IJPT
International Journal of Pharmacy & Technology

ISSN: 0975-766X

Available Online through *Research Article*
www.ijptonline.com

DEVELOPMENT AND EVALUATION OF FLOATING DRUG DELIVERY SYSTEM FOR DIABETES MELLITUS.

D. M. Deshpande[*], P.D.Chaudhari[1]

[*]Pad.Dr.D.Y.Patil Institute of Pharmaceutical Sciences and Research, Pimpri, Pune-411018; India.

[1]Principal and HOD of Pharmaceutics, Modern College of Pharmacy, Nigdi, Pune-411044; India.

Received on: 21-01-2010 ***Accepted on: 13-02-2010***

ABSTRACT:

Diabetes Mellitus is most common endocrine disease. Diabetes Mellitus is defined conventionally as a lack of insulin secretion due to destruction of pancreatic β- cells. Diabetes is not a single disease entity, but rather a group of metabolic disorders sharing a common underlying feature of hyperglycemia. Hyperglycemia in diabetes, results from defects in insulin secretion, insulin action or both. Rosiglitazone Maleate is antidiabetic drug in Thiazolidinedione class of drugs has been used for treatment of Diabetes type II. Rosiglitazone is a highly selective and potent agonist for the Peroxisome Proliferator-Activated Receptor-gamma (PPARγ). Activation of PPARγ nuclear receptors regulates the transcription of insulin-responsive genes involved in the control of glucose production, transport, and utilization.

Rosiglitazone Maleate is readily soluble in ethanol and a buffered aqueous solution with pH of 2.3; solubility decreases with increasing pH in the physiological range. Thus Rosiglitazone Maleate is needed to be formulated in GRDDS.

In present investigation core tablet formulated with hydrophobic meltable binder such as Compritol 888 and Precirol ATO 5 with drug**:** polymer in 1:1, 1:2 ratio. Then, by using 3^2 full factorial design the formulations in suitable combinations formulated and tablets were evaluated.

HPMC K100M and Sodium bicarbonate were selected as independent parameters in factorial design. Total floating time and floating lag time were selected as dependent parameters.

The final formulations N_7 and N_8 were found to be optimized and follows Peppas model for drug release suggesting that drug release is anomalous from dosage form.

KEY WORDS: Diabetes mellitus, floating drug delivery, full factorial design, Rosiglitazone Maleate.

INTRODUCTION:

The millennium has dawned, development of newer drugs and medicines will be the goal of scientists across the world. In order to achieve satisfying results, a drug has to be properly formulated in proper dosage form. Recently, several technical advancements have led to the development of various Novel Drug Delivery Systems (NDDS) that could revolutionize method of drug delivery and hence could provide definite therapeutic benefits. Oral route of administration is the most important and convenient route for drug delivery. The benefits of long-term delivery technology have not been fully realized for dosage forms designed for oral administration. This is mainly due to the fact that the extent of drug absorption from GIT is determined by GI physiology, irrespective of the control release properties of the device. Although differential absorption from various regions of GI has been known for decades, only recently drug delivery systems have been designed to target drugs to differential regions of GIT. These include gastro retentive systems, delayed release systems and colon targeting. The real issue in the development of oral controlled release dosage form is not just to prolong the delivery of drugs for more than 12 hrs but also to prolong the presence of dosage forms in the stomach or somewhere in the upper small intestine. Dosage forms with prolonged gastric residence time (GRT), i.e. gastro remaining or gastro retentive dosage form (GRDF), will bring about new and

important therapeutic options. For instance, these will significantly extend the period of time over which drugs may be released, and thus prolong dosing intervals and increase patient compliance beyond the compliance level of existing controlled release dosage forms. Finally, GRDF will be used as carriers for drugs with so called absorption windows; these substances are taken up only from very specific sites of the gastrointestinal mucosa, often in a proximal region of the small intestine.

Approaches for Gastric Retention**:** Floating System (Low Density Approach), High Density Systems, Swelling and Expanding Systems, Bio-adhesive Systems, Modified Shape Systems

Criteria for Selection of Drug Candidate for GRDF: Drugs have a particular site for maximum absorption, e.g. Ciprofloxacin; Drugs having low pKa, which remains unionized in stomach for better absorption; Drugs having reduced solubility at higher pH, e.g. Captopril and Chordiazepoxide; Local action as it seen in the treatment of Helicobacter pylori by Amoxicillin, The bioavailability of drugs that get degraded in alkaline pH can be increased by formulating gastro-retentive dosage forms, e.g. Doxifluridine, which degrades in small intestine, To minimize gastric irritation due to sudden increase of drug concentration in the stomach, e.g. NSAIDS

Floating dosage form is also known as hydro dynamically balanced system (HBS). It is an oral dosage form (capsule or tablet) that is designed to prolong the residence time of the dosage form within the GI tract. The retentive characteristics of the dosage form in gastric content are most significant for drugs that are Insoluble in intestinal fluid, drugs that acts locally, drugs that exhibits site-specific absorption.

Two commonly used techniques-

Gas generating systems (Effervescent systems)**:** Contains carbonates or bicarbonates that generate carbon dioxide gas in presence of gastric acid and/or the added organic acid. The carbon dioxide gas thus get entrapped into the matrix of the formulation, reducing its density and imparting floating property

Non-gas generating systems (Non effervescent systems)**:** These are highly porous and highly swellable systems that expand in gastric contents reducing their density and thus imparting floating properties.

Limitations of FDDS:

1) The residence time in the stomach depends upon the digestive state. Hence, FDDS should be administered after the meal.

2) The ability to float relies in the hydration state of the dosage form. In order to keep these tablets floating In vivo, intermittent administration of water (a tumbler full, every 2 hours) is beneficial.

3) The ability of drug to remain in the stomach depends upon the subject being positioned upright.

4) FDDS are not suitable for the drugs that have solubility or stability problems in the gastric fluid.

5) Drug like Nifedipine, which is well absorbed along the entire GIT and which undergoes significant first pass metabolism, may not be a desirable candidate for FDDS since the slow gastric emptying may lead to the reduced systemic bioavailability.

MATERIALS AND METHODS:

Materials –

Rosiglitazone Maleate I.P. (2007) was obtained as a gift sample from the Emcure Research Center, Bhosari MIDC, Pune (India), HPMC K100M and HPMC K15M were received as a gift sample from Colorcon Asia Pvt. Ltd., Verna-Goa. Sodium Bicarbonate (Qualigens Fine Chemicals, Mumbai) was purchased. Compritol 888 and Precirol ATO 5 were obtained from Colorcon India Ltd. (Gattefosse), Mumbai. Other excipients used to prepare tablets were of standard pharmaceutical grade. All other reagents were of analytical grade.

Preparation of Core Tablets:

Core tablets were prepared by Melt Granulation technique using hydrophobic meltable binder Compritol 888 and Precirol ATO 5. Drug and hydrophobic binder are varied in ratios like 1:1, 1:2. Then other excipients like DCP, Magnesium Stearate, and Aerosil are mixed with the granules obtained through sieving in a morter – pestle. The resulting powder mixtures were then compressed into tablets (average tablet weight 75 mg) using a rotary tablet machine equipped with 6 mm concave faced punch (Rimek, Mumbai).

