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Formulation and Evaluation of Floating Drug Delivery System Containing Olmesartan Medoxomil

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ABSTRACT: The present study aimed to develop controlled release Floating Drug Delivery System (FDDS) which will remain in stomach for longer time while controlling drug release to achieve target release profile. The therapy of cardiovascular problems uses the selective angiotensin II receptor blocker Olmesartan Medoxomil. It has weak solubility and high permeability, making it a class II medication in the biopharmaceutics classification system. Because Olmesartan Medoxomil is hydrophobic, it exhibits low dissolution behaviour in GIT media, which results in deprived absorption and later poor bioavailability. The goal of the study is to formulate a floating Olmesartan Medoxomil tablet for oral administration that has the potential to provide a number of advantages, including higher solubility, increased absorption, and improved bioavailability, as well as fewer adverse effects. Using Hydroxy propyl methyl cellulose (HPMC- K15), Ethyl cellulose (EC) and Carbopol 934, the Gastro-retentive Floating Tablets (GFT) were formulated. By using Direct Compression, six batches were formulated.

KEYWORDS: Floating drug delivery system, Gastric retention time, physiology of stomach, Prolong release.

I. INTRODUCTION

Introduction to drug delivery system

[1] The oral route of administration has been used the most for both conventional and novel drug delivery system. These systems have the obvious advantages of ease of administration and patient acceptance, least sterility constraints and flexibility in the design of dosage form. One would always like to have an ideal drug delivery system that will possess two main properties:

• It will be a single dose for the whole duration of treatment.

• It will deliver the active drug directly at the site of action.

Unfortunately, such ideal systems are not available. Thus scientists try to develop systems that can be as close to an ideal system as possible. More than 50% of drugs, available in the market are meant for oral administration. The conventional drugtherapy results influctuation of drug concentration in systemic circulation, causing either toxic effect or no therapeutic effect.

Classification of oral drug delivery system:

[2] Oral controlled drug delivery systems can be broadly classified on the basis of their mechanism of drug release. Primarily, controlled release is achieved by diffusion, degradation and swelling followed by diffusion. Any or all of these mechanisms may occur in a given release systems. Diffusion occurs when bioactive agent passes through the polymer, which forms the building block of controlled release system.

1.Dissolution-controlled release
a) Encapsulation dissolution control
b) Matrix dissolution control
2. Diffusion-controlled release
a) Reservoir devices
b) Matrix devices
3. Osmotic controlled release
4. Ion exchange resins
5. Gastro-retentive systems
a) Mucoadhesive system
b) Raft forming system
c) Floating drug delivery system
d) Swelling and expandable system
e) High density system
f) Magnetic system

Floating drug delivery system:

[3] The floating sustained release dosage forms present most of the characteristics of hydrophilic matrices and are known as ‘hydro dynamically balanced systems’ (‘HBS’) since they

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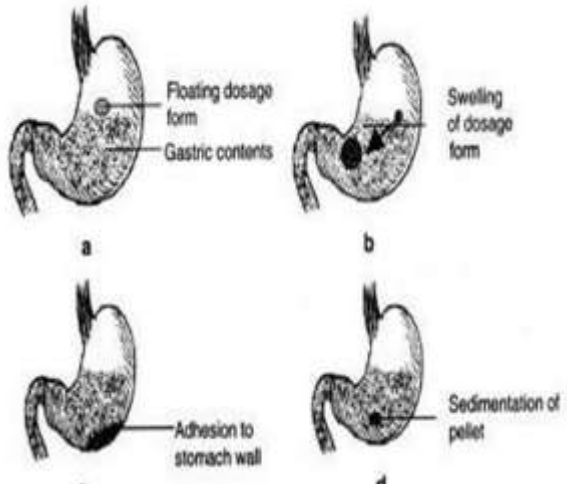
are able to maintain their low apparent density, while the polymer hydrates and builds a gelled barrier at the outer surface.

[4] The drug is released progressively from the swollen matrix, as in the case of conventional hydrophilic matrices. These forms are expected to remain buoyant (3- 4 shours) on the gastric contents without affecting the intrinsic rate of emptying because their bulk density is lower than that of the gastric contents.

Many results have demonstrated the validity of the concept of buoyancy in terms of prolonged GRT of the floating forms, improved bioavailability of drugs and improved clinical situations.

