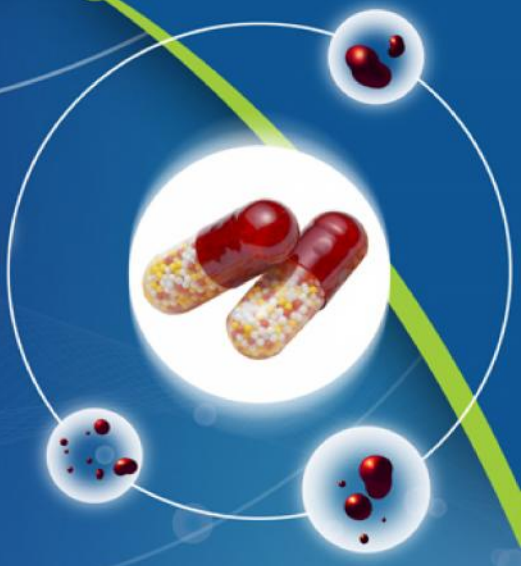
ISSN : 2320 4850

BI MONTHLY

Asian Journal of Pharmaceutical Research And Development

(An International Peer Reviewed Journal of Pharmaceutical Research and Development)

AJPRD



Volume - 03 Issue - 03 MAY-JUN 2015

website: www.ajprd.com
editor@ajprd.com

Asian Journal of Pharmaceutical Research and Development
(An International Peer-Reviewed Journal of Pharmaceutical Research and Development)
www.ajprd.com
ISSN 2320-4850

Research Article

FORMULATION AND EVALUATION OF GASTRORETENTIVE FLOATING TABLETS OF METHYL DOPA

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Received: April 2015 ***Revised and Accepted: May 2015***

ABSTRACT:

The modified release product encompass the dosage form design includes enteric coated tablets (including immediate-release), and extended-release products where drug release is controlled by the dosage form to occur over a period of hours. Concept of targeted delivery is designed for attempting to concentrate the drug in the tissue and reducing the concentration in the remaining tissue of the body. By using the polymer by coupling the drug in the carrier such as microspheres, nanoparticles, liposomes, niosomes, pharmacosomes, aquasomes etc. which modulate the release and absorption characteristics of the drug. Microspheres are characteristically free flowing powders consist of drug and polymers having a particle size ranging from 1-1000 µm. In future by using various technology and strategies in microsphere that find the central place in novel drug delivery.

Keywords: *Targeted delivery, Microspheres, Novel drug delivery*

INTRODUCTION

Hypertension [2] :

Methyldopa is a medication that has been used to treat high blood pressure since the 1960s. While there is some belief methyl dopa reduces blood pressure, there are concerns due to the potential for this drug to cause adverse effects. The aim of this drug to reduces blood pressure, This meta-analysis shows that methyldopa reduces systolic/diastolic blood pressure by approximately 13/8 mmHg compared to placebo. Hypertension is a chronic medical condition in which the blood pressure is elevated. Hypertension can be classified as either essential (primary) or secondary.

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Essential or primary hypertension means that no medical cause can be found to explain the raised blood pressure. About 90-95% of hypertension is essential hypertension. Secondary hypertension indicates that the high blood pressure is a result of another condition, such as kidney disease or tumours (adrenal adenoma or pheochromocytoma). It is estimated that nearly one billion people are affected by hypertension worldwide.

Classification of Hypertension:

- Chronic hypertension
- Pregnancy induced hypertension
  - Pre-eclampsia
  - Eclampsia
  - Pre-eclampsia superimposed on chronic hypertension
  - Gestational hypertension

Anti-hypertensive agents [3]: The anti-hypertensives are a class of drugs that are used to treat hypertension (high blood pressure). Evidence suggests that reduction of the blood pressure by 5 mmHg can decrease the risk of stroke by 34%, of ischaemic heart disease by 21%, and reduce the likelihood of dementia, heart failure, and mortality from cardiovascular disease. There are many classes of anti-hypertensives, which lower blood pressure by different means; among the most important and most widely used are the thiazide diuretics, the ACE inhibitors, the calcium channel blockers, the beta blockers, central sympatholytics and angiotensin II receptor antagonists. Many different types of drugs are used, alone or in combination with other drugs, to treat high blood pressure.