Table 1: Formulation of the core tablets with Compritol 888:-

Sr. No.	Rosiglitazone Maleate :Compritol 888 (mg)	DCP (mg)	Mg.Stearate (0.5%) (mg)	Aerosil (0.5%) (mg)	Total (mg)
D_1 (1:1)	15	59.25	0.375	0.375	75
D_2 (1:2)	22.50	51.75	0.375	0.375	75

Table 2: Formulation of core tablets with Precirol ATO 5:-

Sr. No.	Rosiglitazone Maleate : Precirol ATO 5 (mg)	DCP (mg)	Mg.Stearate (0.5%) (mg)	Aerosil (0.5%) (mg)	Total (mg)
A_1 (1:1)	15	59.25	0.375	0.375	75
A_2 (1:2)	22.50	51.75	0.375	0.375	75

Preparation of Press coated floating tablet:

The press coated tablet contains, a core tablet holding a drug in prescribed quantity which is coated with mix. of hydrophilic polymer and a gas generating agent was done. The tablets were prepared by dry granulation.

Optimization of coating layer with HPMC K 15M for core tablet D_1:-

Floating layer was prepared by using HPMC K 15M and Sodium Bicarbonate in different concentration. A 3^2 randomized full factorial designs developed to optimize formulation. In the optimization method concentration of HPMC and Sodium Bicarbonate kept at 3 independent levels while floating lag time and total floating time in hours selected as dependent variables.

Table 3: Coded Values of Independent Variables for Floating Layer:

Ingredients	Actual Weight/Tablet (mg)	Coded Value
HPMC K 15M	30	-1
	40	0
	50	1
$NaHCO_3$	20	-1
	30	0
	40	1

Table 4: Formulations of press coated tablets with HPMC K 15M for core tablet D_1:

Sr. No.	HPMC K 15M	$NaHCO_3$	Total (mg)
M_1	-1	-1	50
M_2	-1	0	60
M_3	-1	1	70
M_4	0	-1	60
M_5	0	0	70
M_6	0	1	80
M_7	1	-1	70
M_8	1	0	80
M_9	1	1	90

Optimization of coating layer with HPMC K 100M for D_1 :

Floating layer was prepared by using HPMC K 100M and Sodium Bicarbonate in different concentration. A 3^2 randomized full factorial designs developed to optimize formulation.

Table 5: Coded Values of Independent Variables for Floating Layer:

Ingredients	Actual Weight/Tablet (mg)	Coded Value
HPMC K 100M	30	-1
	40	0
	50	1
$NaHCO_3$	20	-1
	30	0
	40	1

Table 6: Formulations of press coated tablets with HPMC K 100M for core tablet D_1:

Sr. No.	HPMC K 100M	$NaHCO_3$	Total (mg)
N_1	-1	-1	50
N_2	-1	0	60
N_3	-1	1	70
N_4	0	-1	60
N_5	0	0	70
N_6	0	1	80
N_7	1	-1	70
N_8	1	0	80
N_9	1	1	90

Table 7: Formulation of press coated tablet with HPMC K 100M for core tablet D_2:

Sr. No.	HPMC K 100M	$NaHCO_3$	Total (mg)
P_7	1	-1	70
P_8	1	0	80

Table 8: Formulation of press coated tablet with HPMC K 100M for core tablet A_1:

Sr. No.	HPMC K 100M	$NaHCO_3$	Total (mg)
R_7	1	-1	70
R_8	1	0	80

Table 9: Formulation of press coated tablet with HPMC K 100M for core tablet A_2:

Sr. No.	HPMC K 100M	$NaHCO_3$	Total (mg)
S_7	1	-1	70
S_8	1	0	80

Characterization of Granules:

(a) Infrared Spectroscopy: Fourier Transform Infrared (FT-IR) spectra of drug, hydrophilic polymers, binders and granules were obtained on Shimadzu 8400S FT-IR spectrophotometer. The spectra were scanned over the wave number range from 3900 – 400 cm^1.

Evaluation of Granules:

a) Angle of Repose: Angle of repose has been defined as the maximum angle possible between the surface of pile of powder and horizontal plane. The angle of repose for the granules of each formulation was determined by the funnel method.

$$\tan \theta = h/r$$

Hence, $\theta = \tan^{-1} h/r$

(b) Flow Rate: Flow rate of a powder has been defined as the rate at which the particular mass emerges through the orifice of funnel of a suitable diameter. The flow rate for granules of each formulation was determined by pouring accurately weighed quantities of granules in funnel with an orifice of 8 mm diameter. The time required for the complete granule mass to emerge out of the orifice was recorded using a stopwatch. The flow rate was calculated from following equation:

$$\text{Flow Rate} = \frac{\text{Weight of granules}}{\text{Time in seconds}}$$

c) Carr's Compressibility Index: An indirect method of measuring powder flow from bulk densities was developed by Carr. Carr's index of each formulation was calculated according to equation given below-

Carr's Compressibility Index (%) = [(Tapped Bulk Density-Bulk Density)/ X 100] /

Tapped Bulk Density

Evaluation of Floating Tablets:

(i) Tablet Thickness and Diameter: Thickness and diameter of tablets are important for uniformity of tablet size.

(ii) Weight Variation Test: To study weight variation, 5 tablets of each formulation were weighed using an electronic balance (AW-220, Shimadzu), and the test was performed according to the official method.

(iii) Uniformity of Content: This test was applicable to tablets that contain less than 10 mg or less than 10%w/w of active ingredient. Content of active ingredient in tablets, taken at random, was determined. Crush tablets and powder equivalent to weight of tablet dissolved in 0.1 N HCl. Drug content was calculated by measuring absorbance at wavelength 318 nm.

(iv) Tablet Hardness: The resistance of tablets to shipping or breakage, under conditions of storage, transportation and handling before usage depends on its hardness. For each formulation, the hardness of 6 tablets was determined using the Monsanto hardness tester (Cadmach).

(v) Friability: Friability is the measure of tablet strength. Roche Friabilator was used for testing the friability. Percent friability (% F) was calculated as follows,

$$\% F = \frac{\text{Initial weight} - \text{final weight}}{\text{Initial weight}} \times 100$$

vi) Floating Behavior: The in-vitro buoyancy was determined by floating lag time. As per the method described by Rosa et. al the tablets were placed in a 100 ml beaker containing 0.1 N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time.

vii) Dissolution Studies: The release rate of Rosiglitazone Maleate from floating tablets was determined using USP Dissolution Testing Apparatus II (Paddle type). The dissolution test was performed using 900 ml of 0.1 N HCL, at 37 ± 0.5°C with 75 rpm. Aliquot (10 ml) of the solution was collected from the dissolution apparatus hourly for 12 hours and were replaced with fresh dissolution medium. The aliquots were filtered through Whatmann filter paper no. 41. Absorbance of these solutions was measured at 318 nm. Analysis of data was done by using "PCP Disso V-2.08" software, India

STABILITY STUDY:

The purpose of stability testing is to give evidence on how the quality of a drug substance or drug product changes with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to set a re-test period for the drug substance or drug product under recommended storage conditions. Stability studies should include testing of those attributes of the drug product that are susceptible to change during storage and are likely to influence quality, safety, and/or efficacy. The testing should cover the physical, chemical, biological, and microbiological attributes. Analytical procedures should be fully validated and stability indicating.

Testing Frequency: For long term studies, frequency of testing should be sufficient to establish the stability profile of the drug product. For products having proposed shelf life of at least 12 months, the frequency of testing at the long term storage condition should normally be every 3

months over the first year, every 6 months over the second year, and annually thereafter through the proposed shelf life.

Table 10: General case stability specifications for storage of new drug product

Study	**Storage condition**	**Minimum time period covered by data at submission**
Long term*	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate**	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

*It is up to the applicant to decide whether long term stability studies are performed at 25 ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH.

