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SWELLABLE AND FLOATING GASTRORETENTIVE FORMULATION FOR SUSTAINED DELIVERY OF METFORMIN HCL

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Key words:

MH, BCS class III, narrow absorption window, MRT, release kinetics

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ABSTRACT: Metformin HCl (MH), is an oral anti-diabetic drug with less bioavailability, and a BCS class III, short plasma half-life as well as narrow absorption window. The objective of this research work is to obtain better delivery of MH to the upper part of GIT by increasing the mean residence time (MRT) in the stomach. For this, Gastroretentive swellable and floating sustained release tablets were prepared to prolong the gastric emptying that provides maximum drug at the site of absorption. Different formulations were prepared by wet granulation with the help of hydrophilic polymers like different grades of hyroxypropyl methyl cellulose (HPMC), xanthan gum (XG), sodium alginate (SA), carbopol 940; hydrophobic polymer like ethyl cellulose (EC); swelling agent like crospovidone (CP) and gas generating agent sodium bicarbonate (SBC). The formulations were evaluated for pre and post-compression characteristics; the formulation F5 gave the optimum result along with >24 hrs floating time and an in vitro release profile very near to desire release. Release kinetic studies showed that all batches followed Super case II transport mechanism and first order kinetics. The optimized formulation F5 also subjected to 40°C and 75% relative humidity for stability test and remained stable during the period of 3 months.

INTRODUCTION: Drug delivery systems (DDSs) are used for maximizing therapeutic index (TI) of the drug and also for the reduction in the side effects. The most preferred route is the oral route especially for the administration of therapeutic drugs because low cost of therapy and ease of administration leads to higher level of patient compliance [1]. Drug that are easily absorbed from the Gastrointestinal Tract (GIT) and having short half life are eliminated quickly from the systemic circulation. Frequent dosing of the drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained release (SR)-controlled released (CR) formulation is an attempt to release the drug slowly into GIT and maintain an effective drug concentration in the systemic circulation [2].

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The efficiency of DDS depends majorly on release of drug substance from the system and absorption of this moiety in GIT. Factor such as stability of the product in GIT, release rate absorption region and localization time of the drug substance induce variability on bioavailability of DDS. The transition time of the dosage form is an important parameter for a complete absorption of drug substance in GIT [3]. However, oral route has several physiological problems including an unpredictable gastric emptying rate that varies from person to person, a brief gastrointestinal (GI) transit time (8-12 h) and the existence of an absorption window in the upper small intestine for several drugs [4, 5].

Drugs that have narrow absorption window in the GIT will have poor absorption. For these drugs Gastroretentive drug delivery systems (GRDDSs) have been developed. Oral sustained release dosages form with prolonged residence time in the stomach helps in absorption of drugs which are less soluble or unstable in the alkaline pH and those which are absorbed from the upper GIT [6]. Several

approaches are currently used to retain the dosage form in the stomach. These include bioadhesive systems [7, 8], swellable and expanding systems [9], floating systems (low density systems) [4, 10, 11], high density systems [12, 13] and magnetic systems [6] have been developed.

To increase the gastric retention time (GRT), one should have a thorough knowledge about the physiology of GIT, and all the limitations should be well understood. The excellent floating system is effective only in the presence of sufficient fluid in the stomach; otherwise, buoyancy of the tablet may be hindered. This limitation can be overcome by using a combination of a floating system with other Gastroretentive approaches [6].

Patel *et al*. seems incomplete bioavailability of MH with CR dosage forms, probably due to the fact that passage of the CR single unit dosage forms from absorption region of the drug is faster than its release and most of the drug released at the colon where MH is poorly absorbed. Thus, they concluded that CR formulation only suitable for MH, if it should be a gastroretentive dosage form, which releases the drug slowly in the stomach for gradual absorption in the intestines. The slow but complete drug release in the stomach is expected to increase bioavailability of the drug as well its complete utilization which may results to, lower dose and GI side effects [14]. M. M. Varma *et al.* developed floating MH tablet with HPMC and/or carbopol and evaluated that tablet floated for 12 h and its release depended on % of polymer in the tablet [15].

Diabetes mellitus (DM) is a regulatory dysfunction of metabolism mainly characterized by chronic hyperglycemia. The two most common types are Type I diabetes (TIDM) and type II diabetes (TIIDM), of which TIIDM is responsible for approximately 90% of all cases of diabetes in the world. The global forward estimative is that at the year 2030, 366 million people will be sufferer from the disease [16].

MH is the first-line drug of choice for the treatment of type II diabetes, especially, in overweight and obese people and those having normal kidney function [17]. MH is an orally administered biguanide which does not induce hypoglycemia at any reasonable dose, unlike other antidiabetic drugs and hence it is called as antihyperglyacemic rather than a hypoglycemic drug [18]. MH is a white to off-white crystalline compound with molecular weight of 165.63 and melting point is 222ºC-226ºC. MH has absolute bioavailability 50 – 60 % with relatively short plasma half-life of 1.5 - 4.5 h [19-23]. It belongs to class III of Biopharmaceutical Classification System (BCS) having high water solubility and low permeability. For drugs that are highly water soluble, both hydrophilic and hydrophobic matrix systems are widely used in oral CR drug delivery to obtain a desirable drug release [24].

Many studies have reported that the oral absorption of MH is mainly confined to the small intestine, i.e. duodenum and jejunum and, to a lesser extent, ileum [25]. The objective of this research work is to obtain better delivery of MH to the stomach and the proximal parts of the small intestine by increasing the MRT in the stomach. For this, Gastroretentive floating and Swellable tablets were prepared to prolong the gastric emptying that provides maximum drug at the site of absorption.