[5] These results also demonstrate that the presence of gastric content is needed to allow the proper achievement of the buoyancy retention principle.

Among the different hydrocolloids recommended for floating form formulations, cellulose ether polymers are most popular, especially hydroxyl propyl methyl celluloses. Fatty material with a bulk density lower than one may be added to the formulation to decrease the water intake rate and increase buoyancy.



Various Forms of Gastro Retentive System

A. Floating Gastro Retentive Drug Delivery System
B. Swelling Gastro Retentive Drug Delivery System
C. Bio-Adhesive Gastro Retentive Drug Delivery Syste
D. High-Density Gastro Retentive Drug Delivery System

[6] Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration.

Classification of Floating Drug Delivery System

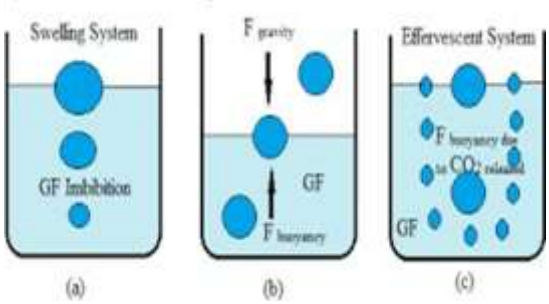
[7] Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS, which are

A. Effervescent System
B. Non-Effervescent System

A. Effervescent System

[8] These are the matrix types of with the help of swellable systems prepared polymers such as methylcellulose and chitosan and various effervescent compounds,eg, sodium bicarbonate tartaric acid, and citric acid. [9] They are formulated in a such a way that when in contact with the acidic gastric contents, CO2 is liberated and entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms:

1. Gas Generating systems
2.Volatile LiquidContainingSystems



B. Non Effervescent System

The Non-effervescent FDDS is based on mechanism of swelling of polymer or bio adhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, hydrophilic gums, polysaccharides and matrix forming material such as polycarbonate,polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymer such as chitosan and carbopol.

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Working principle of this type of FDDS :

[10] Capsule/tablet contains a mixture of drug and hydrocolloids. Upon contact with gastric fluid, the mixture swells and forms a gelatinous barrier thereby remaining buoyant in the gastric juice for an extended period of time.

Advantages of floating dosage forms:

•Enhanced bioavailability
•Reduced frequency of dosing
•Longer duration of action
•Reduced fluctuations of drug concentration
•Site specific drug delivery
•Reduced fluctuations of drug concentration

Disadvantages of floating dosage forms:

• These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently-coat, water.
• Not suitable for drugs that have solubility or stability problem in GIT.
• Drugs such as Nifedipine which is well absorbed along the entire GIT and which undergoes first pass metabolism, may not be desirable.
• Drugs which are irritant to Gastric mucosa is also not desirable or suitable.
• The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems.
• The dosage form should be administered with a full glass of water (200- 250 ml).

II. MATERIAL AND METHODS:

Materials:

Olmesartan Medoxomil was received as a gift sample from VERDANT LIFE SCIENCES PVT., LIMITED, Visakhapatnam, A.P., India. The polymers used in this study (HPMC K15M, Ethyl Cellulose and Carbopol 934), other excipients Sodium Bicarbonate, Citric acid Magnesium stearate, Talc and Lactose) and 0.1N HCL were used.

Instruments:

I.The formulation was examined and evaluated using the Dissolution apparatus (USP Dissolution Apparatus type 2), Hot air oven, UV-Visible Spectrophotometer, Roche Friability tester, Monsanto hardness tester, Sonicator and Weighing Balance.

UV-Visible Spectrophotometer

Roche Friability Tester

Tablet Punching Machine

Dissolution Apparatus
(USP Dissolution Apparatus type 2)

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Preparation of standard curve of Olmesartan Medoxomil in 0.1 N HCL:

Accurately weighed Olmesartan Medoxomil (10mg) was placed in 100 ml volumetric flask, 10ml of 0.1 N HCL was added to it and sonicate for 20 minute and then made up the volume to 100 ml with 0.1 N HCL. Form the above solution, 1 ml of solution was pipette out and diluted to 10 ml with 0.1 N HCL. The resultant solution obtained was 10 µg/ml and was scanned in UV range of 200 to 400 nm. Olmesartan Medoxomil showed maximum absorbance at 246 nm. Thus, 246 nm was taken as max.