**If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

RESULTS AND DISCUSSION:

Evaluation of Core Tablets:

Each formulation was evaluated for weight variation, diameter, thickness, hardness, friability and % drug content. All the formulations showed acceptable pharmacopoeial limits for weight variation, friability and % drug content.

Table 11: *In vitro* evaluation of core tablet:

Formulation	Weight (mg)	Diameter (mm)	Thickness (mm)	Hardness (kg/cm^2)	Friability (% loss of Weight)	% Drug content
D_1	75.13±0.87	6.02±0.14	2.54±0.05	4.83±0.28	0.30±0.25	99.46±0.15
D_2	75.45±1.04	6.13±0.31	2.59±0.11	5.16±0.17	0.16±0.21	98.02±0.22
A_1	75.64±0.42	6.11±0.48	2.53±0.20	5.03±0.44	0.21±0.13	99.87±0.10
A_2	75.27±0.18	6.16±0.33	2.49±0.23	4.94±0.24	0.26±0.04	100.21±0.45

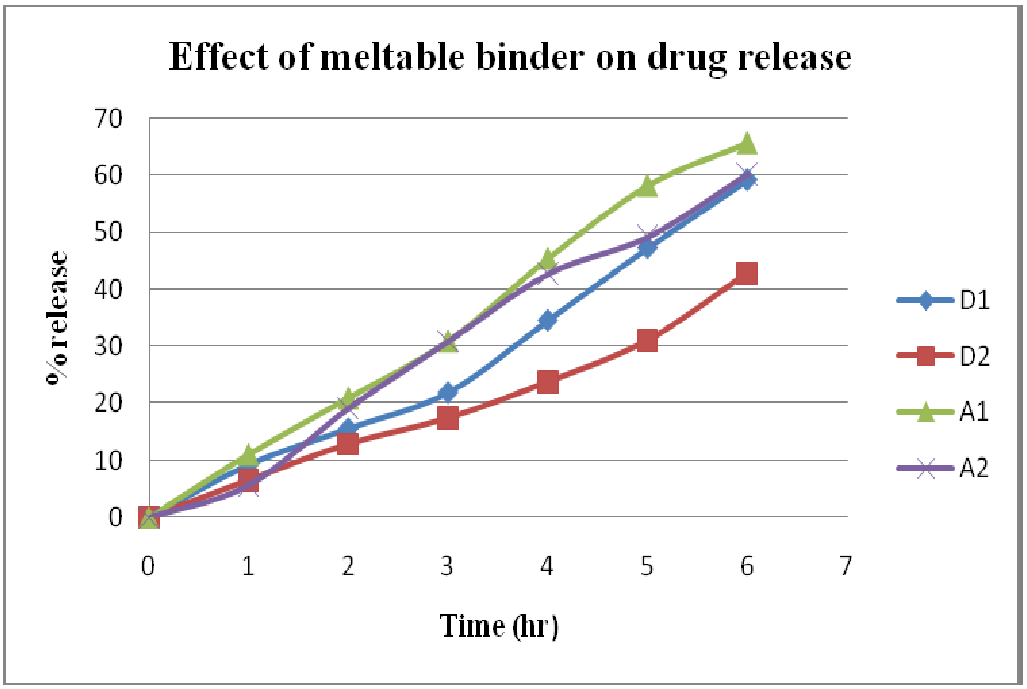
***In vitro* dissolution study of core tablets:**

In vitro dissolution study was carried out to determine effect of hydrophobic meltable binder ratios on drug release profile from uncoated tablets containing Dicalcium Phosphate

Table 12: Effect of Hydrophobic meltable binder ratio on Drug Release Profile

Time (hr)	**% Drug Release**			
	D_1	**D_2**	**A_1**	**A_4**
0	0	0	0	0
1	9.301±1.23	6.620±0.42	11.087±1.12	5.727±0.32
2	15.606±0.56	12.911±0.53	20.976±1.45	19.160±0.56
3	21.946±1.02	17.450±1.18	30.920±0.89	30.880±0.84
4	34.575±0.87	23.800±0.91	45.385±0.83	42.665±1.21
5	47.273±1.11	31.078±1.27	58.143±1.30	49.154±0.99
6	59.148±0.76	42.863±1.36	65.610±0.78	60.145±1.34

Fig 1: Effect of hydrophobic meltable binder on drug release:-

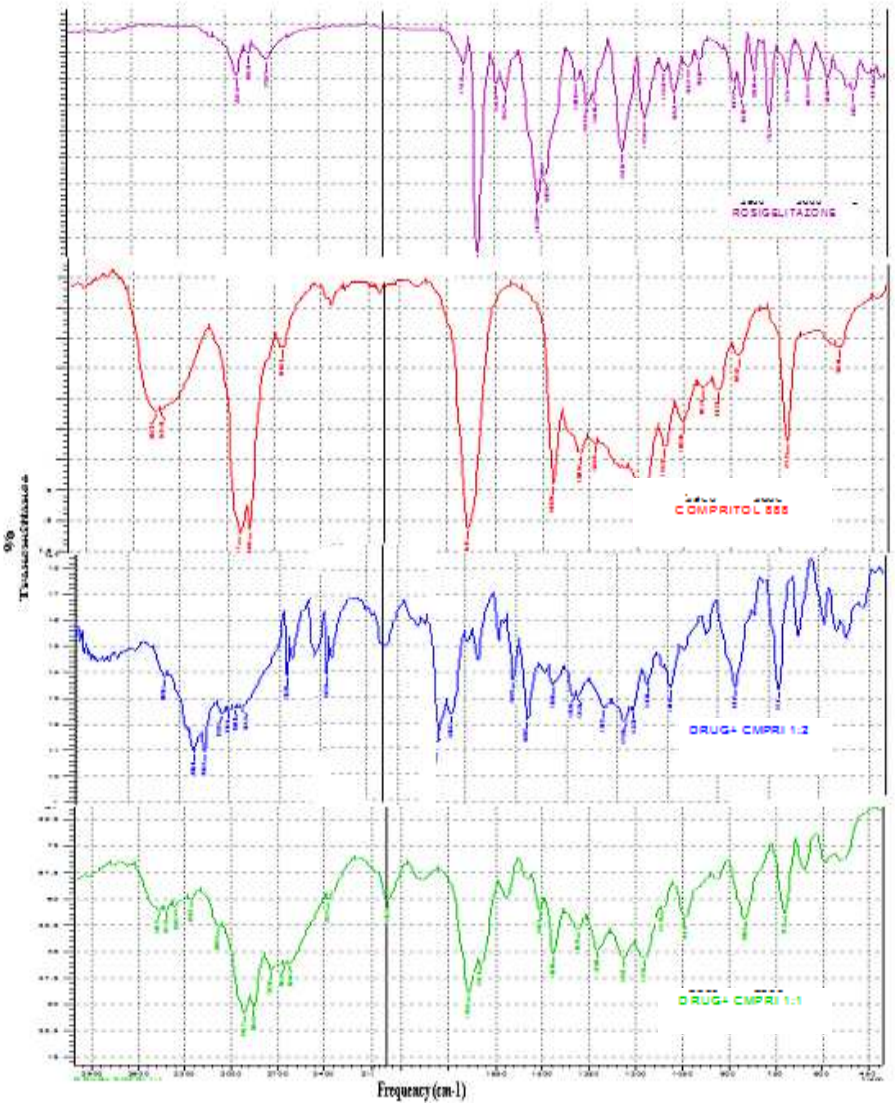


As the ratio of the drug to meltable binder increases from 1:1 to 1:2, the drug release decreases.