The major categories are:

- Angiotensin-converting Enzyme Inhibitors: ACE inhibitors work by preventing a chemical in the blood, angiotensin I, from being converted into a substance that increases salt and water retention in the body. These drugs also make blood vessels relax, which further reduces blood pressure.
- Angiotensin II Receptor Antagonists: These drugs act at a later step in the same process that ACE inhibitors affect. Like ACE inhibitors, they lower blood pressure by relaxing blood vessels
- Beta blockers: Beta blockers affect the body's response to certain nerve impulses. This, in turn, decreases the force and rate of the heart's contractions, which lowers blood pressure.
- Blood Vessel Dilators (Vasodilators): These drugs lower blood pressure by relaxing muscles in the blood vessel walls.
- Calcium Channel Blockers: Drugs in this group slow the movement of calcium into the cells of blood vessels. This relaxes the blood vessels and lowers blood pressure.
- Diuretics: These drugs control blood pressure by eliminating excess salt and water from the body.
- Nerve Blockers: These drugs control nerve impulses along certain nerve pathways. This allows blood vessels to relax and lowers blood pressure.

Gastro Retentive Drug Delivery System [4]: Oral drug delivery system is the most popular delivery system due to its ease of administration. In the past, oral route has been explored for the systemic delivery of drugs through different types of dosage forms. However the drug or the active moiety must be absorbed well throughout the Gastrointestinal Tract (GIT) in order to produce an optimized therapeutic effect. Absorption may be hindered, if there is a narrow absorption window for drug absorption in the GIT or if the drug is unstable in the GI fluids. Thus the real challenge is to develop an oral controlled release dosage form not only to prolong the delivery but also to prolong the retention of the dosage form in the stomach or small intestine until the entire drug is released.

Gastric emptying time

50% of stomach contents emptied	2.5 to 3 hrs
Total emptying of the stomach	4 to 5 hrs
50% emptying of the small intestine	2.5 to 3 hrs
Transit through the colon	30 to 40 hrs

Factors Affecting Gastric Retention [4]:

There are several factors that can affect gastric emptying (and hence GRT) of an oral dosage form. These factors include:

- Shape of the dosage form: It is reported that tetrahedron and ring-shaped devices have a better gastric residence time as compared with other shapes.
- Gender: Generally females have slower gastric emptying rates than males.
- Density of the dosage form: A dosage form having a density of less than that of the gastric fluids floats.
- Size of the dosage form: Small-sized tablets leave the stomach during the digestive phase while the large-sized tablets are emptied during the housekeeping waves. Dosage forms having a diameter of more than 7.5 mm show a better gastric residence time compared with one having 9.9 mm.

- Temperature of meal: Cold meal increases and hot meal decreases the emptying of gastric contents. Composition and Viscosity of meal: Fats, particularly fatty acids inhibit gastric secretion and have a pronounced reductive effect on the rate of emptying. Proteins and starch are shown to have inhibitory effect on gastric emptying, though to a less extent. As the viscosity of the gastric fluids is increased, there is a corresponding decrease in the rate of emptying.
- Posture: When subjects were kept in the supine position it was observed that the floating forms could only prolong their stay because of their size; otherwise the buoyancy remained no longer an advantage for gastric retention.

Approaches:

There are various approaches have been pursued to increase the retention of an oral dosage form in the stomach. Gastro retentive systems remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs.

These may be:

- Swelling and Expanding Drug Delivery Systems: These type of dosage forms are such that after swallowing, these products swell to an extent that prevents their exit from the stomach through the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These systems may be referred to as “plug type system” since they exhibit a tendency to remain lodged at the pyloric sphincter.
- Modified Shape Systems: These systems are non disintegrating geometric shapes moulded from silastic elastomer or extruded from polyethylene blends, which extend the GRT depending on size, shape and flexural modulus of the drug delivery device.
- Floating Dug Delivery Systems (FDDS) or Hydrodynamically Balanced Systems (HBS): These are systems which have a bulk density lower than gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system.
- Delayed gastric emptying systems: These approaches of interest include feeding of indigestible polymers or fatty acid salts that change the motility pattern of the stomach to a fed state, thereby decreasing the gastric emptying rate and permitting considerable prolongation of drug release.