MATERIALS AND METHODS:

Materials:

Metformin HCl (MH), hydrophilic polymers (HPMC K100LV, HPMC K4M, HPMC K15M, HPMC K100M, XG, SA, and Carbopol 940), hydrophobic polymer (EC), swelling agent (CP), Effervescent agents (SBC & Citric acid), binding agent (PVP K90) and lubricating agents (Aerosil and Magnesium stearate) were used and all materials were provided by Asian Pharmaceuticals Pvt. Ltd, Rupandehi, Nepal. Other reagents used during formulations were analytical grades.

Methods:

Preparation of tablets:

MH tablets were prepared by wet granulation method using hydrophilic polymer (different grades of HPMC, SA, XG and carbopol 940), hydrophobic polymer (EC), gas generating agents and swelling agent in each formulation. The compositions of different in formulations are listed in **Table 1**. All ingredients were passed through sieve no. 60 separately. EC was dissolved in methylene chloride

and bound MH only and dried. Then hydrophilic polymer, gas generating agent and swelling agent were mixed uniformly and granulated with hydroalcoholic solution of PVP K90. The wet mass was passed through sieve no. 18 and dried at 50ºC for 2 hrs. Dried granules were passed through sieve no. 24 and lubricated with aerosil and magnesium stearate. The granules were compressed with 21.1 mm biconvex one side scoring punch at hardness more than 10.00 kg/cm^2. Tablet weight was adjusted to 1450 mg.

TABLE 1: COMPOSITIONS OF SWELLABLE FLOATING METFORMIN HCL SR TABLET.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Metformin HCL	1000	1000	1000	1000	1000	1000	1000	1000	1000
HPMC K15M	137.75	--	--	--	--	--	--	72.52	--
HPMC K100M	--	137.75	167.35	--	--	--	94.85	94.85	94.85
Sodium Alginate	--	--	--	167.35	--	--	--	--	--
Xanthan Gum	--	--	--	--	167.35	--	72.52	--	--
Carbopol 940	--	--	--	--	--	167.35	--	--	72.52
Ethyl Cellulose	72.5	72.5	72.5	72.5	72.5	72.5	72.5	72.5	72.5
Crospovidone	58.0	65.25	43.5	43.5	43.5	43.5	43.5	43.5	43.5
Sodium Bicarbonate	101.5	101.5	101.5	101.5	101.5	101.5	101.5	101.5	101.5
PVP K90	65.85	58.6	50.75	50.75	50.75	50.75	50.75	50.75	50.75
Aerosil	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2
Magnesium Stearate	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2
Total (mg/tab)	1450.00	1450.00	1450.00	1450.00	1450.00	1450.00	1450.00	1450.00	1450.00

***In-vitro* evaluation of swellable floating SR tablets:**

Evaluation of powder blends:

The lubricated granules were evaluated for bulk density, tapped densilty, compressibility index (Carr's index) and Hausner's ratio.

Angle of Repose (Ɵ):

The frictional forces in a loose powder or granules can be measured by angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane [11].

The granules were allowed to flow through the funnel fixed to a stand at a definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

$$\theta = tan^{-1}(h|r) \text{..... (i)}$$

Where, θ = angle of repose, h = height of the heap, r = radius of the heap.

Compressibility index (Carr's index):

The flow ability of powder can be evaluated by comparing the bulk density (ρ_o) and tapped density (ρ_t) of powder and the rate at which it packed down [11]. Compressibility index was calculated by-

$$Compressibility\ index = \frac{\rho_t - \rho_o}{\rho_t} \times 100 \text{..... (ii)}$$

$$Hausner's\ ratio = \frac{\rho_t}{\rho_o} \text{ ..... (iii)}$$

Post-compression parameters evaluation:

Physical parameters of tablet:

The tablets were evaluated for weight variation test, hardness using Monsanto hardness tester, thickness using calibrated vernier caliper and friability by using Veego friabilator.

***In vitro* buoyancy studies/ floating test:**

In vitro buoyancy was determined by measuring floating lag time (FLT) and total duration of floating time (TFT). The tablets were placed in a 250 ml glass beaker containing 0.1N HCl. The time required for the tablet to rise to the surface of the media and float was determined as FLT. The duration in which the tablet remains floating was determined as TFT [26].

Swelling index/ water uptake studies

The swelling behavior of dosage unit can be measured either by studying its dimensional changes, weight gain, or water uptake. Water

uptake study of the dosage form was conducted by using USP dissolution apparatus-II in 900 ml of distilled water which was maintained at 37±0.5°C, rotated at 50 rpm. At selected regular intervals, the tablet was withdrawn and weighed. Percentages swelling of the tablets were expressed as percentage water uptake (%WU) [6].

$$\%WU = (W_t - W_o) \times 100/W_o \text{ ……..} \quad \text{(iv)}$$

Where, W_t is the weight of the swollen tablet, and W_o is the initial weight of the tablet.

Drug content:

Five tablets of each formulation were weighed and powdered. The quantity of powder equivalent to 100 mg of drug was transferred into 100 ml volumetric flask, it was shaken with 70 ml of distilled water and volume was adjusted to 100 ml with water. The solution was filtered, 1 ml form this filtrate was taken and diluted to 100 ml and absorbance was recorded by using U.V. spectrophotometer at 233nm [15].

***In vitro* dissolution studies:**

In vitro dissolution studies were studied by using USP dissolution apparatus-II, in 900 ml of 0.1 N HCl (pH 1.2) at 50 rpm and temperature was maintained at 37±0.5°C. A small aliquot of sample was withdrawn at predetermined time intervals 2, 4, 8, 12, 16 and 24 h. Every time, the dissolution medium was replaced with same volume of fresh 0.1 N HCl. Samples were filtered and diluted with fresh buffer and analyzed in UV spectrophotometer at its analytical wavelength 233 nm [27].

Drug Release Kinetics:

The drug release kinetics were studied by plotting the data obtained from the in vitro drug release in various kinetic models like zero-order, first-order, Higuchi's, and Hixson–Crowell model.