Preparation of floating tablets of Olmesartan Medoxomil:

The composition of different formulations of Olmesartan Medoxomil floating tablets is shown in table. Direct compression method had been employed to prepare floating tablets of Olmesartan Medoxomil with HPMC K15M, Ethyl Cellulose and Carbopol 934. All ingredients were weighed accurately and passed through mesh #60. To mix thoroughly polymer and drug blended geometrically in mortar pestle for 15 mins and then sodium bicarbonate, magnesium stearate, talc and lactose were mixed one by one. After thorough mixing these ingredients the powder blend was passed through mess #44. The tablets were compressed on Karnavati tablet press.

Chemicals Used in Study

Composition of floating tablets Olmesartan Medoxomil

Ingredients(mg)	F1	F2	F3	F4	F5	F6
Olmesartan Medoxomil	40	40	40	40	40	40

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HPMC-K 15M	80	90	70	60	80	50
Ethyl Cellulose	20	10	30	40	15	50
Carbopol 934	-	-	-	-	5	-
Sodium Bicarbonate	70	70	70	70	70	70
Citric acid	35	35	35	35	35	35
Magnesium stearate	8	8	8	8	8	8
Talc	7	7	7	7	7	7
Lactose	50	50	50	50	50	50
Total weight	300	300	300	300	300	300

Precompression Evaluation of powder blend:

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

Bulk density

[11] Bulk density was determined by the following formula;

Bulk density=Sample weight/ Sample volume

Tapped density

The tapped density was determined by tapping method, in which the cylinder containing known amount of powder was subjected to a fixed number of taps (100) until the bed of powder had reached its minimum level. The final volume after tapping 'Vo' was recorded and the tapped density was calculated by the following formula;

Tapped density= mass/Vo

Carr's Compressibility index (CL)

It is determined to predict flowability and calculated by following formula;

$$CL = \frac{(\text{Tapped density} - \text{Bulk density}) * 100}{\text{Tapped density}}$$

Haussner's ratio

It is determined to predict flowability and calculated by following formula;

Tapped density/ Bulk density

Angle of repose

It is measured by passing the samples through funnel on the horizontal surface. The height (h) and radius (r) of the cone funnel was measured. The angle of repose ( ) is given by following formula;

The angle of repose ( )= tan-1 h/r

Evaluation of floating tablet:

The prepared tablets were evaluated for the following parameters:

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 = $\pi r2h$

Thickness of Tablets

The thickness of six tablets was measured using Vernier callipers. The extent to which the thickness of each tablet deviated from ± 5% of the standard value was determined**.**

Hardness

The hardness of the tablet was determined by Monsanto hardness tester. Six tablets from each batch were selected and evaluated, and the average value with standard deviation was recorded**.**

Friability

The Friability of tablets was performed in a Roche Friabilator. It consists of a plastic chamber that revolves at 25 rpm.

Ten tablets were weighed together and then placed in the chamber. The Friabilator was operated for 100 revolutions and the tablets were

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subjected to the combined effects of abrasion and shock because the plastic chamber carrying the tablets drops them at a distance of six inches with every revolution. The tablets are then dusted and re-weighed. The friability (F) is given by the formula.

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} * 100$$

Weight Variation

Twenty tablets were individually weighed, and average weight was calculated. The individual weight was compared to the average weight. The tablets pass the test if not more than two tablets are outside the percentage limit and if no tablet differs by more than twotimes the percentage the percentage limit. In-vitro buoyancy studies.

The in vitro buoyancy was determined by floating lag time method. The tablets were placed in 100 ml beaker containing 0.1 N HCl. The time required for the tablets to float was determined as floating lag time. Total floating time was also determined.

In-vitro Dissolution Studies

[12] In vitro dissolution study was performed by using USP Type II Apparatus (Paddle type) at 100 rpm. Dissolution test was performed using 0.1N HCL as dissolution medium and the temperature was maintained at 37 ± 0.5ºC. Aliquot of dissolution medium was withdrawn at specific time intervals i.e. 1,2,3.4,5,6…. up to 24hrs.

The samples were filtered through a 0.45 membrane filter and diluted to a suitable concentration with 0.1N HCl. Absorbance of these solutions was measured at 257 nm UV spectrophotometer. Cumulative percentage of drug release was calculated using the equation obtained from a standard curve.

In vitro buoyancy studies

[13] In vitro buoyancy study was determined by buoyancy lag time as per the method described by Rosa et al.

