v$. Where $v = \pi r^2 h$

In vitro buoyancy studies

In vitro buoyancy study was determined by buoyancy lag time as per the method described by Rosa et al [7, 4,8, 9,]. The tablet was placed in a100ml beaker containing 0.1 N HCl. The time taken for the tablet to rise on the surface was considered as floating lag time and the total time duration till the tablet was float on the surface was taken as total floating time.

Swelling studies

Swelling index of the tablet conducted to determine the molecular parameters of swollen polymer used in tablet fabrication. Previously weighed tablets are placed in 100ml beaker containing 0.1NHCl and at the time intervals from 1hr-24hr .Tablets get removed, blotted with a tissue paper and weighed. This can be calculated by the formula:

Swelling index= $(Wt-W_0) \times 100 / W_0$

Where Wt=weight of the tablets at time't', W₀= initial weight of the tablet

In vitro Dissolution Test

Drug release rate from the floating tablets were determined using United States Pharmacopeia (USP) Dissolution Testing Apparatus 2 (paddle method; Veego Scientific, Mumbai, India) apparatus. The test was conducted using 900 ml 0.1 N HCl at 100 rpm and a temperature of 37°C.5ml sample solution was withdrawn at different time interval.

RESULT AND DISCUSSION

1. Flow properties of powder blend

Flow properties of the powder blend (before compression) were characterised using angle of repose, Carr's index and Hausner's ratio. Angle of repose of the powder blend was found to be 25-28°. This indicates the excellent flow property. Carr's index was within the range of 11-15 indicated the good flow property of powder blend. Hausner's ratio of the powder blend was in the range of 1.18-1.24. This indicates the fair flow property.

2. Evaluation of floating tablet

Physical properties of Olmesartan Medoxomil floating tablet

Olmesartan Medoxomil floating tablets were smooth and white in colour. Hardness of the prepared floating tablets was ranged within 4.5 -6 kg / cm². The thickness of the tablet was determined was

found to be in the range of 3mm-3.2mm. Drug content in the formulation were found within 100±2.5% labelled amount. The friability of the floating tablet was found to be in the range of 0.47-0.6%.

Table 2: Flow property of final powder blend

Code	Angle of repose(°)	Hausner's ratio	Carr's index
F1	27.29	1.23	12.46
F2	26.36	1.18	11
F3	27.39	1.21	10.51
F4	25.61	1.19	12.76
F5	27.2	1.23	11.81
F6	27.9	1.21	12.63

SEM analysis

The surface morphological images of olmesartan powder showed irregular crystals. This leads to poor flow property. But when in tablet images showed amorphous structure, that leads to increase flow property and improve drug absorption.

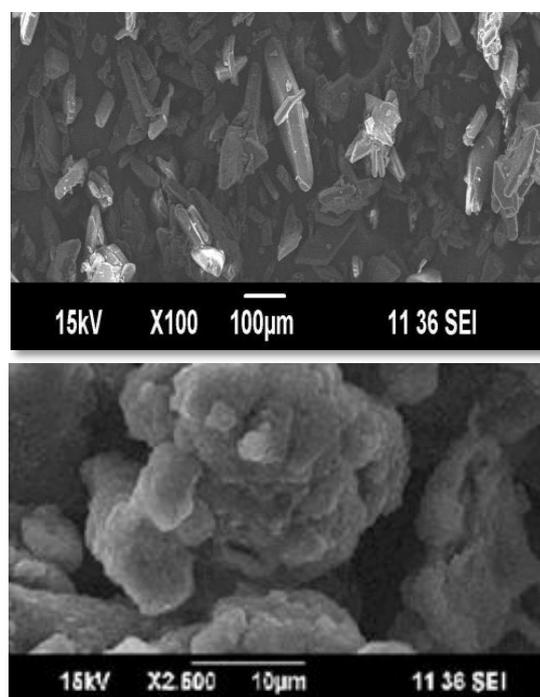


Fig. 1: SEM images of Olmesartan Medoxomil and F3 formulation

Dose calculation for sustained release tablet of Olmesartan Medoxomil

The amount of drug needed to be sustained was obtained as 51.17. Approximately 50mg drug is used in this study.