Zero-order (Eq. v) data is plotted as cumulative percentage drug released versus time.

$$C = K_o t \text{ ……..} \quad \textbf{(v)}$$

Where C is the concentration, K_o is the zero-order rate constant expressed as concentration/time, and t is time in hours.

First order (Eq. vi) is obtained by plotting log cumulative percentage drug released versus time.

$$Log\ C = Log\ C_o - kt/2.303 \text{ ……} \quad \textbf{(vi)}$$

Where C_0 is the initial concentration of the drug, k is the first-order rate constant, and t is the time.

As per Higuchi's (Eq. vii) data is plotted as cumulative percentage drug released versus square root of the time.

$$Q = Kt^{1/2} \text{……} \quad \textbf{(vii)}$$

Where K is the constant of the system, and t is the time.

The mechanism of drug release is evaluated by plotting the percentage of drug released versus log time according to Krosmeyer-Peppas equation (Eq. viii). Exponent n indicates the mechanism of drug release calculated through the slope of straight line.

$$\frac{M_T}{M_\infty} = Kt^n \text{……..} \quad \textbf{(viii)}$$

Where M_T/M_∞ is the fractional solute release, t is the release time; K is a constant characteristic of the drug/polymer system [6]. If the exponent n = 0.5 then the drug release follows the Fickian diffusion (diffusion controlled release); if 0.5< n< 1, then it is said to be non-Fickian or anomalous release; if n = 1 then drug release follows Case – II transport; if n ≥1, then drug release follows Super Case – II transport (swelling controlled release) [28].

Drug-Polymer Interaction Studies:

FTIR studies:

To investigate any possible interactions between the drug and the polymers used, the FTIR spectra of pure MH and its physical mixtures (1:1) with polymer (HPMC K100M, XG, Carbopol 940 and EC) were obtained using Shimadzu IRPrestige-21 FTIR. The samples were prepared using KBr and scanned from 4000 – 400 cm^{-1}. The change in spectra of the drug in the presence of polymer was investigated which indicates the physical interaction of drug molecule with the polymer [18].

Differential Scanning Calorimetric Studies:
Differential scanning calorimetry (DSC) (Perkin-Elmer Thermal Analysis) experiments were carried out for pure API (MH), and formulation F5 in order to characterize the physical state of the drug. Samples of formulation were placed in aluminium pans and hermitically sealed. The instrument was calibrated using indium as the standard. Samples were heated in sealed aluminium pans between 40°C and 350°C at a heating rate of 10°C/min under inert nitrogen purge gas at the rate of 20 mL/min [29].

Stability study:

To determine the change in *in vitro* release profile on storage, a short-term stability study of the optimal batch was performed at 40°C in a stability chamber with 75% relative humidity (RH). Samples were withdrawn after 3 months and evaluated for any change in *in vitro* drug release pattern [30].

RESULT AND DISCUSSION:

Incompatibility studies:

FTIR: MH and different polymers were subjected to incompatibility test with FTIR and the graph obtained from FTIR showed MH was compatible with each polymer.