The tablet was placed in a 100ml 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 index

The swelling index of tablets was determined in 0.1N HCl (pH 1.2) at room temperature.The swollen weight of the tablets was determined at predefined time intervals. The swelling index was calculated by the following equation:

$$\text{Swelling index} = (Wt. - W0/W0)*100$$

Where, W0 is the initial weight of tablet, and Wt. is the weight of the tablet at time t.

Accelerated stability study.

[14] [15]The tablets of best batch were packed in aluminium pouch and charged for accelerated stability studies at 40 °C and 75% RH for 1 month in a humidity jar.

III. RESULT AND DISCUSSION:

Calibration curve of Olmesartan Medoxomil:

Data for calibration curve for Olmesartan Medoxomil

Concentration (in ppm)	Absorbance at 246nm(λ)
4	0.17750
8	0.33817
12	0.50899

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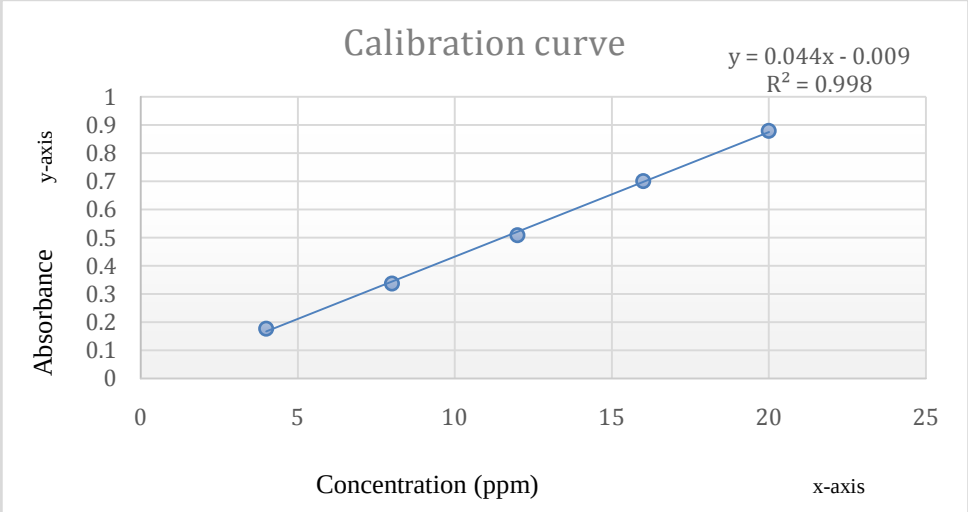
16	0.70190
20	0.88020



Calibration curve for Olmesartan Medoxomil

The value of R^2=0.9989 on the basis of above result it is concluded that Olmesartan Medoxomilobeys beer-lambert's law.

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 25-280.. 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 1.15-1.28. This indicates the fair flow property.

Flow property of powder blend

Code	Angle of repose(0)	Hausner's ratio	Carr's index
F1	27	1.28	12.50
F2	26	1.12	11
F3	27	1.15	10.90
F4	25	1.22	12.70
F5	25	1.22	11.85
F6	28	1.19	12.70

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Evaluation of physical properties of floating tablets:

Evaluation parameter of tablets of different batches

Tablet batch	weight variation test(mg)	Thickness mm	Hardness (kg/cm^2)	friability %
F1	296.70±2.00	3.00	4.4±0.50	0.20±0.05
F2	298.50±2.00	3.00	3.3±0.50	0.30±0.05
F3	297.20±2.00	3.00	3.7±0.50	0.30±0.05
F4	301.00±2.00	3.00	3.6±0.50	0.40±0.05
F5	298.60±2.00	3.00	4.7±0.50	0.40±0.05
F6	300.10±2.00	3.00	5.0±0.50	0.50±0.05

According to the data in the tableeach trial tablets weight fell between 296 to 301 mg/tablet. Trials 1 to 6 have acceptable level of hardness ranging from 3.3 to 5 kg/cm2. All tablets in these formulations have same diameter. The tablets from all 6 batches have friability limits within acceptable range.

As a result, the physical properties of floating tablets were satisfactorily evaluated.

In Vitro buoyancy studies:

The in-vitro buoyancy was determined by floating lag time method. The tablets were placed in 100 ml beaker containing 0.1N HCl. The time required for the tablets to float was determined as floating lag time.