Tablet density

The tablet density of the entire tablet was found to be in the range of 0.84-0.89. Tablet density is less than that of gastric fluid so the tablets float on the surface of gastric medium.

FTIR Spectroscopy

Olmesartan showed characteristic peak at 2974cm⁻¹ (aliphatic C-H stretching), 3039cm⁻¹(aromatic C-H stretching), 3271cm⁻¹- a broad peak intermolecular hydrogen bonding .1720(C=O of carboxylic group), 1483 cm⁻¹ -C-N stretching. IR spectrometric images of drug, polymers and all the formulation were shown in the figure 2 [11]. The formulation containing polymers showed all the peaks of Olmesartan Medoxomil with no change in the intensity .This indicate there is no interaction between drug and the polymers.

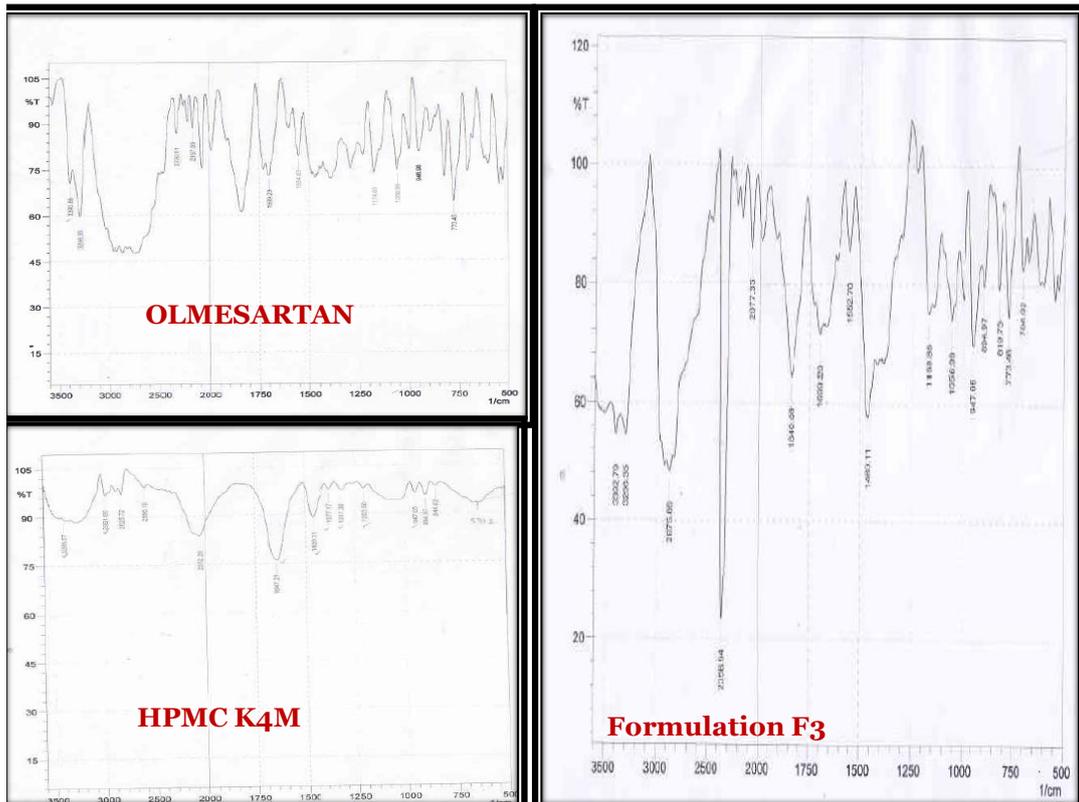


Fig. 2: FTIR spectrum of Olmesartan Medoxomil, HPMC K4M and optimised formulation F3

In vitro buoyancy study

In vitro buoyancy study was carried out in 0.1 N HCl. NaHCO₃ act as a gas generating agent in this floating tablet formulation. NaHCO₃ reacted with hydrochloric acid and evolved carbon dioxide gets entrapped in the gel barrier formed by the hydration of polymer, this helped the tablet for the immediate floatation [7].