Floating Drug Delivery System [5,7]: Floating systems or hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time.

Classification of Floating Drug Delivery Systems (FDDS) : Floating drug delivery systems are classified depending on the 2 formulation variables:

- Effervescent systems.
- Non-effervescent systems.

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

Non-effervescent Floating Dosage Forms: Non-effervescent floating dosage forms use a gel forming or swellable cellulose type hydrocolloids, polysaccharides, and matrix-forming polymers like polycarbonate, polyacrylate, polymethacrylate, and polystyrene. The formulation method includes a simple approach of thoroughly mixing the drug and the gel-forming hydrocolloid. After oral administration, this dosage form swells on contact with gastric fluids and attains a bulk density of < 1. The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The so formed swollen gel-like structure acts as a reservoir and allows

sustained release of drug through the

MATERIALS AND METHODS:

Methyl dopa and other reagents of analytical grade were obtained as gift sample from XL Laboratories Pvt. Ltd., Bhiwadi and Finar Chemicals, Ahmedabad.

Preformulation studies : Preformulation is a prerequisite for development of an efficacious, stable and safe dosage form which involves determination of physicochemical properties of drug alone and in combination with excipients that could affect performance of a formulation.

Solubility studies: The solubility study of drug was carried out in three different solvent systems using "Shake flask method". The solvent systems selected for solubility studies were based on dissolution media desired in formulation development. The solubility of Methyl dopa was determined in distilled water, Dichloromethane (DCM), Acetone, Methanol, 0.1N HCl (pH 1.2),

Fourier transformation infra red spectroscopy (FTIR) to study drug-polymer interaction: IR spectroscopy deals with the gelatinous mass.

study of absorption of IR region, which extends from the red end of the visible spectrum to the microwave region. An IR radiation is absorbed by a molecule when the applied IR frequency is equal to the natural frequency of vibration of the molecule. Absorption of IR radiation brings a change in the dipole moment of the molecule.

Procedure:

Integrity of the drug in the formulation was checked by taking an IR spectrum of the selected formulation along with the drug and other excipients. The spectra obtained were compared using Shimadzu FTIR 8400 spectrophotometer. In this study pelletization of potassium bromide (KBr) was employed. Crystals of potassium bromide was completely dried at 100°C for 1 hr and was thoroughly mixed with the sample in the ratio of 1 part of sample and 100 parts of KBr. The mixture was compressed to form a disc using dies. This disc was placed in the sample chamber and a spectrum was obtained through the software program which was further subjected to interpretation.

Table 1: Formulation of Gastroretentive floating tablet of Methyl Dopa.

Ingredient	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Methyldopa	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg
HPMC K15M	22.5 mg	22.5 mg	22.5 mg	45 mg	45 mg	45 mg	67.5 mg	67.5 mg	67.5 mg
HPMC K4M	45 mg	45 mg	45 mg	45 mg	45 mg	45 mg	45 mg	45 mg	45 mg
Sodium bicarbonate	40 mg	60 mg	80 mg	40 mg	60 mg	80 mg	40 mg	60 mg	80 mg
Di-calcium phosphate	36.1 mg	16.1 mg	-	13.6 mg	-	-	-	-	-
Ascorbic acid (0.1%)	0.4 mg	0.4 mg	0.4 mg	0.4 mg	0.4 mg	0.4 mg	0.4 mg	0.4 mg	0.4 mg
Magnesium stearate (0.5%)	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg
Talc (1%)	4 mg	4 mg	4 mg	4 mg	4 mg	4 mg	4 mg	4 mg	4 mg

Method of preparation of tablets:

The floating tablets were prepared by direct compression method. Drug and the selected polymers were accurately weighed and geometrically blended in a mortar and pestle for 15 mins. then other excipients such as sodium bicarbonate, talc and magnesium stearate were added. The mixed powder blend was passed through # 60 mesh. The powder was then subjected to pre-compressional evaluation such as angle of repose, % compressibility, flow rate, etc. Tablets were compressed on a 10 station rotary CIP tablet punching machine using 10 mm flat round punches to obtain tablets weighing around 400mg. Finally the post-compressional evaluations such as hardness, floating lag time, buoyancy, friability, weight variation, drug content, and *in-vitro* release studies were carried out.