Also Compritol 888 was found to be effective retardant in comparison with Precirol ATO 5.

- **Characterization of Granules:**

Fig 2: IR Spectrums of Pure Drug, Polymer and Drug: Polymer.



IR spectrum of all formulations clearly indicates there is no any significant change occurs in the spectra due to hydrophobic meltable binder Compritol 888.

Evaluation of Granules:

a) Angle of Repose: Angle of repose of all formulation granules was found to be in range of 24.30 ± 0.03 to 32.5 ± 0.05. Values of angle of repose are rarely less than 20°, and values of up to 40° indicates reasonable flow potential. Obtained values of angle of repose were found to be good to flow granules.

(b) Flow Rate: Flow rate ranges from 1.03 ± 0.03 to 1.26 ± 0.05 gm/min. The granules were showing good flow rate. Hence, the flow rate of the granules is good.

c) Carr's Compressibility Index: Values of Carr's index lies between 16.25 ± 0.35 to 19.97 ± 0.03 Values of Carr's index below 15 % usually show good flow characteristics, but readings above 25 % indicate poor flowability.

Evaluation of Floating Tablets:

(i) Tablet Thickness and Diameter: Thickness of the formulations M1 to M9 varied from 2.63 ± 0.02 to 2.82 ± 0.02 mm and diameter of the above formulations varied from 8.01 ± 0.33 to 8.08 ± 0.15 mm, while of formulations N1 to N9 showed thickness from 2.64 ± 0.06 to 2.81 ± 0.02 mm and diameter 8.02 ± 0.21 to 8.08 ± 0.36 mm respectively.

(ii) Weight Variation Test: Weight of the floating tablet varied as the coat of the tablet increase with the increase in polymer concentration. The weight of tablets was found to be 125.08 ± 0.58 to 165.25 ± 0.93.

(iii) Uniformity of Content: This test was applicable to tablets that contain less than 10 mg or less than 10%w/w of active ingredient. The tablet comply with the test if not more than one of the individual values thus obtained was outside the limits 85 to 115 % of the average value and none is outside the limits 75 to 125 % of the average value.

All the formulations from M_1 to M_9 showed acceptable range of uniformity of content from 96.63 ± 0.21 to 100.01 ± 0.09, same observation was seen for N_1 to N_9 i.e. from 97.63 ± 0.11 to 99.94 ± 0.08.

(iv) Tablet Hardness: Hardness of tablets of each formulation was measured and found in the range of 4.50 ± 0.85 to 5.80 ± 0.95 kg/ cm2. Each sample was analyzed in triplicate.

(v) Friability: Percentage weight loss of the tablets of each formulation was measured and found to be in the range of 0.6 ± 0.02 to 0.8 ± 0.04%.The percentage friability for all the formulations was below 1% indicating that the friability is within the prescribed limits. Each sample was analyzed in triplicate (n = 3).

vi) Floating Behavior: From the results of floating behavior studies, it was found that as the concentration of effervescent mixture increased, the floating lag time, floating duration decreased and vice versa. A reverse trend was observed on increasing the polymer concentration. In the primary studies observed that compression force also affect the floating lag time, so force kept constant around so as to get the hardness of tablet near about 5 kg/cm^3.

Table 13: Floating lag time (seconds)

Formulations	* Floating Lag Time (Sec)	Formulations	* Floating Lag Time (Sec)
M_1	76	**N_1**	85
M_2	64	**N_2**	70
M_3	52	**N_3**	55
M_4	80	**N_4**	90
M_5	71	**N_5**	80
M_6	59	**N_6**	65
M_7	73	**N_7**	85
M_8	60	**N_8**	75
M_9	52	**N_9**	60

* Each sample was analyzed in triplicate (n = 3)

vii) Dissolution Studies: Hydrophilic systems are commonly used to sustained release of orally administered drugs. Because the drug core of polymer tablets is glassy, drug contained in them can't diffuse unless swelling takes place. Such hydrophilic polymers when come in contact with the dissolution medium, may swell & make a continuous gel layer, erode or undergo combination of the two. The swelling action of hydrophilic polymers is controlled by the rate of their hydration in dissolution medium.

Table 14: % drug release of M_1 to M_5 formulations:

Time (Hrs.)	*Avg. Cumulative % Drug Release				
	M_1	**M_2**	**M_3**	**M_4**	**M_5**
1	9.301±0.076	2.153±1.06	4.834±0.36	4.385±0.38	11.989±0.34
2	5.779±0.54	1.272±0.78	2.180±0.76	3.074±0.69	6.687±0.26
3	11.171±1.07	6.639±0.54	13.806±0.23	15.598±0.31	21.912±0.59
4	15.699±0.35	12.930±0.88	16.563±0.56	22.832±0.86	27.393±1.06
5	20.253±0.52	20.149±0.91	20.228±0.86	35.466±0.29	33.798±1.21
6	26.618±0.69	24.727±0.32	26.593±0.45	40.128±0.96	44.704±0.68
7	-	-	-	52.856±0.59	56.564±0.96
8	-	-	-	61.187±0.69	64.021±0.24
9	-	-	-	-	-
10	-	-	-	-	-
11	-	-	-	-	-
12	-	-	-	-	-

* Each sample was analyzed in triplicate (n = 3)

Table 15: % drug release of M_6 to M_9 formulations

Time (Hrs.)	*Avg. Cumulative % Drug Release			
	M_6	**M_7**	**M_8**	**M_9**
1	11.087±0.23	18.235±0.54	10.194±0.27	13.768±0.59
2	4.895±0.56	24.590±0.67	16.504±0.51	6.697±0.21
3	16.536±0.98	31.873±0.49	21.063±0.61	21.921±0.32
4	24.668±0.54	42.770±0.72	29.220±0.39	27.403±0.98
5	29.271±0.68	48.365±0.81	40.101±0.14	35.595±0.79
6	38.366±0.26	63.818±0.21	50.149±0.87	45.618±0.46
7	46.617±0.38	71.315±0.70	65.612±0.69	56.589±0.57
8	56.700±0.19	82.425±0.61	73.119±0.78	62.259±0.78
9	-	-	-	-
10	-	-	-	-
11	-	-	-	-
12	-	-	-	-

* Each sample was analyzed in triplicate (n = 3)