In vitro buoyancy study showed that all the batches from F1 to F6 have floating lag time less than 40 seconds because of evolution and entrapment of carbon dioxide inside the hydrated polymer matrices, resulting from the interaction between gas generating agent and dissolution medium which led to lowering the density of matrices enabling the tablets to float.

On the other hand, as a solvent front penetrated the polymer layer, swelling of HPMC K15M and Carbopol 934 caused to increase in volume of tablet resulted in net reduction in density of the tablet, which prolonged the duration of floatation up to 24 hrs.

Batch	Floating lag time(sec)	Floating time
F1	26	21hrs
F2	32	18hrs
F3	24	17hrs.
F4	28	16hrs.

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F5	26	24hrs.
F6	30	13hrs.

Swelling index:

Swelling index of the tablet include the absorption of liquid medium then increases the weight of the tablet. This is very important characteristics of the polymer which control the drug release from the formulation via diffusion from these studies it was found that increase the concentration of HPMC K15M increases the swelling property. F5 showed maximum swelling among all HPMC containing formulations. HPMC K15M tablet when in contact with dissolution medium swell due to breakage of hydrogen bond between the polymer chain and form a thick gel layer and eroded simultaneously. The table no: result indicated that the swelling index of all the formulations changed after different time interval.

At 0 hours

At 24 hours

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At 24 hr

Swelling index of all batches

Batch	Swelling index(%)
F1	290
F2	307
F3	232
F4	195
F5	321
F6	139

IN-VITRO RELEASE STUDIES:

Dissolution studies were carried out in 0.1N HCl for all batches of formulations using USP type 2 dissolution apparatus (paddle type). HPMC K15M, Ethyl Cellulose and Carbopol 934 polymers were used in this study. It has been concluded that viscosity directly affect the drug release from the tablet formulation. Formulation F1, F2, F3, F4, F5 and F6 were used to study the effect of viscosity of polymer on the drug release. From this study the formulation F5 with high viscosity HPMC K15M showed a prolonged 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 comparatively release drug quite rapidly. Low viscosity grade polymers which produced a faster drug release. The higher initial drug dissolution was observed in all the 6 formulations. The tablet containing HPMC K15M, Ethyl Cellulose and Carbopol 934 showed prolonged release that can potentially release its whole drug in 24 hours.

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Drug release profile of all formulations

Time (hrs)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)
0	0	0	0	0	0	0
0.5	2.70	2.87	4.25	3.64	2.07	4.51
1	4.39	5.34	6.55	5.43	3.43	8.08
1.5	6.54	7.03	8.21	9.56	4.90	11.44
2	8.22	9.80	9.42	12.76	7.31	14.20
2.5	10.87	11.96	12.64	16.88	8.83	18.34
3	13.65	14.10	15.42	20.53	10.37	22.60
3.5	15.41	16.71	18.36	24.36	13.76	26.09
4	17.24	19.08	21.48	27.87	15.47	29.12
4.5	19.82	21.27	25.49	30.01	16.83	32.83
5	22.36	24.12	28.87	33.50	18.42	35.67
5.5	25.73	27.49	30.64	36.75	20.66	39.86
6	27.03	30.05	33.48	40.43	22.18	44.15
6.5	29.54	33.74	36.56	43.31	23.48	48.52
7	31.97	35.23	39.31	46.85	24.59	52.41
7.5	34.20	38.86	42.52	50.25	27.28	56.05
8	36.78	41.39	45.08	55.98	30.22	62.21