From table 3 it was observed that the tablets with HPMC (F1, F2, F3 and F6) exhibited short floating lag time and floated till 24hours. The formulation containing combination of HPMC K4M (80mg) , NaHCO₃ (70mg) and citric acid (35mg) was found to achieve *in vitro* buoyancy and total floating time up to 24hrs. HPMC tablet hydrated quickly when it contacts with the test medium. The generated gas gets entrapped on the gel layer formed by the hydration of polymer and keeps the tablet buoyant on the surface around 24hrs. The formulation F4 and F5 containing sodium alginate and carrageenan showed higher floating lag time compared to other formulations.

Swelling studies

Swelling index of the tablet include the absorption of liquid medium then increase the weight of the tablet. This is very important characteristics of polymer which control the drug release from the formulation via diffusion. From the studies it was found that increase the concentration of HPMC K4M increase the swelling property. F3 showed maximum swelling among the HPMC containing formulations (F1, F2&F3). The effect of swelling behaviour of different polymers was also determined (F3, F4 &F5). HPMC tablet when in contact with the dissolution medium swell due to the breakage of hydrogen bond between the polymer chain and form a thick gel layer and eroded simultaneously. This result indicated that the swelling index of the all formulation changed after 12hrs. The formulation containing sodium alginate (F4) and carrageenan (F5) swelled rapidly in axial direction. The swelling index decreased in the order of F1, F2, F3, F5, F4 formulations respectively [7,8,10].

