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Formulation and Optimization of Expandable Gastro Retentive Floating Matrix Tablet of Mosapridecitrate Using Factorial Design

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ABSTRACT

Present study Formulation and Optimization of Expandable Gastro Retentive Floating Matrix Tablet of Mosapride Citrate using Factorial Design. Compatibility study of a drug substance with 4 classes of excipients, each at 3 levels. The measured response here is the degradation observed after 1 month at 50°C (50% RH) with the help of 3^4// 3^2 Factorial Design. Nine formulations of Mosapride Citrate was formulated using the non-aqueous wet granulation technique. Physiochemical properties of tablet and granules were examined prior compression to get a tablet. Tablets were characterized as drug content, percentage weight variation, thickness, Hardness, percentage friability and *in-vitro* drug release pattern and studied for 12 hours in USP Type-II apparatus using 900 ml Phosphate buffer at 37±0.5 °C. The dissolution release profile of the drug in a tablet was performed by various drug release kinetic modeling. F5 gave the best results for the critical parameters of release profile, FLT, FT, and matrix integrity and was also in compliance with the rest of the evaluation parameters. The dissolution profile showed that the formulation F5 followed the Korsmeyer Peppas kinetics of drug release as the „r" value for F5 is 0.9996 and the „n" value of 0.5612 indicates anomalous diffusion or non-fickian dissolution. Thus, the release from F5 is by anomalous diffusion and erosion. This study reveals successful application of Factorial design and optimization technique for the development of GRDDS and found to exhibit a satisfactory sustained release profile which may result in improved bioavailability.

INTRODUCTION

The oral bioavailability can be affected by limited absorption site. The development of modified release product like once daily dosing becomes difficult and hence the concept of absorption window has become popular [1].The Therapeutic window of many drugs is limited by their short circulating half-life and absorption from a defined segment of the intestine. These limitations lead to frequent dosing to achieve the required therapeutic effect [2]. This results in "pill burden" and consequently decreased patient compliance. The phenomenon of absorption via a limited part of GI tract has been termed as "narrow absorption window", and once the dosage form passes the absorption window, the drug will neither be bio-available nor effective. A rational approach to enhance bioavailability and improve pharmacokinetic and pharmacodynamic profiles is to retain the drug reservoir above its absorption area, i.e. in the stomach and to release the drug in a controlled manner so as to achieve zero order kinetics (i.e. oral infusion) for a prolonged period of time [3].

The need for gastro-retentive dosage forms (GRDDF) has led to extensive efforts in both academia and industry towards the development of such drug delivery systems [4].Another group of drugs that could benefit from retained and controlled release in the stomach are those meant for the treatment of pathologies located in the stomach, the duodenum or the small intestine.

Several approaches to extend the gastric retention time have been developed including an intra-gastric floating system, a high-density system, a mucoadhesive system, a magnetic system and a super-porous hydro-gel system. An important issue in developing these systems is how to avoid inter-unit and inter-subject variations in GI residence times[5]. Another problem is how to improve absorption of poorly absorbed drugs by using such systems. Drugs with narrow absorption windows in GI tract are particularly susceptible to variation in both bioavailability and time to achieve peak plasma levels. If successful, gastro-retentive controlled release formulations could offer a potential solution to the problem by offering a prolonged gastric residence time[6].

Mosapride citrate, a pro-kinetic agent which is indicated in the treatment of GERD, functional dyspepsia, diabetic gastro-pathy, etc., is an important drug in this therapy. In its conventional dosage, it is required to be taken 3 to 4 times a day. It has a narrow absorption window, and a short half-life of 1.4 to 2 hrs. Thus it was an ideal candidate for GRDDF. It is,

therefore, necessary to design a drug delivery system that will not only alleviate the shortcomings of conventional delivery vehicles but also deliver the drug at a continuous predetermined rate to the site of action for a prolonged period of time [7].

The present study is undertaken for the development of gastro retentive technology which will deliver the drug at a predetermined rate to achieve the required concentration at the site of action for a prolonged period of time. This technology ensures the maximum utilization of the drug with minimum side effects, enhanced patient compliance, minimize drug accumulation due to chronic dosing and obtain less potentiation or deduction in drug activity with chronic use [8].