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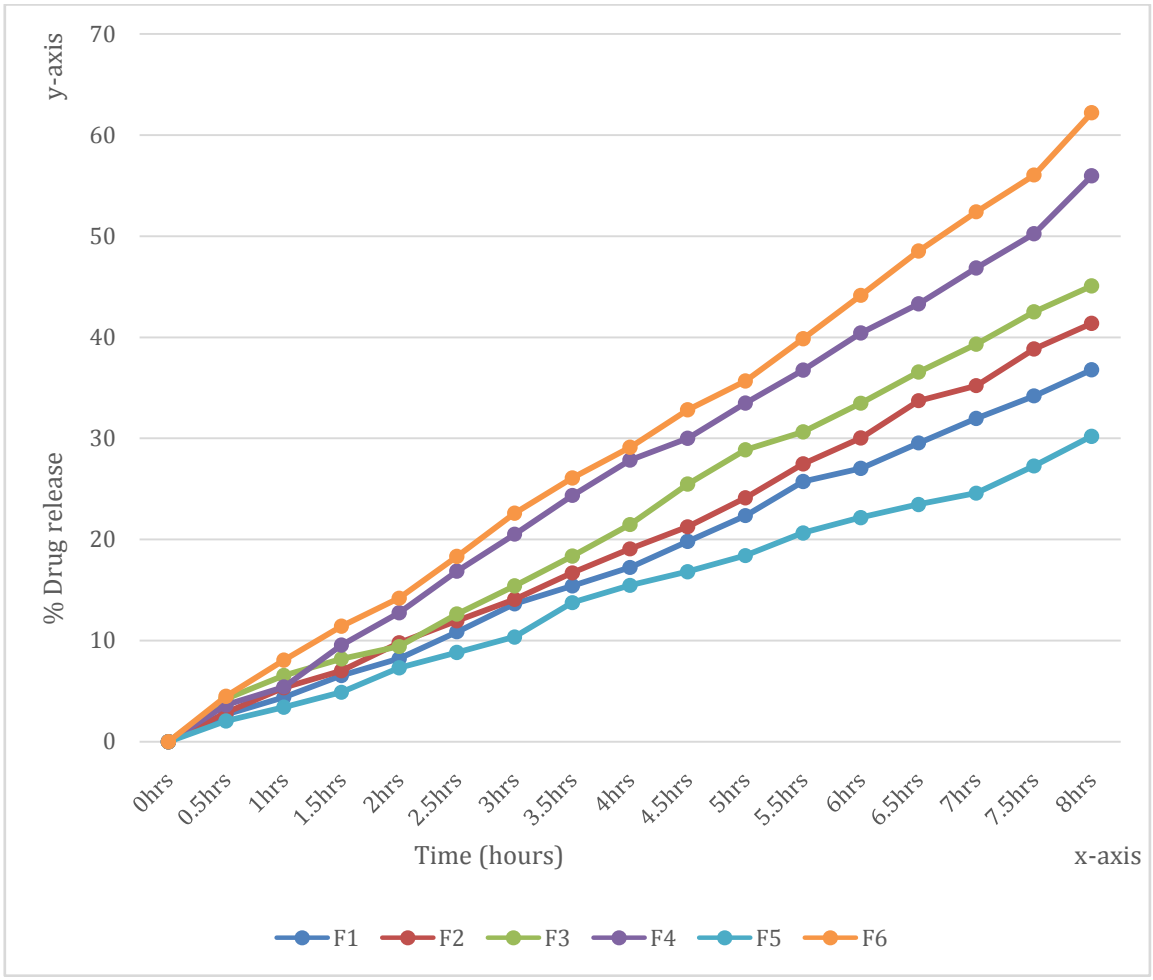

%drug release vs time graph of all formulations

Accelerated Stability Studies

Gastro retentive tablets of Olmesartan Medoxomil formulated in the present study were subjected to accelerated stability studies in Aluminium / Aluminium pouch pack as aluminium strip is considered the best protecting packaging material but in the present study simulation was made using aluminium foil pouch. As the dosage form is formulated for site-specific drug delivery to stomach, no change should occur in its floating lag time and drug dissolution profile. Dose dumping and failure of buoyancy are probable effects anticipated during the stability study of such dosage forms. The tablets of best batch F5 were packed in aluminium pouch and charged for accelerated stability studies at 40 °C and elevated Relative humidity for 1 month.

Comparison of best formulation F5 with marketed preparation:

The comparative in vitro dissolution study of F5 and marketed formulation was shown in the figure no: x. This study showed that the optimized formulation has a potential to release drug over 24hrs.

Marketed formulation (OLMESAR 40mg tablet) released the drug 90% in 8hrs whereas the prepared formulation F5 released only about 30% at 8hr.