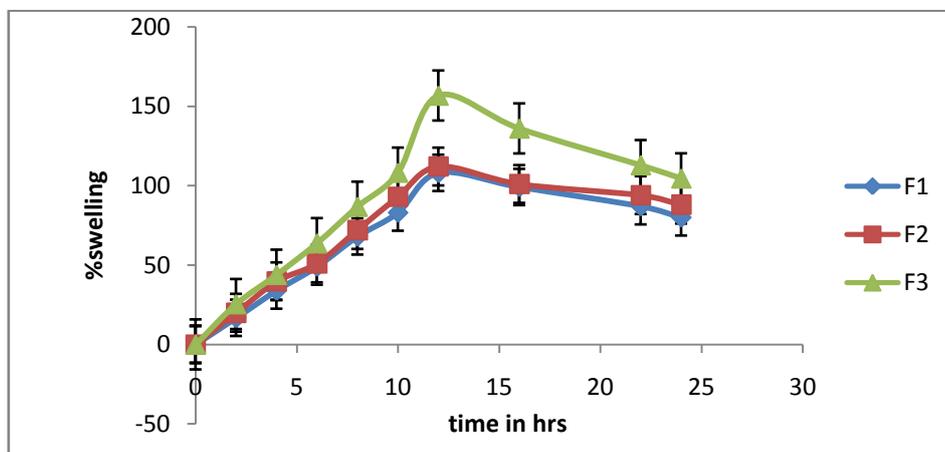


Fig. 3: swelling index of HPMC formulations

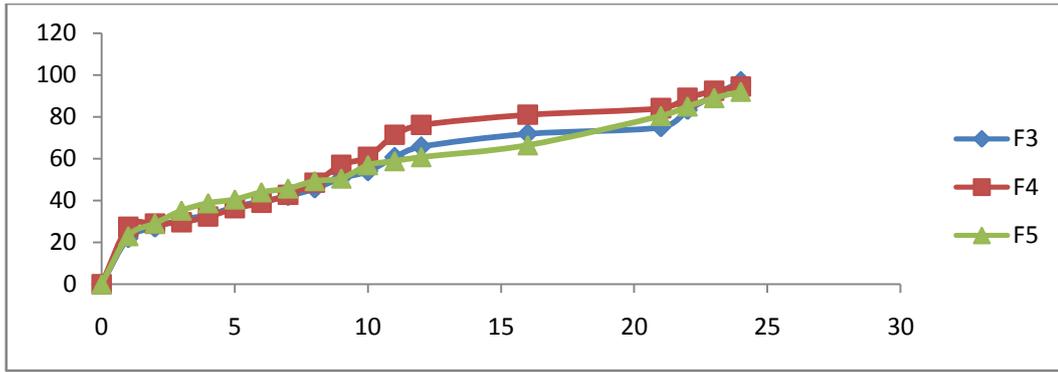


Fig. 4: comparison of swelling index of F3, F4 and F5 floating tablets

Table 3: physic chemical characterisation of Olmesartan Medoxomil floating tablet

Formulation code	Weight of the tablet (mg) SD n=20	Hardness Kg/cm ² SD n= 3	Friability (%)	Drug content% SD n= 3	Floating lag time (s) SD n=3
F1	301(1.31)	4.9(0.654)	0.48	97.74 (0.96)	68(0.512)
F2	302(1.67)	5.3(0.453)	0.56	101.23(1.17)	74(0.172)
F3	298(1.51)	5.5 (0.172)	0.51	98.55(1.56)	55.8 (0.743)
F4	302(1.36)	5.7(0.074)	0.5	99.44(0.74)	192.5(0.023)
F5	300(1.42)	4.9(0.741)	0.59	100.53(1.32)	208.1(0.165)
F6	304(1.56)	5.3(0.147)	0.47	97.12(1.66)	68.5(0.641)

In-vitro release studies

- Effect of different viscosity grade of HPMC polymer on drug release

Dissolution studies were carried out in 0.1N HCl for all batches of formulations.3 different grades of HPMC polymers were used in this study. It has been concluded that viscosity directly affect the drug release from the tablet formulation. Formulation F1 (HPMC E50LV), F2(HPMC K100 LV) and F3 (HPMC K4M) were used to study the effect of viscosity of polymer on the drug release. From this study the formulation F3 with high viscosity HPMC K4M showed a sustained release of drug for 24hrs. This may be due to the high viscosity of the polymer, when it was in contact with gastric medium formed a thick gel.

That is responsible for the slow drug release. The other formulations F1and F2 released the drug with in 16hrs. Low viscosity grade polymers which produced a faster drug release [10].

- Effect of gas forming agents on drug release from the floating tablets

The study of effect of gas forming agents indicates that the drug release was higher in the case of NaHCO₃ compared to CaCO₃.This is due to the high gas forming property and high aqueous solubility of NaHCO₃ [4,7].

- Effect of different polymers on drug release from floating tablet of Olmesartan Medoxomil

The higher initial drug dissolution was observed in all the 3 formulation. The tablet containing HPMC K4M showed maximum drug release (97%) in 24hrs. This is due to the rapid hydration of HPMC polymer in 0.1 N HCl. But the natural polymers sodium alginate (F4) and carrageenan(F5) release 94.37 and 92 % of the drug at end of 24 hrs.