MATERIALS AND METHODS:

MATERIALS:

Mosapride citrate was obtained from Cipla Dewas (Madhya Pradesh) India. Pregelatinised starch(PGS), Microcrystalline Cellulose, Lactose, Polyvinyl pyrrolidoneK30 (PVPK30), Carbopol were obtained as gift sample from BioChem Healthcare l Pvt Ltd Ujjain (M.P.)and all other chemicals and reagent were of analytical grade.

METHODS:

Method for Preparation

In the present study, we want to study the compatibility of a drug substance (Mosapride citrate dihydrate) with 4 classes of excipients, each at 3 levels [9]. The measured response here is the degradation observed after 1 month at 50^{o}C (50% RH).

3^4// 3^2 Factorial Design in coded variables

The symmetrical factors are arranged in 4 levels in Table 1 below. The assigned codes are 0, 1 and 2levels for the desired candidates. The design of the experiments for proto formulations are given as in Table 1 for a 3^4// 3^2 Fractional factorial design [10].

Table 1: Factorial Design using variables

S.No.	X1	X2	X3	X4	% Degradation Y	
1	PGS	Starch	None	GB	3.1	Y1
2	PGS	PVP K30	IM-OR	Stearic acid	4.3	Y2
3	PGS	Gelatin	Carbapol	MgS	3.7	Y3
4	MCC	Starch	IM-OR	MgS	2.2	Y4
5	MCC	PVP K30	Carbapol	GB	3.8	Y5
6	MCC	Gelatin	None	Stearic acid	5.2	Y6
7	Lactose	Starch	Carbapol	Stearic acid	4.7	Y7
8	Lactose	PVP K30	None	MgS	0.3	Y8
9	Lactose	Gelatin	IM-OR	GB	1.1	Y9

The negative effect is the reduction of the degradation activity. Based on results and interpretations (table 2) the following excipients were selected to carry out further studies of Mosapride citrate dihydrate GRDDS. Lactose as channel former or diluent. PVP K30 as a binder, IM- OR* as a polymer, Magnesium stearate as a lubricant.

*Four different premixes of IM- OR were used for preliminary formulations and one of them was selected for the final 3^2 full factorial design. The different mixes used are (table 2).

Table 2: Different Premixes of IM-OR Polymer

IM-OR-016	HPMC K100 + Talc
IM-OR-020	HPMC K4M + pregelatinised starch + Talc
IM-OR-021	HPMC K15M +pregelatinised Starch + Talc
IM-OR-023	HPMC K15M+HPMC K100M+Ammonium methacrylate copolymer

Preparation of Tablets

The expandable gastroretentive tablets were prepared by direct compression method. The proportionate composition of various ingredients (table1). The hydrophilic polymers such as HPMC K100M and Sodium Carboxymethyl Cellulose (SCMC) were used as hydrophilic matrix forming agents in each formulation according to the results of trial batches. Microcrystalline Cellulose (MC) was used as diluents. Magnesium Stearate (MS) and talc were used as the lubricant and as Glidant, respectively. All ingredients were mixed thoroughly, and tablets were prepared using a rotary tablet machine of 13 mm punch.

Standard Calibration curve of Mosapride citrate dihydrate in Acetate Buffer pH4

For UV scanning for λ–max of Mosapride citrate, about 20 mg of pure drug weighed and transferred to a 100 ml volumetric flask containing 100 ml of 0.1N HCl solution and sonification did until it gets completely dissolved and filtered by vacuum filter. Then one ml of this solution was diluted to 50ml with 0.1N HCl in a volumetric flask to obtain solution of 4mcg/ml and scanned for λ max. From the curve, peaks for the Mosapride citrate were found at 272nm shown in fig.1 below.