Pre-Compressional Evaluation

Bulk Density

It is a ratio of mass of powder to bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantities of powder mixture were poured into graduated measuring cylinder through large funnel and volume was measured. The measuring cylinder was then tapped 3 times on a hard surface from height of 2-3 inches at 2 second interval till a constant volume was obtained. It was expressed in gm/ml and given by-

$$BD = \frac{Wg}{Bg}$$

Where,

BD = Bulk Density

Wg = Weight of granules

Bg = Bulk volume of granules

Carr's Consolidation Index (% Compressibility)

Carr's Index explains flow properties of the tablet powder. It is expressed in percentage and given by-

$$\text{Consolidation Index} = \frac{Tapped\,Density - Untapped\,Density}{Tapped\,Density} \times 100$$

Angle of Repose

It is defined as the maximum angle possible between the surface of the pile of the powder and horizontal plane. To determine angle of repose fixed funnel method was used. A funnel was fixed with its tip at a given height of 2 inches above a flat horizontal surface to which a graph paper was placed. The powder blend was carefully poured through a funnel till the apex of the conical pile just touches the tip of the funnel. The 'r' was calculated from the circumference obtained on the graph. Θ was then calculated using the formula-

$\text{Tan } \theta = h/r$

Where,

θ = Angle of Repose

h = Height of Pile

r = Radius of the base of the pile

Table 2: Evaluation of flow properties of tablet blend:

S. No.	Formulation	*Bulk Density (g/cc)	*Tapped Density (g/cc)	*% Compressibility	*Angle of repose
1.	F1	0.360±0.003	0.418±0.005	13.83±0.982	20024'±0.9529
2.	F2	0.386±0.004	0.437±0.005	11.60±0.130	21008'±0.2662
3.	F3	0.401±0.004	0.458±0.006	12.08±0.140	22035'±0.3751
4.	F4	0.269±0.003	0.286±0.002	5.83±0.705	20042'±0.3137
5.	F5	0.300±0.006	0.321±0.005	6.97±0.726	22012'±0.3525
6.	F6	0.333±0.003	0.372±0.004	10.05±0.975	22042'±0.3213
7.	F7	0.370±0.004	0.418±0.005	11.17±0.121	22020'±0.5250
8.	F8	0.377±0.004	0.412±0.004	8.21±1.050	22009'±0.6438
9.	F9	0.351±0.003	0.396±0.004	10.64±0.107	21062'±0.254

Post-Compressional Evaluation

Hardness

The Pfizer hardness tester was used to determine the tablet hardness. The tablet was held between affixed and moving jaw. Scale was adjusted to zero; pressure was gradually increased until the tablet fractured. The pressure at that point gives the measure of the hardness of tablet. Hardness was expressed in Kg/ cm^2.

Friability

Friability was determined using Roche Friabilator. Twenty tablets were weighed (W) and placed in the friabilator and then operated at 25 rpm for four mins. The tablets were then deducted and weighed (W0). Friability limit should be < 1%. The difference in the two weights is used to calculate friability.

$$Friability = 100X(1 - \frac{W}{W_0})$$

Where,
W_0 = Initial weight
W = Final weight

Weight Variation Test

Twenty tablets were weighed individually and average weight was calculated. The individual weights were then compared with average weight. The tablet passes the test if not more than two tablets fall outside the percentage limit and none of tablet differ by more than double percentage limit.

$$PD = \frac{W_{avg} - W_{ind}}{W_{avg}} X100$$

Where, PD = Percentage Deviation
W_{avg} = Average Weight of Tablet
W_{ind} = Individual Weight of Tablet

Drug content estimation:

Drug content was determined to check dose uniformity in the formulations. 10 tablets were randomly selected, weighed and powdered. A quantity equivalent to 100 mg of methyldopa was added in to a 100 ml volumetric flask and dissolved in distilled water and made up the volume and filtered. An aliquot of 10 ml was pipette out into 100ml volumetric flask and made up the volume with distilled water. Absorbance was read at 280nm using distilled water as a blank.