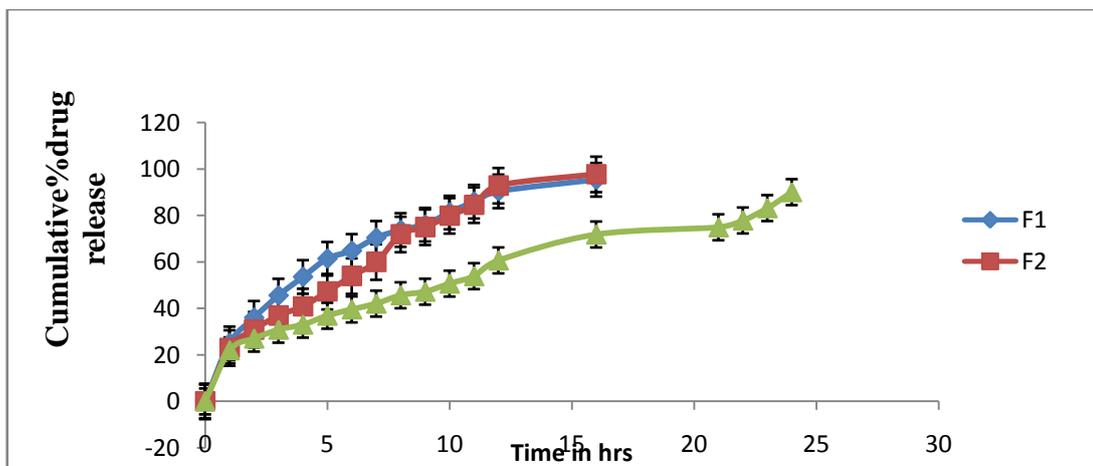


Fig. 5: Effect of different viscosity grade of HPMC polymer on drug release

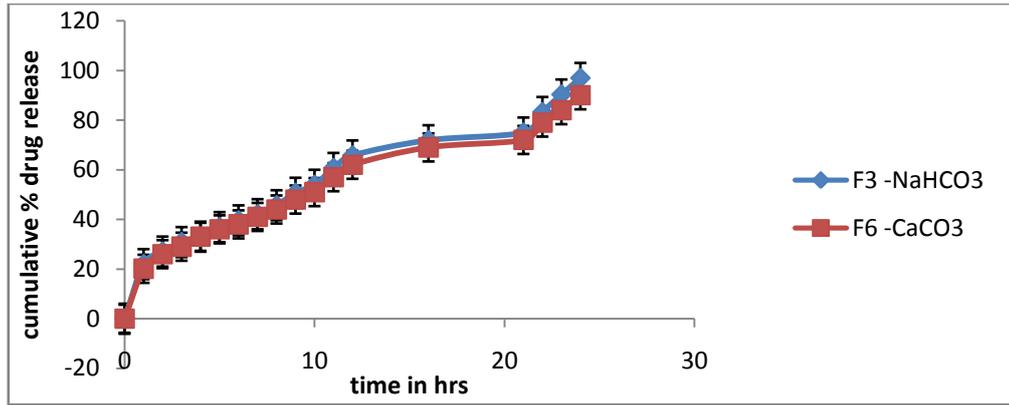


Fig. 6: effect of gas forming agents on F3 and F6 formulations

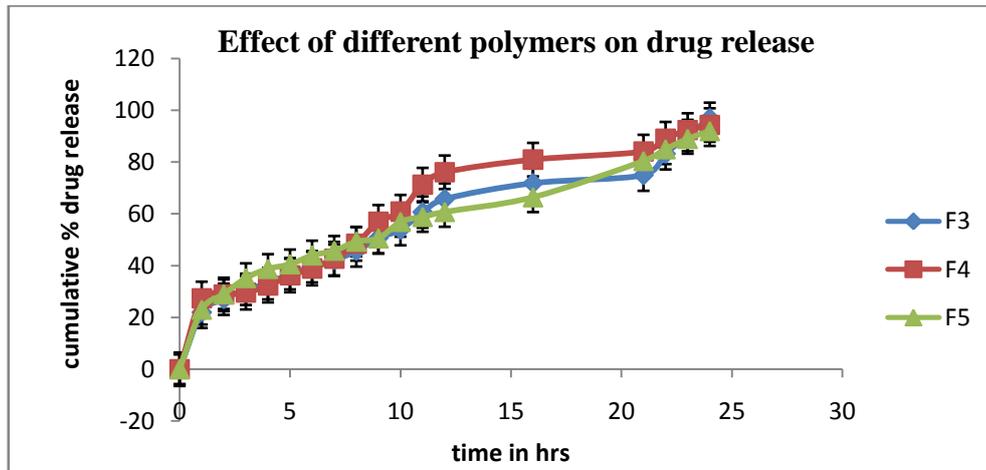


Fig. 7: effect of different polymers on drug release of prepared floating tablets

The values obtained from the in vitro dissolution studies were fitted to different kinetic models such as zero order, first order, Higuchi and Kosemeyer Peppas. Zero order plots were found to be fairly linear with regression values 0.96-0.98. The n value (slope) obtained from the Kosemeyer equation were in between 0.5-0.8. This indicates the release of Olmesartan Medoxomil from the floating tablet follows non-Fickian transport.