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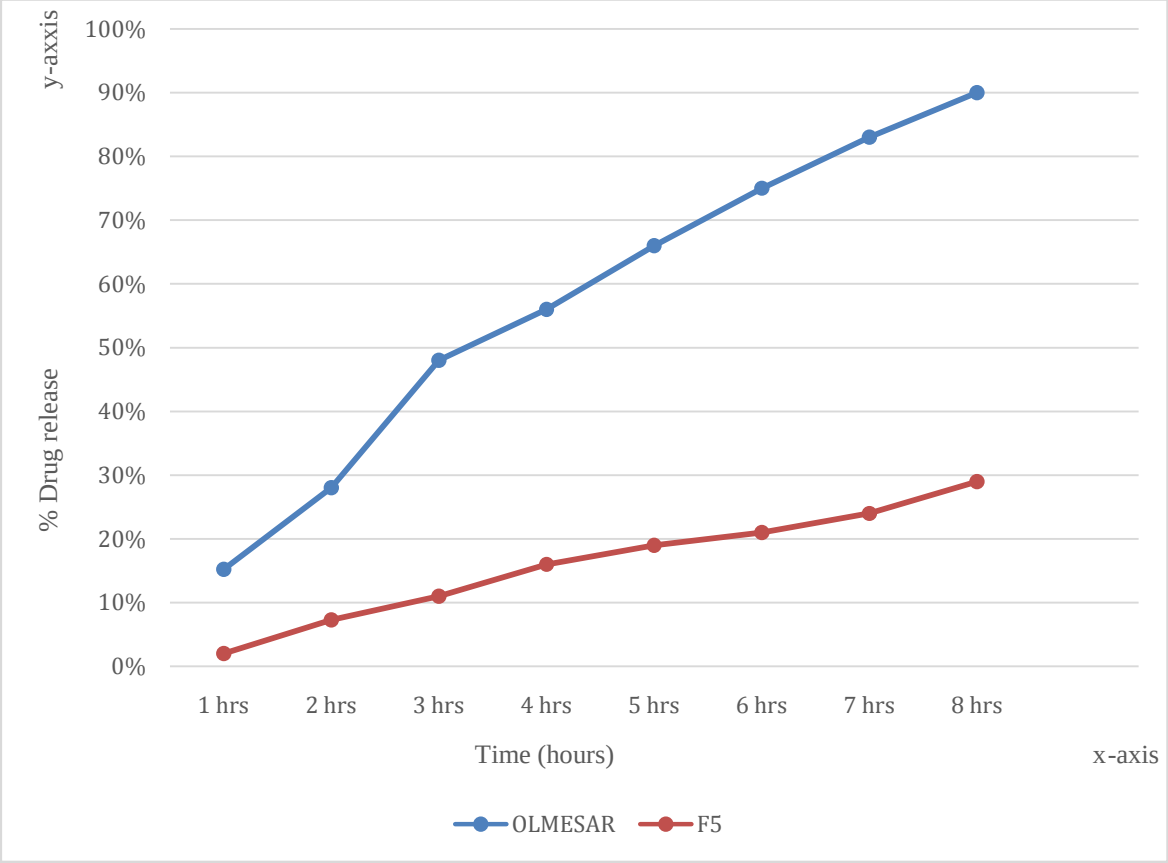

Comparative drug release of OLMESAR and F5

IV. CONCLUSION

For many medications, floating drug delivery devices have shown to be an effective way to increase bioavailability and regulate delivery. The development of more gastro-retentive drug delivery methods will enable the administration of molecules with narrow absorption windows and limited bioavailability as delivery technology becomes more sophisticated.

Olmesartan Medoxomil flotation tablets made with HPMC K15M can be used successfully as an oral controlled release medication delivery device. The formulation's high floating ability is probably going to lengthen its GI residence duration and finally boost the degree of bioavailability.

According to the results of the Stability study, HPMC K15M, Carbopol, and Ethyl Cellulose were drug-compatible and hence suitable for the formulation of floating tablets.

It is concluded from the assessment of the powder blend that both the medication and the excipients have good flow properties, and it is concluded from the evaluation of the tablet formulations that all of the trials have hardness that is within the acceptable range and pass the friability test.

Using 0.1 N HCl solutions, invitro buoyancy investigations were carried out for all the formulations, F1 to F6, and the maximum wavelength was determined to be 246 nm.

For all formulations, in vitro dissolution tests were also carried out; formulation with HPMC K15M,

Ethyl Cellulose and Carbopol 934 i.e. F5, demonstrated controlled release for 24 hours with floating lag time 30 seconds; Spectrophotometry data indicates that this release follows zero order (R^2=0.9989).

Treatment of hypertension with Olmesartan Medoxomil floating tablets is effective. Olmesartan Medoxomil gastro-retentive dosage form helps to minimise the drug's dosage and side effects by reducing how frequently it must be administered.

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