Fig 3: Avg. Cumulative % Drug Release of M_1, M_2, M_3

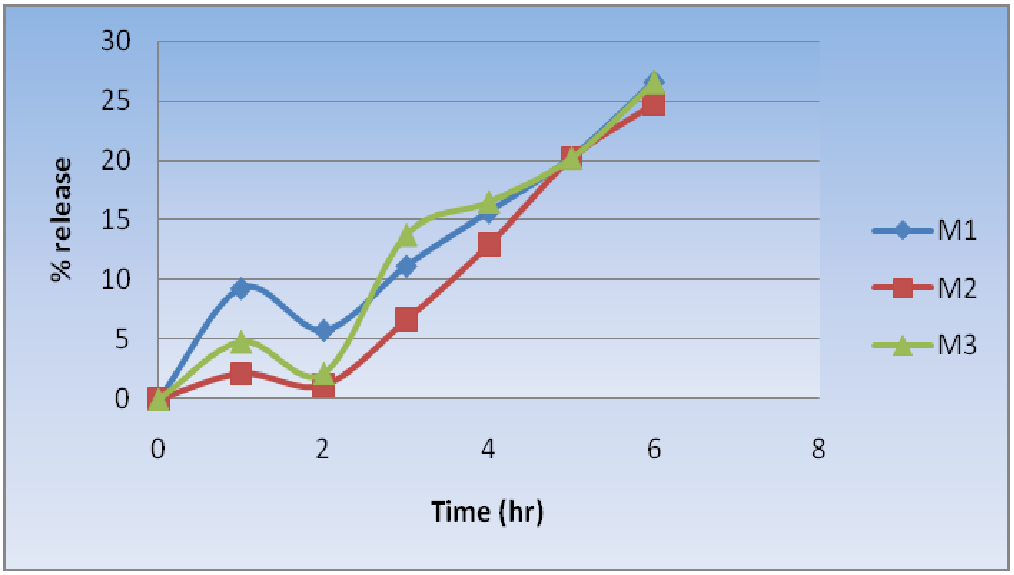


Fig 4: Avg. Cumulative % Drug Release of M_4, M_5, M_6

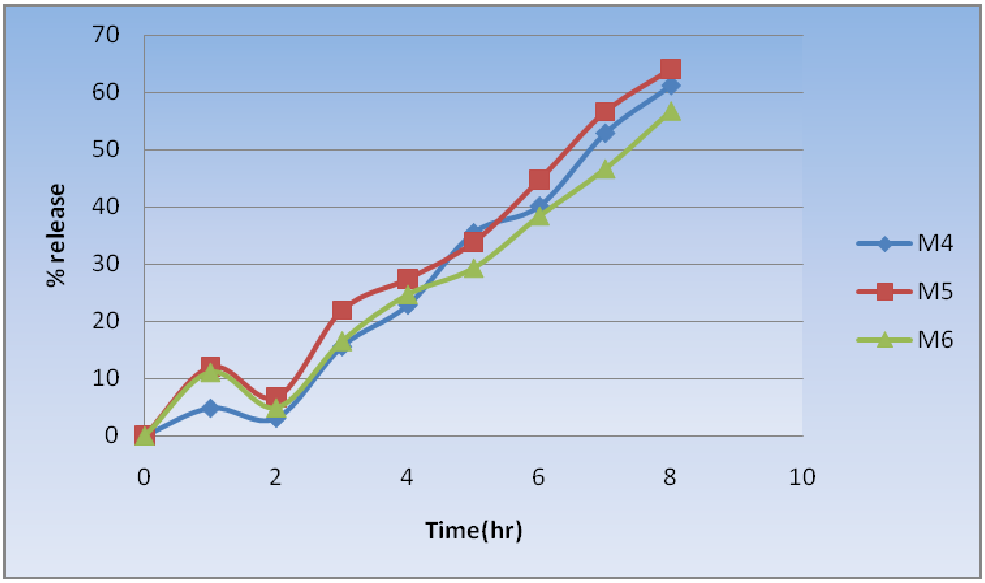


Fig 5: Avg. Cumulative % Drug Release of M_7, M_8, M_9

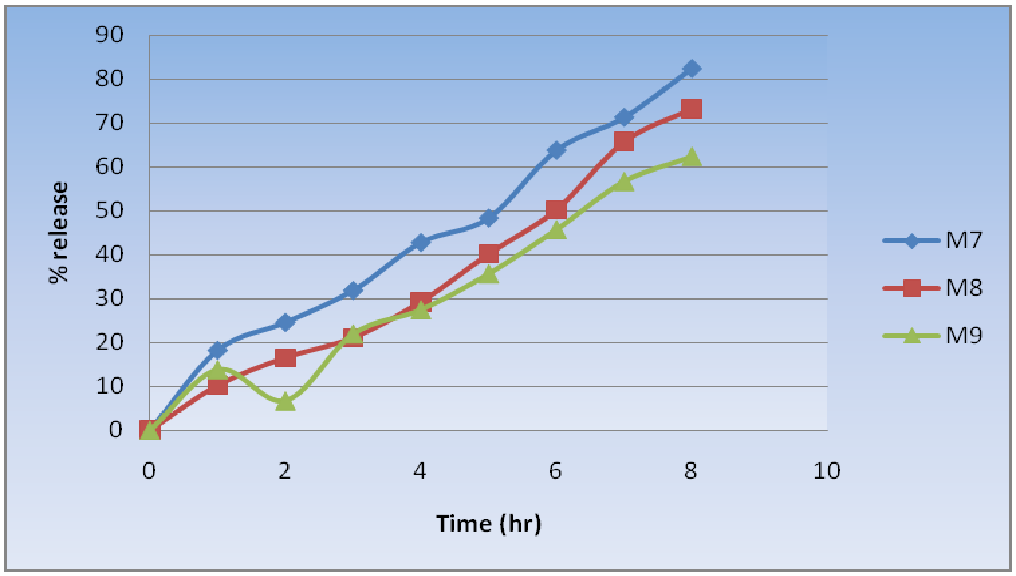


Table 16: Kinetic Models for Formulations Containing HPMC K15M

Formulation	Zero order	1st order	Higuchi	Korsemeyer-Peppas	HIx.Crowell	n
M_1	0.9593	0.9581	0.9031	0.8023	0.9598	0.6715
M_2	0.9364	0.9276	0.8009	0.8884	0.9307	0.6297
M_3	0.9634	0.9607	0.8694	0.8138	0.9619	0.8841
M_4	0.9715	0.9424	0.8517	0.9274	0.9542	0.9623
M_5	0.9818	0.9529	0.8878	0.8907	0.9656	0.9865
M_6	0.9776	0.9539	0.8793	0.5880	0.9641	0.9962
M_7	0.9916	0.9580	0.9499	0.9836	0.9805	0.7450
M_8	0.9897	0.9417	0.8962	0.9839	0.9620	0.9720
M_9	0.9815	0.9609	0.8950	0.8651	0.9706	0.9339

In this situation the drug release is predominantly follows the “Zero Order” release. The R suggests that the drug release depends upon diffusion of drug from the outer layer of the dry coating tablet. But most tablets fails to float up to 12 hrs due to lack of capability of polymer to retain the gas in swollen layer. So, none of these formulations is importance for further study cause it failing to float to 12 hrs which is our main aim of study. The value of ‘n’ clearly depicts that the drug release predominantly follows the “zero order”.

Table 17: %drug release of N_1 to N_5 formulations

Time (Hrs.)	*Avg. Cumulative % Drug Release				
	N_1	N_2	N_3	N_4	N_5
1	11.087±0.35	11.981±0.65	13.768±0.94	8.407±0.98	9.301±0.87
2	13.829±0.56	16.514±0.23	17.418±0.29	12.921±0.26	12.032±0.64
3	21.053±0.85	22.860±0.96	23.768±0.16	19.246±0.54	20.140±0.48
4	27.423±0.65	29.239±0.61	31.046±0.76	24.713±0.81	26.505±0.98
5	38.295±0.12	33.867±0.19	35.684±0.67	37.527±0.46	41.136±1.09
6	45.652±0.48	41.200±0.57	46.600±1.06	46.667±0.31	45.828±0.88
7	52.156±0.69	50.360±0.85	54.003±0.49	54.069±0.61	52.332±1.11
8	64.055±0.89	61.355±0.72	58.765±0.36	65.978±0.66	67.805±0.99
9	70.659±0.76	73.304±0.82	67.125±0.87	72.592±0.97	75.321±0.29
10	-	-	-	84.600±0.93	87.345±0.75
11	-	-	-	-	-
12	-	-	-	-	-