Table 3: Concentration of Mosapride Citrate vs Absorbance

Concentration in mcg/ml	Absorbance at 274nm, acetate buffer pH 4
0	0
4	0.08
10	0.22
16	0.33
20	0.43

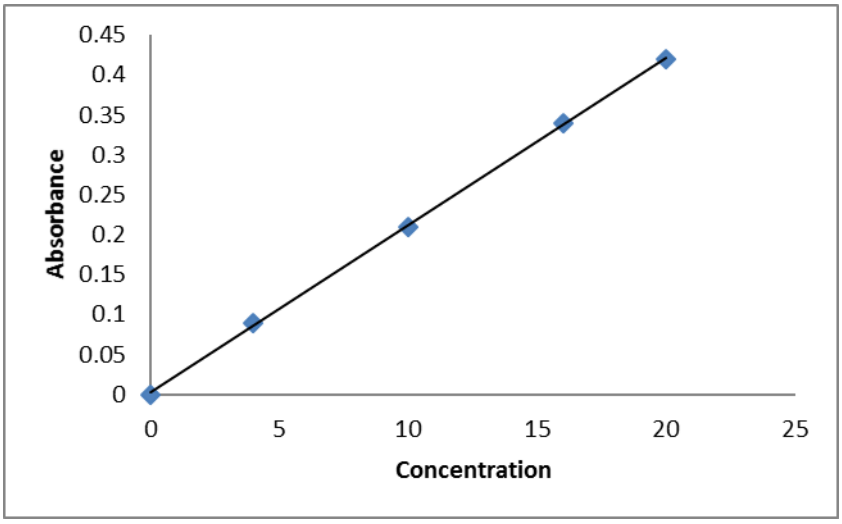

Figure 1: Calibration curve of Mosapride Citrate

Drug and Polymer Flow Properties

For this purpose, all the four polymer mixes viz. IM- OR- 016, IM- OR-020, IM- OR- 021 and IM- OR- 023 were used. A proportionate mixture of drug and each polymer (1:3) mix was prepared and subjected to tests for Bulk density, Tapped density, The Angle of Repose, Carr‟s index and Hausner ratio[11-13].

Bulk density

Apparent bulk density (Db) was determined by pouring the blend into a graduated cylinder. The bulk volume (Db) and weight of the powder (M) were determined. The bulk density (Db) was calculated using following formula. The sample of about 50cm^{3}of powder was carefully introduced into a 100ml graduated cylinder. The cylinder was dropped at 2-second intervals onto a hardwood surface three times from a height of 1 inch. The bulk density of each formulation was then obtained by dividing the weight of the sample in grams by the final volume in cm^3 of the sample contained in the cylinder [14-15]

$$\mathbf{D_b = M / Vp}$$

Where, Db = bulk density, M = weight of samples in grams, Vp = final volume of granules in cm^3

Tapped density

The tapped density was obtained by dividing the mass of a powder by the tapped volume in cm^3. The sample of about 50cm^{3}of powder, previously been passed through a standard sieve no.20, is carefully introduced into a 100ml graduated cylinder[16]. The cylinder was tapped at 2-second intervals onto a hardwood surface 100 times from a height of 1 inch. The tapped density of each formulation was then obtained by dividing the weight of the sample in grams by the final tapped volume in cm^{3}of the sample contained in the cylinder [17]. It was calculated by using equation given below:

$$\mathbf{D_o = M / Vp}$$

Where, D_o = bulk density, M = weight of the sample in grams, V_p = final tapped volume of granules in cm^3.

Carr's index

An indirect method of measuring powder flow from bulk densities was developed by Carr. The percentage compressibility of a powder was a direct measure of the potential powder arch or bridge strength and stability. Carr"s index of each formulation was calculated according to equation[18].

Percentage of Compressibility= Df - Do×100/ Df

Where, Df = Tapped or Consolidated bulk density, Do = Fluff or Poured bulk or bulk density.

Angle of repose

An angle of repose has been defined as the maximum angle possible between the surface of the pile of powder and horizontal plane. The angle of repose for the granules of each formulation was determined by the funnel method. The granules mass was allowed to flow out of the funnel orifice on a plane paper kept on the horizontal surface [19]. An angle of repose was calculated by substituting the values of the base radius R‟ and pile height „H‟ in the following equation:

$$\tan\text{Ø} = H / R$$

Therefore; $\text{Ø} = \tan^{-1}(H / R)$

Hausner ratio

The Hausner ratio is an indication of the compressibility of a powder. It is calculated by the formula,

$$H = P_T / P_B$$

Where, P_B is the freely settled bulk density of the powder, and P_T is the tapped density of the powder.The Hausner's ratio is frequently used as an indication of flowability of a powder. A Hausner ratio greater than 1.25 is considered to be an indication of poor flowability [20].