Table 3: Post compressional evaluation parameters

Formulation Code	*Hardness (Kg/cm^2)	*Friability (%)	*Avg wt (mg) ±SD	*Drug Content %	*Lag Time (Sec)	*Buoyancy (hrs)
F1	2.61	0.55	401.05±0.995	96.82	105	24
F2	3.19	0.60	399.11±0.621	97.07	85	24
F3	2.70	0.67	402.34±0.544	97.57	45	24
F4	2.91	0.52	401.06±0.874	96.15	150	24
F5	3.02	0.65	404.63±1.003	95.06	80	24
F6	2.85	0.68	421.50±0.751	94.49	60	24
F7	2.57	0.56	405.30±0.702	95.42	200	24
F8	3.00	0.61	422.04±0.348	95.78	90	24
F9	3.11	0.63	445.11±0.817	96.55	80	24

Swelling index:

The swelling index of tablets was determined in 0.1N HCl at room temperature by gravimetric method. The swollen weight of the tablet was determined at predefined time intervals over a period of 24 hrs. The results for swelling index are shown in the table no 4 and figure 1 to 3.

Table 4: Swelling index of optimized formulations (F1 to F9)

Formulation Code	Swelling Index (%)								
	0.25 hr	0.5 hr	1 hr	2 hr	3 hr	6 hr	10 hr	12 hr	24 hr
F1	47.4	95	107.5	125	140	145	157.5	180	210
F2	50	95	105	120	142.5	165	177.5	200	275
F3	58.5	95.1	107.3	121.9	139	160.9	165.9	187.8	253.7
F4	46.5	105	120	135	150	157.5	182.5	202.5	272.5
F5	51.3	97.4	112.8	138.5	151.3	156.3	169.2	184.6	284.6
F6	57.9	106.7	117.8	133.3	151.3	158.9	174.3	182.1	287.2
F7	45	110	122.5	145	155	180	197.5	222.5	322.5
F8	46.2	125.6	141.0	158.7	169.2	176.8	197.4	212.7	366.6
F9	46.2	107.6	123	143.5	161.5	182	192.3	235.8	335.8