*Each sample was analyzed in triplicate (n = 3)

Table 18: % drug release of N_6 to N_9 formulations

Time (Hrs.)	*Avg. Cumulative % Drug Release			
	N_6	N_7	N_8	N_9
1	4.834±0.48	6.620±0.24	8.407±0.58	9.301±1.23
2	11.114±0.41	11.124±0.35	12.028±0.26	15.606±1.09
3	21.003±1.02	18.333±0.64	20.135±0.48	22.840±0.98
4	30.189±0.19	28.262±0.95	23.819±0.43	34.580±0.88
5	38.396±0.88	33.778±1.03	31.991±0.85	42.811±0.92
6	43.967±0.56	45.578±0.86	41.101±0.33	56.448±0.86
7	50.461±0.32	50.295±1.25	52.047±0.18	62.118±1.05
8	70.391±0.29	58.611±0.94	56.799±1.31	66.031±0.76
9	77.922±0.90	64.291±0.77	66.043±0.79	71.751±0.67
10	89.960±1.00	75.361±0.65	79.803±0.69	78.394±0.99
11	-	91.851±0.83	93.638±0.55	87.752±0.96
12	-	98.603±0.98	99.507±0.80	96.266±0.89

*Each sample was analyzed in triplicate (n = 3)

Fig 6: Avg. Cumulative % Drug Release of N_1, N_2, N_3

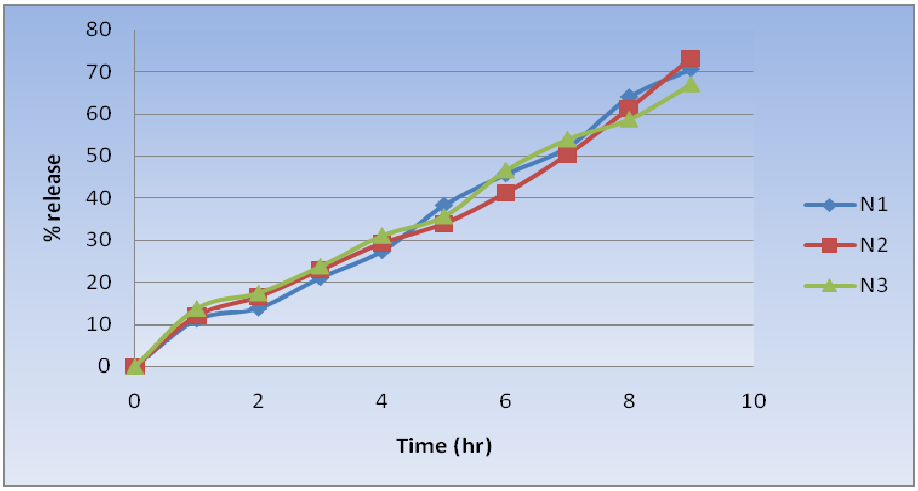


Fig 7: Avg. Cumulative % Drug Release of N_4, N_5, N_6

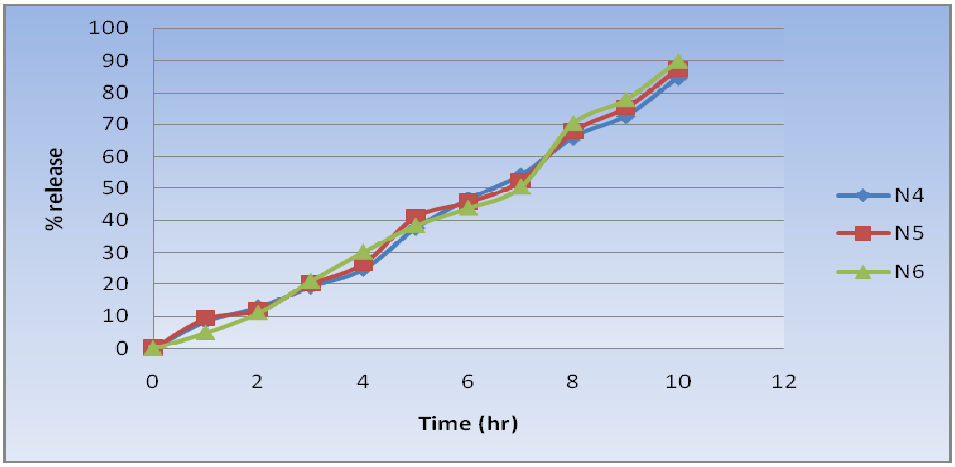


Fig 8: Avg. Cumulative % Drug Release of N_7, N_8, N_9

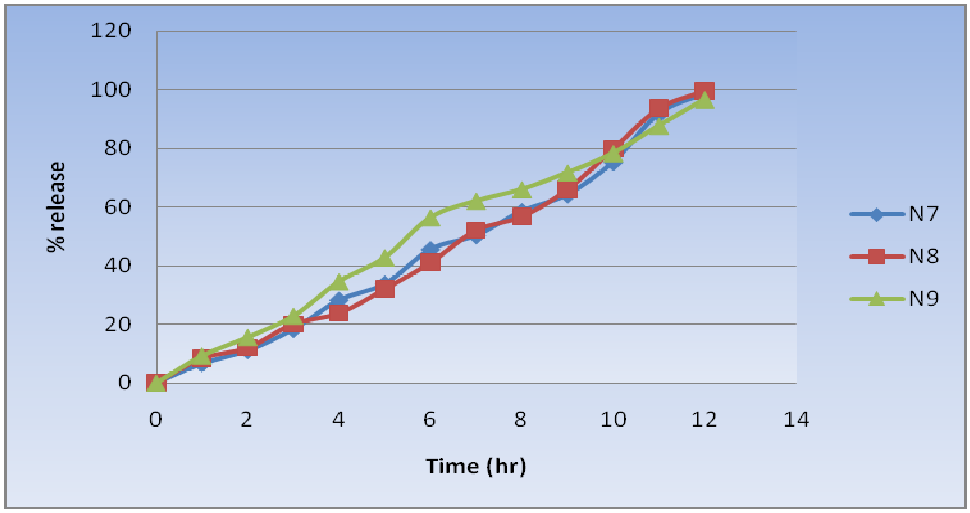


Table 19: Kinetic Models for Formulations Containing HPMC K 100M

Formulation	Zero order	1st order	Higuchi	Korsemeyer-Peppas	HIx.Crowell	n
N_1	0.9959	0.9643	0.9170	0.9810	0.9795	0.9063
N_2	0.9904	0.9425	0.9165	0.9816	0.9649	0.8223
N_3	0.9933	0.9833	0.9471	0.9826	0.9915	0.7697
N_4	0.9917	0.9144	0.8948	0.9909	0.9500	0.9855
N_5	0.9907	0.8994	0.8968	0.9871	0.9422	0.9735
N_6	0.9915	0.7876	0.8916	0.9952	0.9184	1.1767
N_7	0.9915	0.7876	0.8916	0.9964	0.8945	1.1107
N_8	0.9878	0.7461	0.8817	0.9889	0.8768	1.0521
N_9	0.9951	0.8943	0.9375	0.9959	0.9614	1.1479

In this case the drug release mechanism follows Zero order model and partially Peppas model. The N7 and N8 formulation found to be optimized as they remain float for 12 hrs and drug release is near about 100%. The derived correlation coefficient (r^2) indicated good fit of Zero order model suggesting that drug release is independent of the drug at the diffusion layer. Also Peppas model suggest that there could be more than one release mechanism involved in this case i.e. anomalous release mechanism.