Table 4: Flow property analysis of Drug & Polymer mixes

Physical properties	**Mix 1**	**Mix 2**	**Mix 3**	**Mix 4**
Bulk density gm/ml	0.432±0.005	0.438±0.002	0.427±0.002	0.438±0.002
Tapped density gm/ml	0.642±0.004	0.649±0.005	0.638±0.005	0.631±0.003
Carr’s index (C.I.)	31.80±1.55	31.61±1.73	32.17±1.24	31.52±1.47
Hausner’s ratio (HR)	1.37±0.045	1.46±0.013	1.48 ±0.018	1.46 ±0.011
Angle of Repose	33°68‟±1.05	32°48‟±1.45	32°06‟±1.65	33°38‟±1.77
Observation	Poor flow	Poor flow	Poor flow	Poor flow

Note: All above readings are an average of 3 evaluations.

Tablets were formulated using these polymers and without drug and studied for floating behavior and tablet integrity. The polymer showing good matrix integrity and floating behavior were selected for further study. The effect of different polymers (table 5) on the floating behavior of tablets.

Table 5: Floating behavior of tablets with different Polymers

Sr. No.	Polymer	Polymer ratio	FLT* secs.	FT** hrs.	Matrix Integrity
1	IM-OR-016	100	35	18	+ +
2	IM-OR-020	100	52	29	+ -
3	IM-OR-021	100	46	17	+ -
4	IM-OR-023	100	26	25	+ +

FLT*: Floating Lag time, FT**: Floating time, + + Excellent; + - Good; - - Poor

From the above (table 5) the polymer IM-OR-023 shows very good results and thus this polymer was selected for 3^2 full factorial design for formulations [22-23]. The above study with a combination of polymers was not taken up based on the results obtained on individual study. Thus the desired polymer, binder, diluents, and lubricant were finalized and their compatibility with Mosapride Citrate Dihydrate was studied using IR spectroscopy. All the IR spectra of the drug with the excipients individually i.e. Drug & Polymer, DrugLactose, Drug & Binder, etc. and also the spectrum of Drug & all three excipients show no changes in the prominent peaks of the Drug. thus the drug is compatible with these excipients.

Selection of Process

From the results of flow properties of drug and excipients studied during preformulation work, it was decided to use the granulation process in which the non-aqueous granulation was selected considering the low solubility of the drug. Isopropyl alcohol was selected as the solvent for the binder.

Factorial Design for Preparation of floating Matrix Tablet

For the present work 3^2 factorial designs were selected. The two independent variables selected were the polymer IM-OR-023 and the binder Polyvinyl Pyrollidone K30 (PVP K30). The following Tables give the amount of variables in 3^2 factorial design batches; Experimental Design and the 9 formulations.

Table 6: Amount of variables in 32 Factorial Design

Coded Values	Actual values (%)	
	X1	X2
-1	37	2
0	42	4
1	47	6
X1=Polymer IM-OR-023, X2=Polyvinyl Pyrrolidone		

The(table 6)shows the amount of variables in 3^2 Factorial designs and gives the coded and actual values of the two variables i.e. the polymer IM-OR-023 and the binder PVP.

Table 7: Experimental Design

Formulation Code	Coded Values		Total weight of Tablet
	X1	X2	(mg)
F1	-1	-1	98
F2	-1	0	98
F3	-1	1	98
F4	0	-1	98
F5	0	0	98
F6	0	1	98
F7	1	-1	98
F8	1	0	98
F9	1	1	98

Experimental design resulting (table 7) from 3^2 factorial design from (table 6).It gives the codes for the 9 formulations with the coded values for the 2 variables X1(polymer) and X2(binder).The weight per core tablet was kept constant at 98mg by varying the weight per tablet of Lactose.