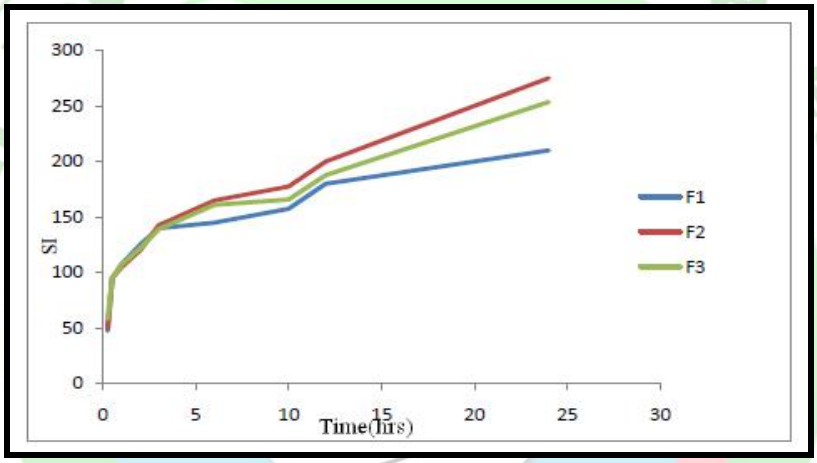

Figure 1: Comparison graph for Swelling Index of F1 to F3

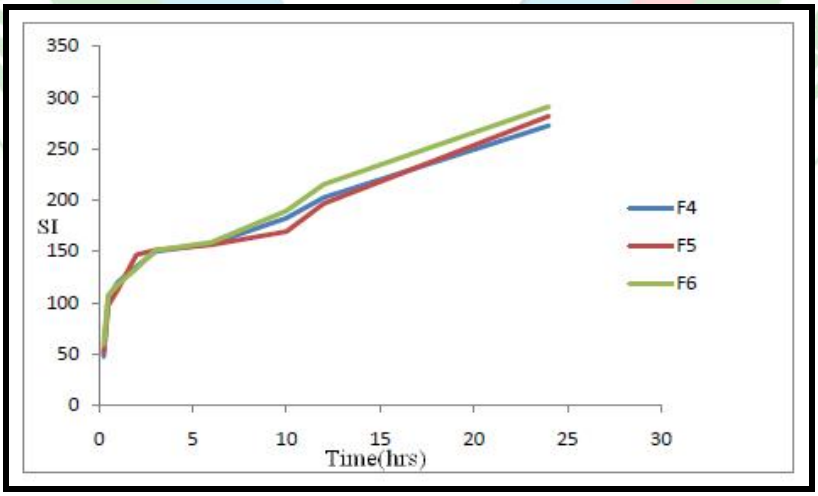

Figure 2: Comparison graph for Swelling Index of F4 to F6

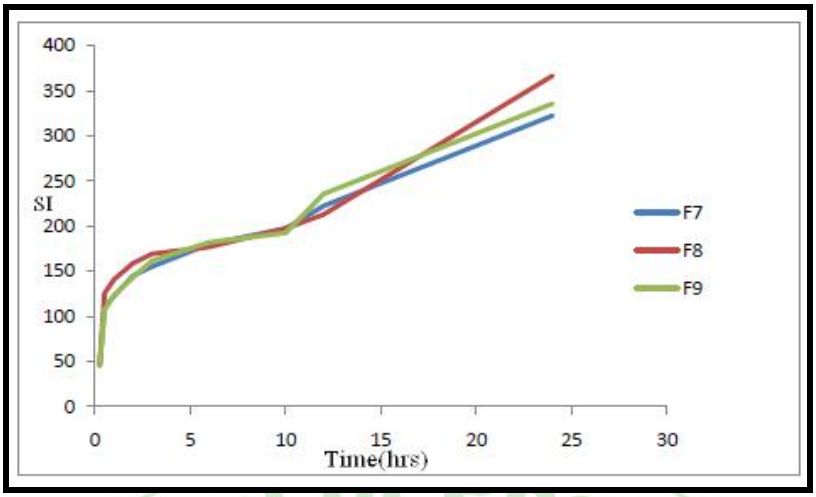

Figure 3: Comparison graph for Swelling Index of F7 to F9

Differential Scanning Calorimertry (DSC):

DSC is a thermo analytical technique in which the difference in the amount of heat required to increase the temperature of a sample and reference are measured as a function of temperature. Both the sample and reference are maintained at nearly same temperature throughout the experiment.

Procedure:

DSC (Perkin-Elmer Thermal Analysis) experiments were carried out in order to characterize the physical state of the drugs. Samples of formulation were placed in aluminium pans and thematically sealed. The heating rate was 10°C per min using nitrogen as the purge gas. The DSC instrument was calibrated for temperature using Indium. In addition, for enthalpy calibration Indium was sealed in aluminium pans with sealed empty pan as a reference.

Fourier transformation infra red spectroscopy (FTIR):

IR spectroscopy deals with the study of absorption of IR region, which extends from the red end of the visible spectrum to the microwave region. An IR radiation is absorbed by a molecule when the applied IR frequency is equal to the natural frequency of vibration of the molecule. Absorption of IR radiation brings a change in the dipole moment of the molecule.