Table 20: % drug release of P_7, P_8, R_7, R_8, S_7 and S_8 formulations

Time (Hrs.)	*Avg. Cumulative % Drug Release					
	P_7	**P_8**	**R_7**	**R_8**	**S_7**	**S_8**
1	3.047±0.98	2.153±0.92	15.554±0.65	18.235±0.45	12.874±0.77	11.087±0.91
2	6.637±0.25	8.419±0.44	21.895±0.47	24.590±0.74	19.200±0.29	18.296±0.82
3	11.141±0.76	12.933±0.66	27.376±0.78	30.980±0.32	34.666±0.99	21.971±0.22
4	13.883±0.32	16.578±0.19	33.781±1.09	37.404±0.54	31.056±0.57	29.239±0.88
5	20.213±0.56	22.030±0.71	41.114±0,87	45.523±0.23	39.267±0.48	40.121±0.49
6	23.898±0.23	27.511±0.55	54.740±0.59	58.408±0.44	47.523±0.68	45.702±0.67
7	29.390±0.43	33.916±0.89	63.974±0.36	70.342±0.48	56.718±0.29	53.099±0.71
8	37.590±0.78	40.356±0.81	83.978±0.72	86.807±0.93	61.494±0.84	65.003±0.87
9	44.050±0.65	47.723±0.33	96.051±0.75	98.002±0.80	68.976±0.96	71.612±0.73
10	56.798±0.94	55.130±0.45	-	-	85.432±0.33	86.295±0.79
11	68.722±0.69	67.045±0.32	-	-	95.723±0.55	97.271±0.39
12	78.030±0.60	79.916±0.75	-	-	-	-

Fig 9: Comparison graph of N7, N8, P7, P8.

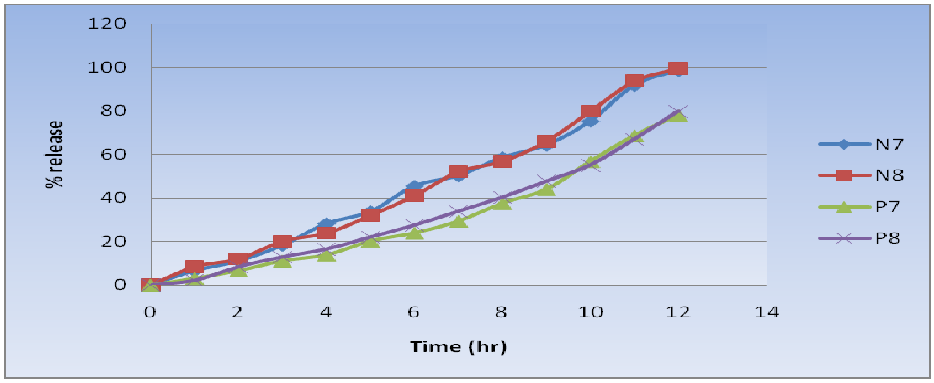


Fig 10: Comparison graph of N7, N8, R7, R8.

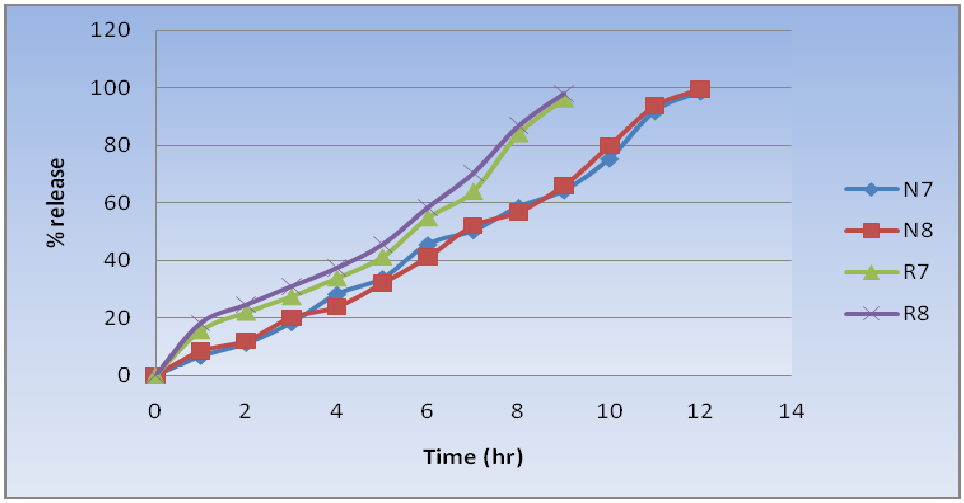
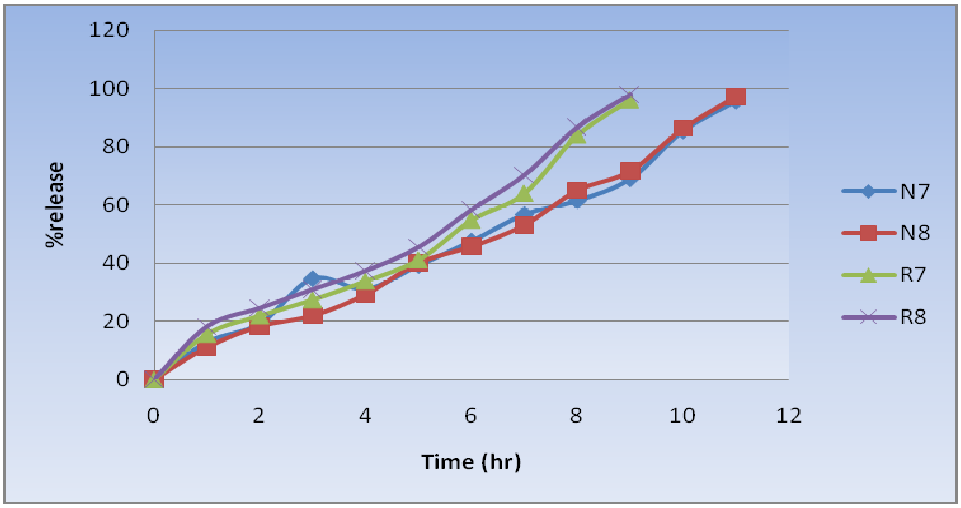


Fig 11: Comparison graph of S7, S8, R7, R8.



➢ Stability studies:

The selected formulations of Compression coated floating tablets i.e. N7, N8 were stored for 45 days at ambient conditions for assessing their stability. The tablets were evaluated for various at predetermined frequencies (fifteen days and thirty days, forty five days).

1. Drug content:

Table 21: Data for the drug contents of selected Dry coated tablets stored at ambient environmental conditions.

Formulations	**Drug content**		
	(After 15 days)	**(after 30 days)**	**(after 45 days)**
N7	98.21±0.82	97.94±0.22	97.22±0.37
N8	97.47±1.2	96.89±0.41	95.89±0.74

*each sample analyzed in triplicate (n=3)

2. Data for floating lag time for selected Dry coated tablets stored at ambient environmental conditions:

These two formulations were floating instantly and showing a little extra increase in floating lag time.

Table 22: Density values of selected floating matrix tablets stored at ambient environmental conditions

Formulations	**Floating lag time (sec)**		
	After 15 days	**After 30 days**	**After 45 days**
N7	94	97	99
N8	90	95	97

3. *In-vitro* dissolution studies:

The selected Compression coated floating tablet formulations were analyzed for the drug release after storage at ambient conditions for 45 days.

Table 23: *In-vitro* drug release from the of selected floating matrix tablets stored at ambient environmental conditions.