Table 8: Formulation of Factorial Design Batches

A. Uncoated Matrix

S.No.	Tablet ingredients (mg)	Formulation Code								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Mosapride citrate dihydrate Eq. to Mosapride citrate unhydrous	14.27	14.27	14.27	14.27	14.27	14.27	14.27	14.27	14.27
2	Lactose	40.37	38.41	36.46	35.47	33.53	31.57	30.57	27.62	27.66
3	Polymer (IM-OR-023)	36.27	36.27	36.26	41.17	41.15	41.15	46.07	47.06	47.06
4	Polyvinyl Pyrrolidone	1.98	3.93	5.89	1.97	3.93	5.89	1.97	3.93	5.89
5	Isopropyl Alcohol*	qs	qs	qs	qs	qs	qs	qs	qs	qs
6	Mosapride citrate dihydrate Eq. to Mosapride citrate unhydrous	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6
7	Colloidal Silicon Dioxide (Aerosil)	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
8	Talcum Powder	0.86	0.86	0.86	0.86	0.86	0.86	0.86	0.86	0.86
9	Magnesium Stearate	0.86	0.86	0.86	0.86	0.86	0.86	0.86	0.86	0.86
	Weight of Total Uncoated Tablet (mg)	98	98	98	98	98	98	98	98	98

B. Uncoated Matrix

S. No.	Tablet ingredients (mg)	Formulation Code								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Hydroxy Propyl Methyl Cellulose 15cps	0.63	0.63	0.63	0.63	0.63	0.63	0.63	0.63	0.63
2	Talcum powder	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45
3	Titanium dioxide	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6
4	Iron oxide Red	0.14	0.14	0.14	0.14	0.14	0.14	0.14	0.14	0.14
5	Polyethylene Glycol 2000	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15
6	Polyethylene Glycol 6000	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04
7	Isopropyl Alcohol*	qs	qs	qs	qs	qs	qs	qs	qs	qs
8	Methylene chloride*	qs	qs	qs	qs	qs	qs	qs	qs	qs
Weight of Total Coated Tablet (mg)		102	102	102	102	102	102	102	102	102

* Not present in final product

Table 8 gives details of the 9 formulations which were designed based on the pre-formulation studies and 3^2 factorial design. The quantity of Mosapride citrate dihydrate was designed to be added at two stages i.e. intra-granular and extra-granular (the extra-granular amount gives the initial release to achieve plasma levels and the intra-granular quantity gives sustained release of the drug) [24]. Non-aqueous granulation was selected considering the low solubility of the active principle. The amount of isopropyl alcohol used was also kept constant in all experiments.The coating formula selected was the same that was being used for the Mosapride immediate release formulation and thus compatibility was not a consideration. As per experience with the coating materials, it was noted that it had a negligible impact on the dissolution time as it gets dissolved in seconds, whereas the release profile was for 24hours.

Evaluation of lubricated Granules-Flow Properties

The prepared granules were evaluated for parameters like bulk density, tapped density, Carr‟s Index, Angle of Repose and Hausner`s Ratio using the methods discussed earlier.

The observations are recorded in Table 9.

Evaluation of Tablets

Appearance and Shape

The general appearance of the tablet includes the morphological characteristics like size, shape, color, odors, etc. Also, tablets may have lines, break-marks and may bear a symbol or other markings [25].

Uniformity of thickness and Diameter

The uniformity of the diameter and thickness were measured using Vernier Callipers. The average diameter and thickness of the tablets were recorded. The tablets pass the test if none of the individual diameter and thickness value falls outside the prescribed limits [26].

Hardness

Monsanto hardness tester was used to check the hardness of the tablets. The tablets are placed vertically, along with the length of their diameters, between the jaws of the tester, one at a time. The two jaws are placed under tension by spring and screw guage. By turning the screw the load is increased, and at cracking or collapse the applied pressure from the spring is measured in kg/cm^2. An average of 5 tablets is recorded. None of the individual tablets should fall out of the prescribed limit [25].

Weight Variation

To study weight variation 20 tablets of each formulation were individually weighed using an electronic balance, and the test was performed according to the official method. The test passes if average weight of 20 tablets is within ± 3% of the theoretical weight of one tablet and the weights of all the 20 individual tablets are within ±7.5% of the average weight [25]

Friability

Tablets were subjected to tumbling in Roche friability tester. Twenty tablets were weighed and tumbled in the friabilator at 25r.p.m. for 4 minutes [25]. The tablets were again weighed and percent friability was calculated by the following formula.

$$\% \text{ Friability} = W_o - W / W_o \times 100$$

Where W_o =Initial weight of 20 tablets, W = Final weight of 20 tablets

Drug content

Preparation of standard solution

Weigh accurately about 100 mg of Mosapride citrate dihydrate in a dry 50ml volumetric flask and to it add 20ml of Dimethylformamide (DMF) and make up the volume by DMF and shake. Pippete out 5ml of this solution to another dry 50ml volumetric flask and make up the volume with DMF and shake. Further, dilute 5ml of this solution to 50ml with DMF.