***In-vitro* Release studies:**

In-vitro release studies were carried out in USP XXIII dissolution test apparatus I using pH 1.2 buffer as dissolution medium at 370 ± 0.50C and rotational speed of 75 rpm for 24 hrs. 5 ml of sample was withdrawn at different time intervals and 1 ml was taken, volume made up to 10 ml with 0.1N HCl and then estimated spectrophotometrically at 280nm against blank treated in similar manner. Dissolution mechanism of the formulations was analyzed by plotting drug release versus time plot.

Data Analysis:

The results of *in-vitro* release studies obtained for F1 to F9 were analyzed by following models-

Zero Order Kinetics: A zero-order release would be predicted by the following equation-

$A_t = A_0 - K_0 t$….1

Where,

A_t= Drug release at time 't'

A_0 = Initial drug concentration

K_0 = Zero-order rate constant (hr^{-1})

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys zero-order release kinetics, with a slope equal to K_0.

First Order Kinetics: A first-order release would be predicted by the following equation-

$\text{Log } C = \text{Log } C_0 - 303.2\ Kt$ …2

Where,

C = Amount of drug remained at time 't'

C_0 = Initial amount of drug
K = First-order rate constant (hr-1).
When the data is plotted as log cumulative percent drug remaining versus time yields a straight line, indicating that the release follows first-order kinetics. The constant 'K' can be obtained by multiplying 2.303 with slope values.

RESULTS

Preformulation studies:

- **IR Spectroscopy**

The spectrum of the drug shows the functional groups at their frequencies. The IR spectrum of pure drug was found to be similar to the standard spectrum of drug. This was shown in Figure 4.3.2.

- **DSC Study**

DSC thermograms for pure drug, physical mixture and final optimized formulation F3 were obtained. The thermogram of pure drug exhibited the single endothermic peak at around 314°C as the drug melting point lies around 307- 314°C.

- **Solubility study**

This study includes selection of suitable solvent to dissolve the pure drug as well as excipients used for the design of tablets. This was shown in table 5.

Table 5: Quantitative Saturation Solubility of Methyl dopa

Sl. No.	Solvent Systems	Quantitative Saturation Solubility (mg/ml) ± S.D.
1	Water	0.026 ± 0.034
2	Dichloromethane (DCM)	11.140 ± 0.140
3	0.1 N HCl (pH 1.2)	11.300 ± 0.122
4	Methanol	5.007 ± 0.110
5	Acetone	0.340 ± 0.096

*** (values are mean ±S.D, n=3)**

- **Flow properties:**

Flow properties play an important role in pharmaceuticals especially in tablet formulation.

Bulk Density and Tapped Density

The tapped and the untapped density of the powder blend were found to be in the range of 0.286 to 0.458 g/cc and 0.270 to 0.402 g/cc respectively.

Angle of repose

The angles of repose and % compressibility were in the range of $20^0 24$ to $22^0 42$ and 5 to 13% respectively which indicates excellent flow properties.

- **Pre-compressional evaluation:**

The prepared floating tablets were evaluated for hardness, friability, uniformity of weight, uniformity of drug content, swelling index, floating lag time, *in-vitro* floating time, *in-vitro* dissolution, stability study and drug-polymer interaction.

Hardness

The hardness of the prepared floating tablets was found to be in the range of 2.5 to 3.2 Kg/cm².

Friability

The friability of all tablets was less than 1% i.e., in the range of 0.51 to 0.69%. The percentage deviation from the mean weights of all the batches of prepared floating tablets was found to be within the prescribed limits as per IP. The values of the drug content were in the range of 94 to 97 % in all the prepared batches as observed from the data given in table -3.

- **Drug-formulation compatibility studies**

FTIR:

IR spectrum of Methyldopa exhibited characteristic peaks at 3473.42 cm–1 and 1643.24 cm–1 due to N–H stretching and C=O stretching of carboxyl group respectively. The peaks at 3215.11 cm–1 were due to phenolic –

OH group. The C–H absorption frequency was noticed at 2839.02 cm–1 in confirmation of presence of alkyl moieties. IR spectrum of physical mixture and final formulation F3 showed peaks at 3478.38 cm–1, 3477.42 cm–1 due to N–H stretching and at 1642.04 cm–1, 1643.24 cm–1 due to C=O stretching of the carboxyl group respectively. The peaks at 3214.15 cm–1 and 3216.08 cm–1 in the physical mixture and final formulation F3 respectively represent the phenolic –OH group. The presence of above peaks confirmed undisturbed drug in the formulation. Hence, there were no drug-carrier interactions.