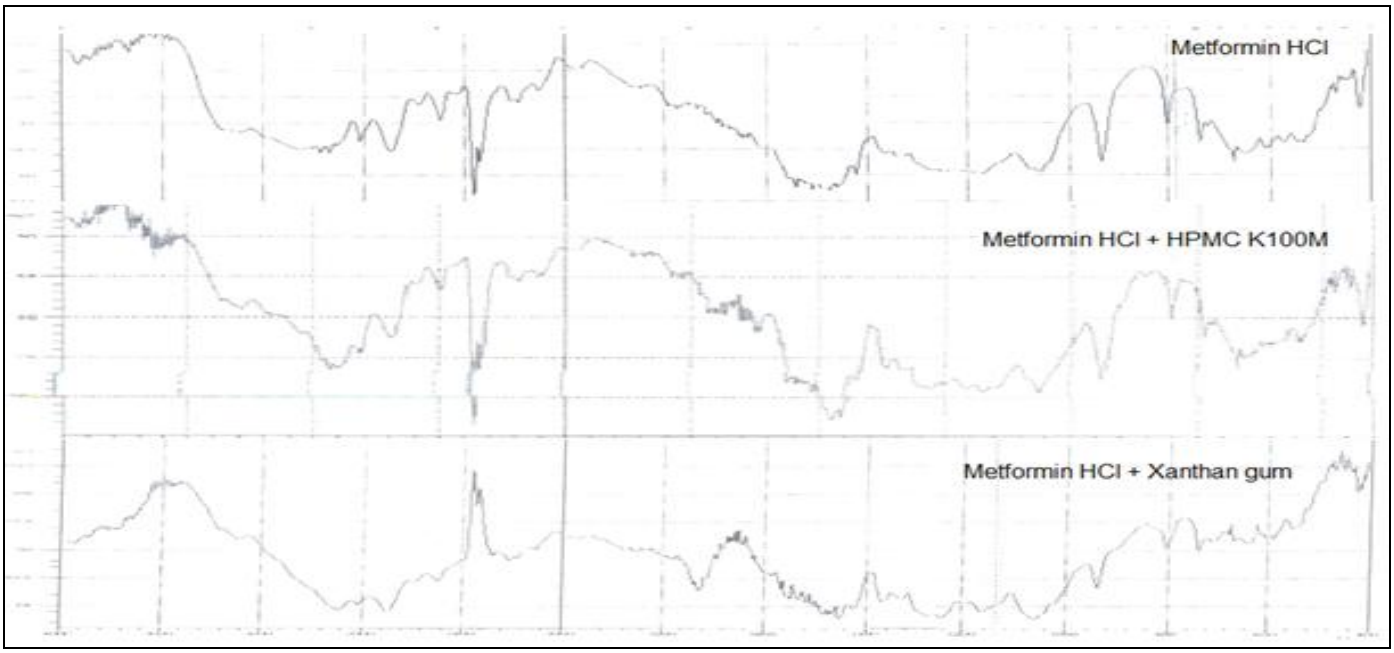

FIG. 1: FTIR GRAPH OF PURE METFORMIN HCL, METFORMIN HCL + XANTHAN GUM AND METFORMIN HCL+ HPMC K100M

The asymmetric N-H stretching of C=N-H group occurred around 3370 cm^{-1} and 3280 cm^{-1}; and symmetric N-H stretching of C=N-H group occurred around 3200 cm^{-1} and 3070 cm^{-1}; at 1550-1460 cm^{-1} a band of NH_2 stretching deformation was seen and also wagging of NH_2 was found around 940 cm^{-1} and 800 cm^{-1}. Peak around 1650 cm^{-1} - 1630 cm^{-1} was seen due to C=N stretching and peak around 620 cm^{-1}- 520 cm^{-1} were also seen because of CNC deformation. Peaks were observed around 1240 cm^{-1} – 1160 cm^{-1} due to C-N stretching of aliphatic amine. Asymmetric and symmetric stretching peaks of C-H of methyl group were seen at 2950 cm^{-1} – 2890 cm^{-1} and 2820 cm^{-1} respectively. The availability of observed functional group at respective wave number confirmed that used drug was MH and these function groups were also available in combination with other polymers at their respective wave numbers with little shift which confirmed that the used polymers were compatible with MH.

DSC:

DSC thermogram of pure MH and formulation F5 are shown in **Fig. 2**. The thermal curve of pure MH exhibited an initial flat profile followed by a sharp endothermic effect, with a T_{onset} at 236.64°C and a T_{peak} at 239.37°C and an associated fusion enthalpy of 315.545 J g^{-1}, indicative of its anhydrous crystalline state. However, characteristic peak of

MH was observed in DSC curves of the drug-loaded F5 at 231.33°C and two other peaks observed at 166.21°C and 252.45°C indicate polymers EC and XG used in the formulation F5. The observed curve of F5 suggesting that drug is molecularly dispersed in the polymer matrix and did not show any interactions.

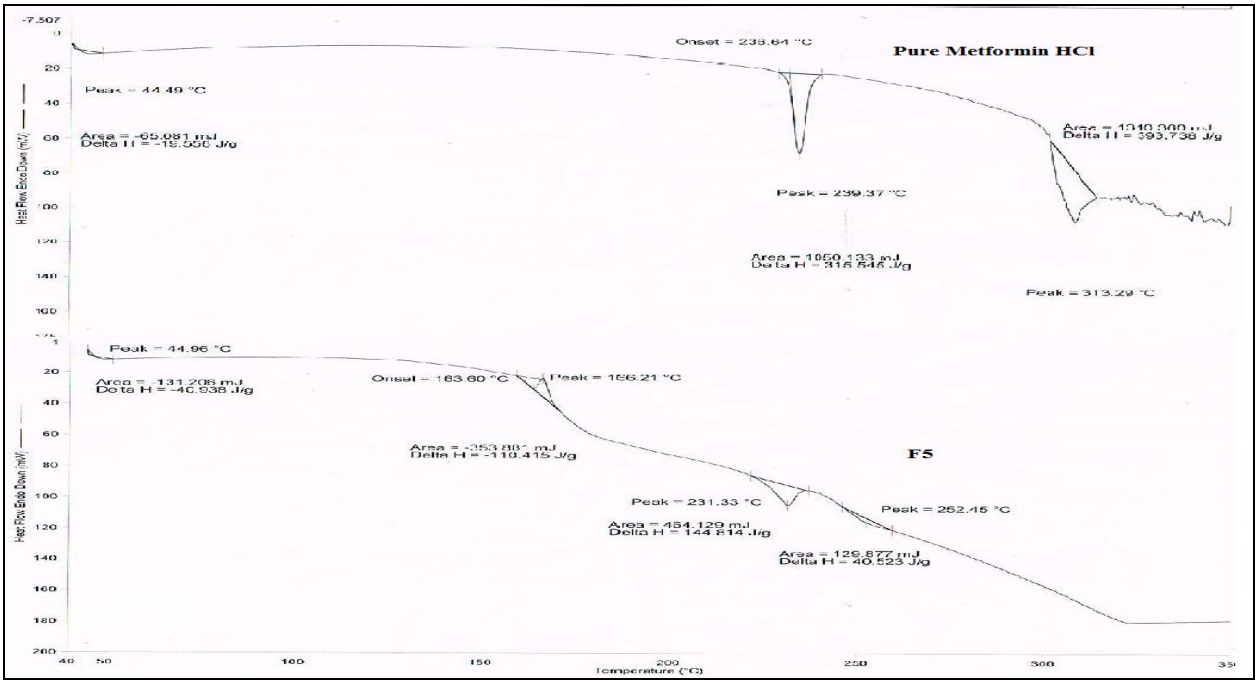

FIG. 2: DSC SPECTRUM OF PURE METFORMIN HCL AND OPTIMIZED FORMULATION F5.

Evaluation of pre-compressed granules:

The physical parameters of lubricated granules like Carr's index, Hausner's ratio and angle of repose of formulation F1 to F9 are within limit and mentioned at **Table 2**.

TABLE 2: VARIOUS PRE-COMPRESSION EVALUATED PARAMETERS

Batch No.	Bulk Density	Tapped Density	Carr's Index	Hausner's Ratio	Angle of repose
F1	0.54	0.66	18.18%	1.22	30.34^0
F2	0.526	0.664	20.78%	1.26	32.36^0
F3	0.500	0.666	24.92%	1.33	31.38^0
F4	0.588	0.714	17.64%	1.21	29.68^0
F5	0.555	0.666	16.66%	1.2	30.11^0
F6	0.558	0.67	16.71%	1.2	32.43^0
F7	0.545	0.668	18.41%	1.23	30.54^0
F8	0.520	0.662	21.45%	1.27	31.71^0
F9	0.522	0.658	20.66%	1.26	33.30^0

Formulation F5 had 16.66% Carr's index value which was best than other formulation, however, F1, F4 and F6 had also showed better value of Carr's index i.e. 18.18%, 17.64% and 1671% respectively. Apart from these Carr's index of other formulation were also good which indicate fair flow property of granules and did not require any kind of aid to enhance its flow characteristic, similarly F5 and F6 had same Hausner's ratio value i.e. 1.2 which also indicate fair flow characteristic but had different value of angle of repose i.e. 30.11º and 32.43º respectively. However, F4 showed best angle of repose i.e. 29.68º.