Time (hr)	*Cumulative % Drug Release			
	N7 (% drug release)		N8 (% drug release)	
	Before 45 days	After 45 days	Before 45 days	After 45 days
2	11.124±0.35	19.783±0.72	12.028±0.26	16.332±0.23
4	28.262±0.95	36.098±0.37	23.819±0.43	34.890±0.57
6	45.578±0.86	59.895±1.09	41.101±0.33	50.598±0.94
8	58.611±0.94	67.779±0.44	56.799±1.31	61.977±0.77
10	75.361±0.65	79.823±0.29	79.803±0.69	77.328±0.92
12	98.603±0.98	97.049±0.51	99.507±0.80	97.852±0.31

*Each formulation was analyzed in triplicate (n=3)

- **Summary:**

Floating drug delivery system is designed to prolong the residence time of the dosage form within the GI tract. It is the formulation of a drug and gel forming hydrocolloids meant to remain buoyant on stomach contents. This not only prolongs GI residence time but also increases absorptions. Drug dissolution and release, from the floating tablet/ capsule in gastrointestinal fluids; occur at the stomach, under fairly controlled condition. The retententive characteristics of the dosage forms in gastric content are most significant for drugs.

Rosiglitazone Maleate is an oral antidibetic agent, which acts primarily by increasing insulin sensitivity. It is effective only in the presence of insulin. It decreases insulin resistance at peripheral sites and in the liver. This results in insulin independent glucose disposal and

decreased hepatic glucose output. These effects are accomplished by selective binding at the Peroxiseme Prolifertative Activated Receptor-Gamma (PPAR-Ϋ), which is found in adipose tissue, skeletal muscle and the liver. As Rosiglitazone Maleate possessed short half life round 3.5 hours, low pKa and maximum solubility in buffered aqueous solution with pH 2.3, it was good candidate for floating drug delivery system

- **Conclusions:**

Friability, uniformity of content and weight of tablets complied with IP limits. Floating Lag Time of tablets depends on concentration of Sodium Bicarbonate, concentration & viscosity grade of HPMC. As concentration of Sodium Bicarbonate and HPMC increased floating lag time decreased. Use of high viscosity polymer can also decrease the floating lag time but, this use of high viscosity polymer increase the matrix integrity and resultant weight of tablets.

In dissolution studies optimized formulations that contained HPMC K100M float up to 12 hr and give a sustained release as desired. It was observed that by increasing concentration of hydrophobic meltable polymers release rate of drug was retarded. Compritol 888 found to be a choice of release retardant as compared to Precirol ATO 5.

Higher value of correlation co-efficient (r^2) in Multiple Regression Analysis clearly establish relationship between independent and dependant variable, delivered sound knowledge for further studies in future.

REFERENCES:

1) Chein Y W. *Novel Drug Delivery Systems*. 2nd Edn. Published by Marcel Dekker. Inc. New York. 1992; 50,pp1-139.
2) Aulton M E. *Pharmaceutics: The Science of Dosage Form Design*. 2nd Edn. Published by Livingstone C. Elsevier science Ltd. 2002; pp315-320.
3) Arora S, Ali J, Ahuja A, Khar R K, Baboota S. Floating drug delivery systems: a review. *AAPS PharmSciTech* 2005; 6 (3) Article 47.
4) Costa P, Lobo J M S. Modeling and comparison of dissolution profiles. *Eur J Pharm Sci.* 2001; 13,pp123-133.
5) Shimpi S, Chauhan B, Mahadik K R, Paradkar A. Preparation and evaluation of diltiazem hydrochloride-Gelucire43/01 floating granules prepared by melt granulation. *AAPS PharmSciTech.* 2004; 5: E43.
6) Dave B S, Amin A F, Patel M M. Gastroretentive drug delivery system of Ranitidine Hydrochloride: Formulation and *In vitro* evaluation. *AAPS PharmSciTech.* 2004; 5(2): Article 34.
7) Lachman L, Liberman H A, Kanig J L. *The Theory and Practice of Industrial Pharmacy*. Varghese publishing house. Mumbai. 3rd Edn. 1990; 296-302.
8) Indian Pharmacopoeia. Government of India. Ministry of Health and Family Welfare. Published by the controller of Publications. Delhi. Vol. II. 2007; 1674-1676.
9) Mukesh C.Gohel, Pavak R.Mehta, Rikita K. Dave and Nehal H. Bariya, A more relevant dissolution method for evaluation of floating drug delivery system Dissolution technologies, Nov.2004, 22-25.

10) Ziyaur Rehman, Mushir Ali, RK Khar, Design and evaluation of bilayer floating tablets of captopril, Acta Pharm., 56 (2006), 49–57.

11) Dasharath M. Patel, Natvarlal M. Patel, Nitesh N. Pandya, and Pranav D. Jogani, Gastroretentive drug delivery system of carbamazepine: formulation optimization using simplex lattice design: A technical note, AAPS PharmSciTech 2007; 8 (1) Article 11.

12) Ministry of Health and Welfare, Japan; Guidelines for the design and evaluation of oral prolonged release dosage form, March 11, 1988.

13) Viral F. Patel and Natavarlal M. Patel, Intragastric floating drug delivery system of Cefuroxime Axetil: In vitro eavaluation, AAPS PharmSciTech 2006; 7 (1) Article 17.

14) Mine O¨ zyazıcı , Evren H. Go¨kc¸e, Go¨khan Ertan, Release and Diffusional modelling of metronidazole lipid matrices, European J. of Pharm. and Biopharma. 2006, 63, 331-339.

15) C. De Brabander, C. Vervaet, J.P. Remon, Development and Evaluation of sustained release mini matrices prepared via hot melt extrusion, J.of controlled release, 2003, 89,235-247.

16) J. Goole , F. Vanderbist , K. Amighi , Development and evaluation of new multiple unit Levodopa sustained release floating dosage forms, Int.J.of Pharm. 2007, 334, 35-41.

17) Sasa Baumgartner , Julijana Kristl , Franc Vrecˇer , Polona Vodopivec ,
Bojan Zorko, Optimisation of floating matrix tablets and evaluation of their gastric residence time, Int.J.of Pharm, 2000, 195, 125-135.

18) Amnon Hoffman et.al. Pharmacokinetic and pharmacodynamic aspects of gastroretentive dosage forms, Int.J.of Pharm, 2004, 277, 141-153.

19) A.H. El-Kamel, M.S. Sokar, S.S. Al Gamal, V.F. Naggar , Preparation and Evaluation of ketoprofen floating oral delivery system, Int.J.of Pharm, 2001, 220, 13-21.

20) Yong-Dan Tang, Subbu S. Venkatraman, Freddy Y.C. Boey, Li-Wei Wang, Sustained release of hydrophobic and hydrophilic drugs from a floating dosage form, Int.J.of Pharm, 2007, 336, 159-165.

21) Quan Liu, Reza Fassihi, Zero-order delivery of a highly soluble, low dose drug alfuzosin hydrochloride via gastro retentive system, Int.J.of Pharm, 2008, 348, 27-34.

22) S.S.Patel, M.S.Patel, N.M.Patel, Flowability and Packability testing of directly compressible excipients, The Indian Pharmacist, May 2008, 65-69.

***For correspondence**

Mr.Deepak M.Deshpande

Pad.Dr.D.Y.Patil Institute of Pharmaceutical Sciences and Research,

Pimpri, Pune-411018; India.

Email: deepak.deshpande2424@gmail.com.