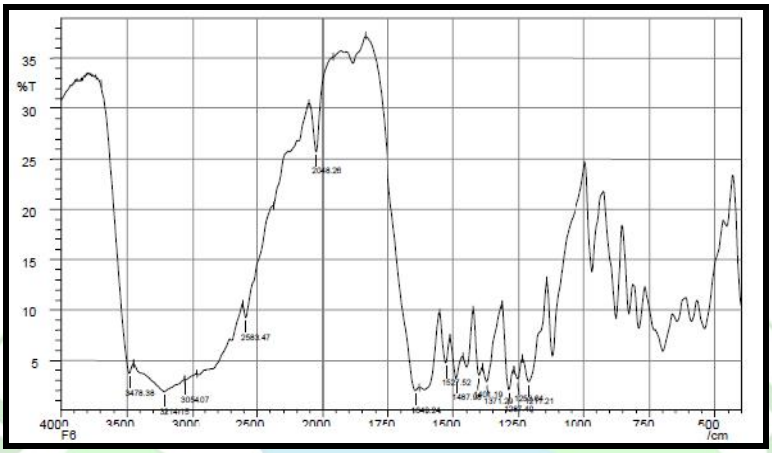

Figure 4: FTIR for physical mixture

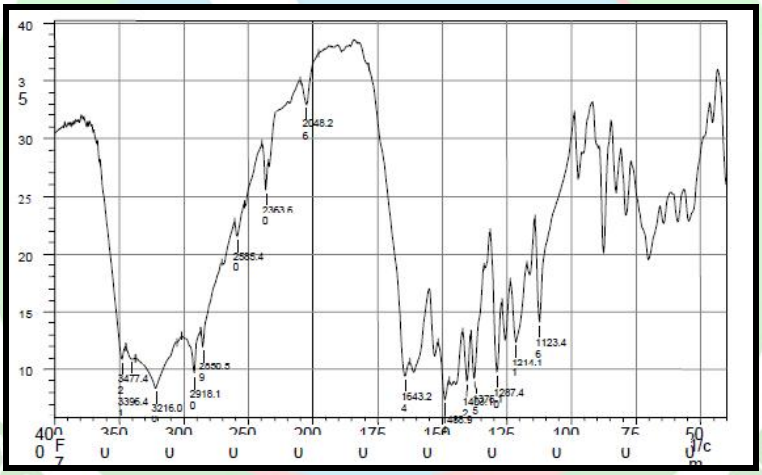

Figure 5: FTIR for formulation

DSC Studies:

DSC thermograms (Figures 3) for final optimized formulation F3 were obtained. The thermogram of pure drug exhibited the single endothermic peak at around 314°C as the drug melting point lies around 307- 314°C.

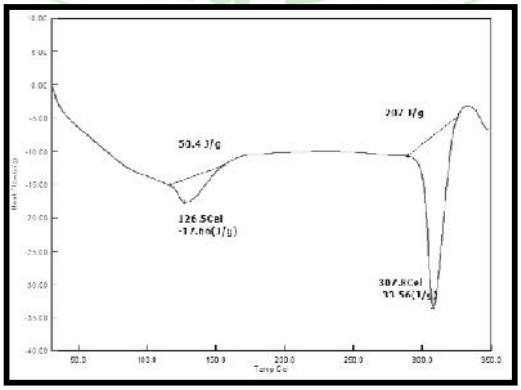

Figure 6: DSC for formulation

CONCLUSION

Floating systems or hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the 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. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal.

ACKNOWLEDGEMENTS

I am thank full to XL Laboratories Pvt. Ltd., Finar Chemicals and Dr. M .P. Khinchi Principal of Kota College of Pharmacy, Kota (Raj.) for his valuable support and providing facilities to carry out this research work.

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