Post compression parameters:

The physical parameters of compressed swellable floating tablets like weight variation, thickness, hardness, friability of formulation F1 to F9 are mentioned at **Table 3**. The weight variation of all formulation are complies according to the USP.

Similarly thickness and diameters of tablets of all formulations were almost same and complies.

TABLE 3: VARIOUS POST-COMPRESSED EVALUATION PARAMETERS

Batch No.	Avg. Wt. (mg)	Thickness (mm)	Diameter (mm)	Hardness (Kg/cm2)	Friability (%)
F1	1465.85 ± 4.77	8.35 ± 0.043	21.1	15.5 ± 0.53	0.04%
F2	1453.45 ± 7.25	8.30 ± 0.017	21.1	16 ± 0.35	0.023%
F3	1448.3 ± 7.71	8.36 ± 0.024	21.1	13.3 ± 0.45	0.04%
F4	1453.8 ± 7.47	8.42 ± 0.017	21.1	12.0 ± 1.65	0.055%
F5	1451.1 ± 7.38	8.46 ± 0.023	21.1	10.0 ± 0.35	0.022%
F6	1451.25 ± 7.38	8.34 ± 0.061	21.1	12.7 ± 1.35	0.055%
F7	1451.1 ± 6.15	8.40 ± 0.029	21.1	11.0 ± 0.71	0.017%
F8	1452.0 ± 7.52	8.38 ± 0.043	21.1	14.6 ± 1.24	0.035%
F9	1450.45 ± 7.15	8.38 ± 0.029	21.1	15.0 ± 0.61	0.046%

Hardness:

The drug release profile as well as FLT also depend upon the hardness of the tablet, lower the hardness of the tablet decrease FLT and increase the drug release from the tablet. Therefore, hardness of the tablets was optimized not less than 10.00 Kg/cm^2. However, the formulations have almost same thickness and diameters, the variation in hardness might be due to the presence of different polymers. This indicates that formulations containing HPMC (F1, F2, F3, F8 and F9) showed excellent compressibility and thus provide tremendous hardness to the tablet. But the formulations containing XG (F5 and F7) did not provide much hardness as like HPMC, though formulation containing SA (F4) and carbopol 940 (F6) showed good hardness.

Friability:

Friability of all formulation were found less than 1% and thus all formulations were complies. This indicates all formulations could bear mechanical stress during handling. Among all formulations XG comprising formulations (F5 and F7) showed least friability i.e. 0.022% and 0.017%, however, formulation comprising SA (F4) and carbopol 940 (F6 and F9) showed maximum friability i.e. 0.055%, 0.055% and 0.046% respectively.

Buoyancy test/Floating test:

The buoyancy characteristics (FLT & TFT) of the swellable floating tablets are mentioned at **Table 4**. The buoyancy of the tablet was dependent on type of polymers and quantity of SBC. During research, quantity of SBC had been changed to various concentrations which results increase in the concentration of SBC decreases the FLT and also enhance the drug release rate. If excess quantity of SBC is used then excess CO_2 gas will generate that may burst the tablet. Therefore, concentration of SBC was optimized to 10.15% of the API (or 7.0% of the total formulation). Formulation F2 containing HPMC K100M showed FLT of 30 seconds but as the concentration of HPMC K100M was increased in F3 FLT had also increased to 2 min. 10 sec.

Similarly the formulation F5 containing XG showed FLT of 60 sec., however, the formulation F4 containing SA failed to float and also dissolved within an hour. Formulation F6 containing carbopol 940 showed FLT of 13 min along with poor tablet integrity and therefore could not sustain or remained floated for 24 hrs. Except carbopol 940 containing formulations F6 and F9, remaining all formulations floated for >24hrs.

TABLE 4: BUOYANCY CHARACTERISTICS OF DIFFERENT FORMULATIONS

Batch No.	FLT	TFT
F1	7 min. 15 sec.	14 hrs
F2	30 sec.	>24 hrs
F3	2 min. 10 sec.	>24 hrs
F4	Did not float	--
F5	60 sec.	>24 hrs
F6	13 min. (poor integrity)	20 hrs
F7	2 min. 34 sec.	>24 hrs
F8	4 min. 15 sec.	>24 hrs
F9	10 min. 42 sec.	24 hrs

FIG. 3: PICTURE OF OPTIMIZED FORMULATION F5 WITH ITS FLOATING BEHAVIOR

Swelling Index:

The percentage swelling obtained from water uptake studies of all formulations is shown in **Fig. 3**. As in the preliminary studies formulation with HPMC K100LV and HPMC K4M showed poor swelling and tablet integrity, thus such formulations with HPMC K100LV and HPMC K4M were not further evaluated for swellable and floating tablets. Similarly, formulation F4 containing SA also did not show any swelling property as tablet dissolved within an hour.

Formulation F6 and F9 containing carbopol 940 swelled up rapidly and disintegrated into fragments due to their poor tablet integrity. In the formulations CP was used as swelling agent. Formulation F8 containing HPMC K15M and HPMC K100M showed excellent swelling upto 166.39%, same as other formulations F3 (with increased quantity of HPMC K100M), F5 (XG) and F7 (HPMC K100M & XG) also showed good swelling effect as 138.21%, 154.10% and 145.39% respectively.