Comparison of optimised formulation F3 with marketed formulation (Olmax)

The comparative in vitro dissolution study of F3 and marketed formulation was shown in the figure. This study showed that the optimized formulation has a controlled release over 24 hrs. Marketed formulation (OLMAX 40mg tablet) released the drug 98% in 10 hrs, whereas the prepared formulation F3 released only 54% at 10 hrs.

Table 4: Different kinetic models for floating tablet of Olmesartan Medoxomil

Kinetic model	Parameter	F1	F2	F3	F4	F5	F6
Zero order	R ²	0.978	0.951	0.981	0.960	0.966	0.978
First order	R ²	0.856	0.874	0.864	0.751	0.793	0.810
Higuchi	R ²	0.963	0.954	0.958	0.944	0.959	0.962
Peppas	n	0.720	0.691	0.623	0.760	0.768	0.781

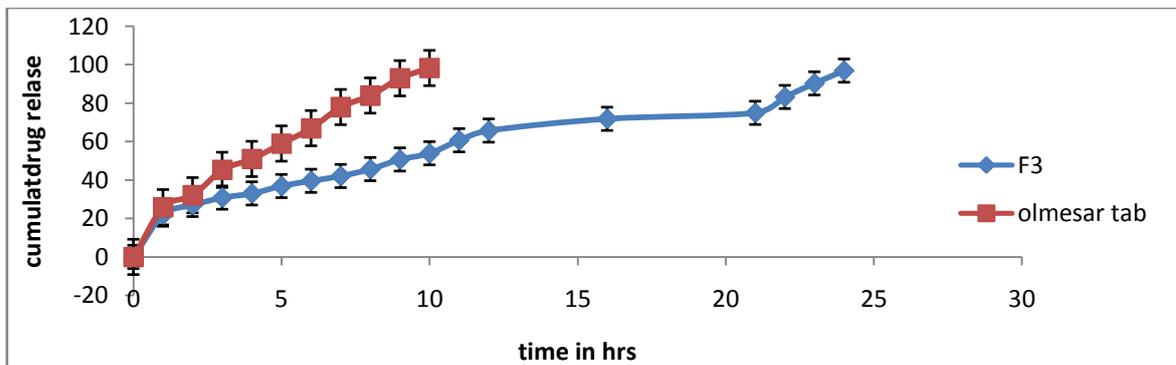


Fig. 8: comparison of optimised formulation with marketed formulation

Stability Studies

The prepared tablet containing HPMC K4M (F3) was selected for stability studies. The tablets were stored in 40° /75%RH in air tight container for 3months. There was no significant changes in their physic-chemical properties and their drug release studies [12].

Table 5: Physico chemical characteristics of prepared floating tablets during shelf life

Characteristics	1 month	2 months	3months
Physical appearance	Smooth and white	Smooth and white	Smooth and white
Hardness (Kg/cm ²)	5.5 ±0.172	5.5±0.014	5.4±0.546
Drug content (%)	98.55%	98.34%	97.61%
Floating lag time (s)	55.8 ±0.743	57.5±0.046	54.5 ±0.21
In vitro drug release up to 24hrs (%)	96.45	96.33	96.23

CONCLUSION

The floating tablet was a promising approach to produce in vitro buoyancy. The formulation F3 containing HPMC K4M showed a better drug release for 24hrs with floating lag time less than 55 seconds due to its high viscosity. The drug release from the tablets was sufficiently sustained and non-fickian transport of drug from the tablet was obtained.

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