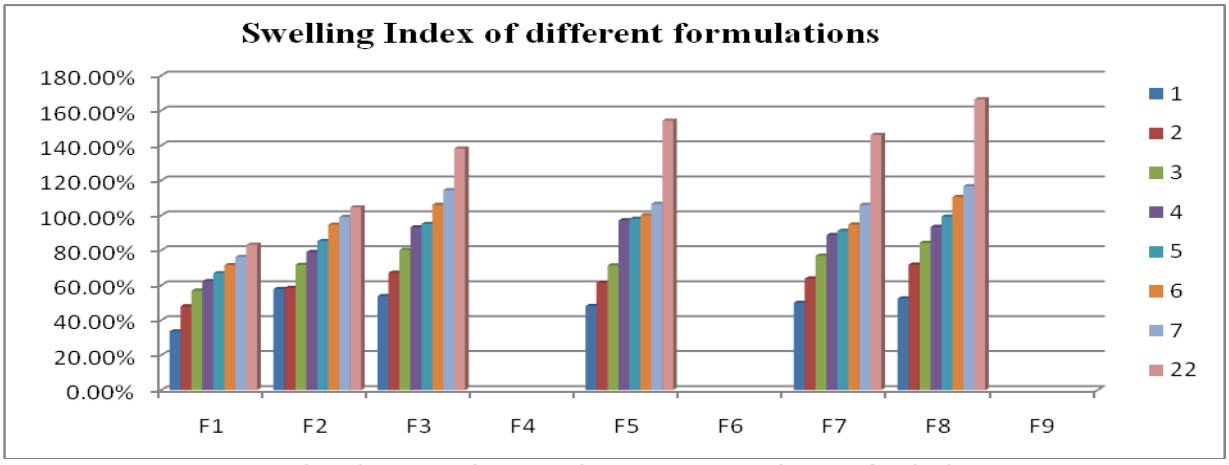

FIG. 4: SWELLING INDEX OF DIFFERENT FORMULATIONS

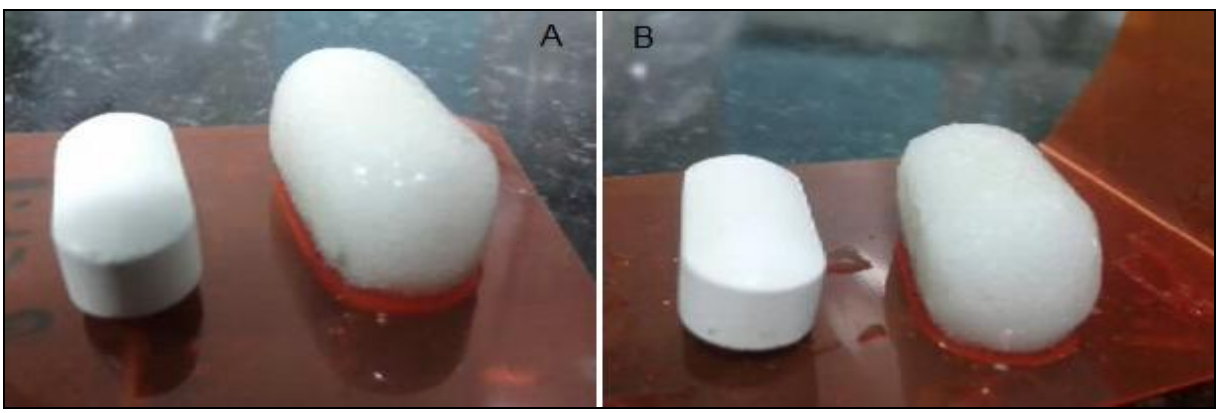

FIG. 5: PICTURE OF TWO FORMULATIONS IN THEIR DRY AND WET STATE A) F8 AND B) F5

Drug Content:

According to USP XXXII monograph, MH tablets contain NLT 95.0% and NMT 105.0% of MH and the obtained data indicated that all formulations were complied with USP. The obtained percentage value of drug content is mentioned at **Table 5**. The represented data showed that the MH can be uniformly mixed with all polymers.

TABLE 5: DRUG CONTENT OF DIFFERENT FORMULATIONS

Batch No.	F1	F2	F3	F4	F5	F6	F7	F8	F9
Assay	98.99%	99.246%	99.035%	97.19%	102.26%	101.001%	98.94%	101.83%	99.43%

***In vitro* dissolution studies:**

According to the USP and a patent article (EP1322158B1) of MH SR tablet, formulation containing 1000 mg drug should release up to 30% of drug within 2 hrs to provide loading dose. It was found during study that highly soluble MH could not be retarded by hydrophilic polymers alone; therefore, EC a hydrophobic polymer was introduced in the formulation which played a significant role to retard the drug release rate from the swellable floating SR tablet. The percentage drug release at various time intervals was mentioned at **Table 6**.

Formulation containing HPMC K15M (F1) released 46.398% ± 0.67% within 2 hrs and at the end of 12 hrs it showed release of drug was 98.238% ± 2.33%. The polymer HPMC K15M did not exist for 24 hrs might be due to its low viscosity and concentration. Unlike formulation F1, Formulation F2 and F3 containing HPMC K100M remained sustained and floated for >24 hrs due to its higher viscosity and released drug 39.483% ± 1.82% and 35.488% ± 0.69% within 2 hrs and 99.285% ± 1.62% and 98.93% ± 2.58% at the end of 24 hrs respectively. The drug release rate of F3 was more retarded than F2 as the concentration of HPMC K100M was increased in F3. Similarly, formulation F5 containing XG as polymer showed good release retardant as it released drug 36.431% ± 1.79% at 2 hrs and 98.392% ± 0.93% at the end of 24 hrs.

Formulation F4 and F6 containing SA and carbopol 940 as polymer did not show any sustaining effect as they released 93.776% ± 1.06% and 98.78% ± 1.51% at 2 hrs and also tablets did not exist more than 4 hrs due to their poor integrity. Formulation F7 and F8 containing HPMC K100M in combination to XG and HPMC K15M respectively also showed retardant effect but the synergistic effect of polymers was not as good as they provided individually. 46.179% ± 0.65%, 48.487% ± 0.5% and 85.167% ± 5.76% of drug was released from F7, F8 and F9 at first 2 hrs respectively and 97.09% ± 1.22% and 99.769% ± 0.84% of drug was released at 24 hrs form F7 and F8. While F9 showed its complete release up to 12 hrs i.e. 99.09% ± 1.23%.

TABLE 6: DRUG RELEASE PROFILE OF DIFFERENT FORMULATIONS

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
2 hrs	46.398 ± 0.67	39.483 ± 1.82	35.488 ± 0.69	93.776 ± 1.06	36.431 ± 1.79	98.78 ± 1.51	46.179 ± 0.65	48.487 ± 0.5	85.167 ± 5.76
4 hrs	66.778 ± 1.70	54.913 ± 0.82	53.45 ± 0.97	99.807 ± 2.14	53.083 ± 1.29	99.39 ± 0.06	65.112 ± 1.52	65.531 ± 0.74	90.003 ± 2.26
8 hrs	82.385 ± 4.80	72.876 ± 2.28	74.332 ± 1.11	--	72.85 ± 1.05	--	85.949 ± 1.58	85.151 ± 0.89	96.78 ± 0.31
12 hrs	98.238 ± 2.33	87.84 ± 0.55	85.404 ± 2.46	--	84.00 ± 1.02	--	90.977 ± 0.69	95.21 ± 0.55	99.09 ± 1.23
16 hrs	--	90.754 ± 1.35	93.46 ± 2.07	--	94.802 ± 1.63	--	94.64 ± 0.83	97.837 ± 0.24	--
24 hrs	--	99.285 ± 1.62	98.93 ± 2.58	--	98.392 ± 0.93	--	97.09 ± 1.22	99.769 ± 0.84	--

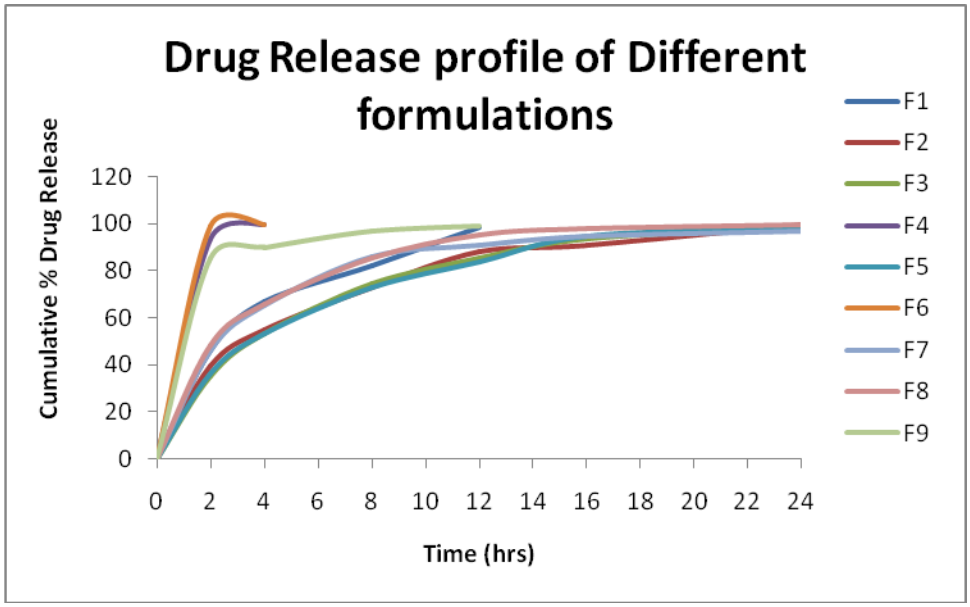

FIG. 6: *IN VITRO* DISSOLUTION PROFILE OF DIFFERENT FORMULATIONS

Drug release kinetics:

To analyze mechanism of drug release from the swellable floating SR tablet of MH, the *in-vitro* dissolution data were fitted to various mathematical models like Zero Order, First Order, Higuchi Model and Korsmeyer-Peppas Model. The results of the curve fitting into these above mentioned mathematical models are mentioned in **Table 7**. MH release followed First Order kinetics. The correlation coefficient (R^2) values were higher in First Order kinetics model than those in Zero Order model and Higuchi model. When the release data were analyzed as per Korsmeyer-Peppas equation, the release exponent "n" was found to be in the range of 1.1354 – 3.3205, which was more than 1, indicating Super Case II Transport. This indicated the releases of drug from all formulations followed the mechanism of swelling controlled release.

TABLE 7: CORRELATION COEFFICIENT (R^2) VALUES OF THE ANALYSIS OF RELEASE DATA AS PER VARIOUS KINETIC MODELS

Formulations	Zero Order R^2	First Order R^2	Higuchi Model R^2	Korsmeyer-Peppas Model	
				R^2	"n" Value
F1	0.8362	0.9369	0.9867	0.6821	1.5757
F2	0.7627	0.9613	0.9586	0.6631	1.1558
F3	0.7987	0.9907	0.9621	0.6827	1.1731
F4	0.7951	0.9959	0.9458	0.7602	3.3205
F5	0.7816	0.991	0.9641	0.6792	1.1685
F6	0.747	0.8498	0.9217	0.751	3.3175
F7	0.6406	0.9433	0.8884	0.6219	1.1354
F8	0.6534	0.9974	0.8976	0.621	1.1407
F9	0.4898	0.9336	0.7752	0.5711	1.5173

Formulation F1 containing HPMC K15M polymer was followed Higuchi model with R^2 value 0.9867 and 'n' value of 1.5757. Similarly F2 and F3 containing polymer HPMC K100M followed First order kinetics with R^2 value of 0.9613 and 0.9907 and 'n' value of 1.1558 and 1.1731 respectively. The 'n' value was higher in formulation containing HPMC K15M because of its low viscosity. As like F1, F4 and F6 containing SA and carbopol 940 polymers, also had highest 'n' value i.e. 3.3205 and 3.3175 respectively. It was because of their poor tablet integrity but F4 followed First order kinetic with R^2 value 0.9959 while F6 Followed Higuchi model with R^2 value 0.9217. As carbopol 940 had poor tablet integrity and HPMC K100M had better tablet integrity, their combination formulation F9 also showed higher 'n' value i.e. 1.5173 but F9 followed First order kinetic with R^2 value 0.9336.

Formulation F5 containing XG as polymer also had better tablet integrity due to which F5 had low 'n' value 1.1685 along with R^2 value 0.991 which also followed First order kinetics. Formulation F7 had least 'n' value as it comprised with both HPMC K100M and XG because of which its viscosity increased. F7 also followed First order kinetic with R^2 value 0.9433. Among all formulation F8 was very close to First order kinetic with maximum R^2 value 0.9974 and 'n' value 1.1407 which contained HPMC K15M and HPMC K100M both polymers.

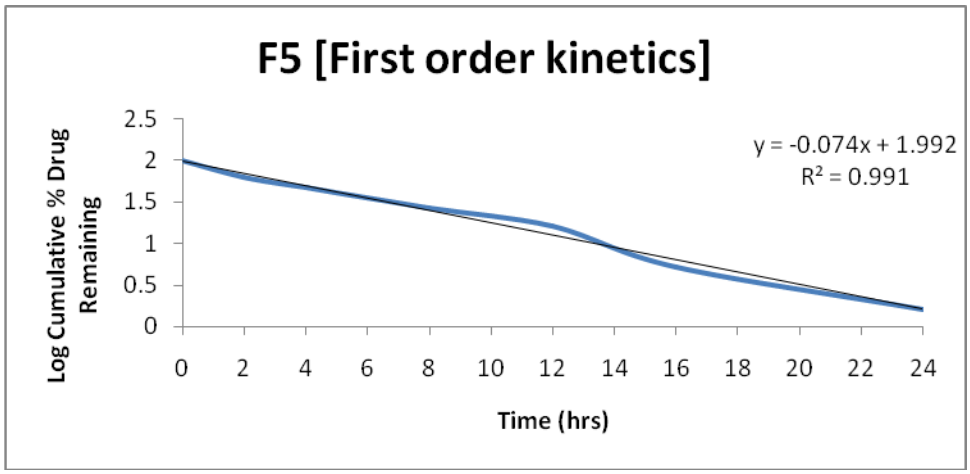

FIG. 7: FIRST ORDER RELEASE KINETICS OF OPTIMIZED FORMULATION F5.

Stability study:

Stability study was carried out by storing optimized formulation at 40 ± 2°C and 75 ± 5% RH for 3 months. At the end of the studies, samples were analyzed for the hardness, drug content, *in vitro* drug release, FLT and TFT. There was not any change in morphological condition during the stability study and also not any measurable change in the remaining parameter, as shown in **Table 8**. *In vitro* drug release was 97.83% ± 1.42% after 24 hrs.

TABLE 8: EVALUATION PARAMETERS OF TABLET AFTER 3 MONTHS STABILITY STUDY.

Batch No.	Hardness	Drug content	% Drug release	FLT	TFT
F5	11.0 ± 0.23	101.33%	97.83% ± 1.44% (at 24 hrs)	57 Sec.	>24 hrs

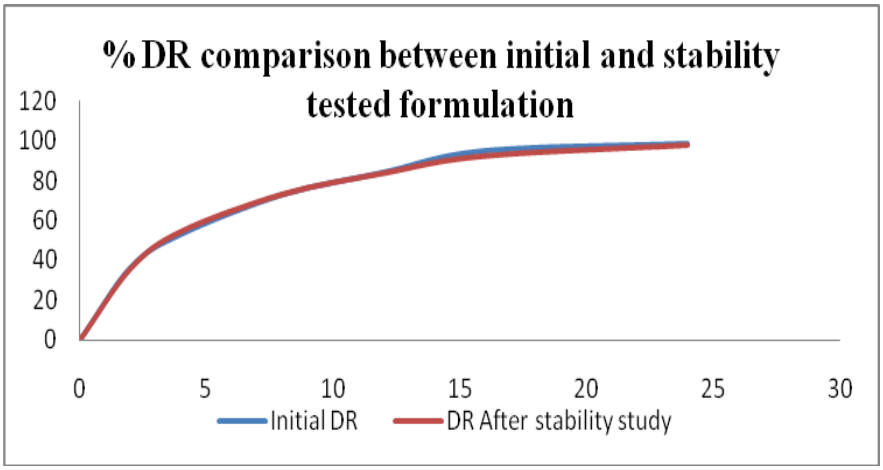

FIG. 8: COMPARISON BETWEEN INITIAL AND STABILITY STUDY OF % DRUG RELEASE

CONCLUSION: Although, formulation containing HPMC K100M (F2 & F3) and XG (F5) showed best retarding effect to the freely soluble drug as well as reduced FLT, but formulation containing both HPMC K100M and HPMC K15M (F8) did not provide a better synergistic effect neither for reduced FLT nor for drug release but it gave best swelling effect 166.39%.

The findings of the present study demonstrate that the higher concentration of hydrophilic polymer in combination with hydrophobic polymer may provide swellable floating SR MH tablets over 24 hrs. The optimized formulations (F5) having XG and EC had FLT 60 sec. as well as TFT >24 hrs, followed First Order kinetic model with R^2 value 0.991 and 'n' value 1.1685, and the mechanism of drug release was found to be Super Case II Transport. Swelling studies and *in vitro* floating studies indicated that the formulation was suitable for swellable and floating gastroretentive SR tablet.

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