Preparation of test solution

Crush 5 tablets of Mosapride citrate dihydrate to a fine powder using mortar and pestle. Weigh sample equivalent to 20mg of Mosapride citrate dihydrate in a dry 100ml volumetric

flask, to its add 20ml of DMF and make the volume by DMF and shake and sonicate for 5 hours. Filter the solution. Pippete 5ml of filtrate to a 50ml volumetric flask and make the volume with DMF Measure the absorbance at about 274nm using a UV spectrophotometer and DMF as a blank [26].

***In-vitro* Buoyancy study**

All formulations were subjected to buoyancy test. Buoyancy test was done using USP type II apparatus at 50 r.p.m. maintained at 37± 0.5^{o}C. Tablets were placed in 900ml jars containing acetate buffer pH 4.0 as dissolution medium. The Floating Lag Time (FLT) and Floating Time (FT) were noted [27].

Swelling Study

The previous weighed tablets were placed in dissolution vessels containing Acetate buffer pH 4.0 at 37± 0.5o C. at 24hrs. The tablet and basket were blotted to remove excess water and then weighed [28-30]. The swelling index percent was calculated using the following equation

$$\textbf{Swelling Index \% = W24 – } W_0 \textbf{ / } W_0 \textbf{ × 100}$$

Where W_0 = initial weight of Tablet

W24 = Weight of Tablet at 24hrs.

Dissolution Studies

The *In-vitro* drug release studies of Mosapride Citrate floating matrix tablets were carried out using USP dissolution apparatus Type II (paddle method). The dissolution test was performed using 900ml of acetate buffer pH 4.0 as a medium at 100 rpm [31]. The temperature of the medium at 37± 0.5^{o}C and the study was carried out for 24 hrs. Samples of 5ml were withdrawn at the end of 1,2,4,8,12,16,20 and 24 hrs respectively and the withdrawn samples were replaced with fresh dissolution medium. The samples were filtered using whatman no. 41 filter paper. The absorbance of the samples was measured at 274nm using UV Visible spectrophotometer and using Acetate buffer pH 4.0 as blank. With the objective of selecting the final formulation three plots of Cumulative percent release versus time was done for the 3 groups of factorial design formulations viz. X1(-1), X1(0) and X1(1) i.e. Formulations.

Kinetics of drug Release

The dissolution profiles of all the batches were fitted to Zero order kinetics, First order kinetics, Higuchi(Matrix), Hixon-Crowell, Korsmeyer and Peppas to ascertain the kinetic modelling of drug release by using a PCP Disso Version 2.08 software [32]and the model with the higher correlation coefficient was considered to be the best model8.The observations are summarized (table 13).

RESULT AND DISCUSSION

Table 9: Flow properties of Lubricated granules

Formulation Code	Bulk Density (g/cm^2)	Tapped Density (g/cm^2)	Carr's Index %	Hausner's Ration	Angle of Repose Ø	Flowability
F1	0.425	0.534	20.42	1.26	$30^o22'$	Fair
F2	0.446	0.579	21.60	1.28	$28^o26'$	Good
F3	0.473	0.583	18.90	1.24	$30^o43'$	Fair
F4	0.452	0.584	22.74	1.29	$29^o52'$	Fair
F5	0.484	0.566	14.16	1.17	$25^o18'$	Very Good
F6	0.492	0.597	17.60	1.22	$28^o43'$	Good
F7	0.448	0.570	21.40	1.27	$27^o37'$	Fair
F8	0.462	0.588	21.40	1.27	$28^o49'$	Fair
F9	0.488	0.595	17.98	1.20	$26^o33'$	Good

Note: All above readings are an average of 3 readings.

Table 10: Evaluation of Tablets of Factorial Design Batches before Coating

Formulation	Appearance	Thickness (mm)	Hardness (Kg/cm^2)	Weight Variation	Friability (%)	Drug Content (%)
F1	Off-white, circular, 6mm, biconvex tab.	3.35±0.05	5.5±0.4	100±1.6	0.404	98.25±1.5
F2	Off white, circular, 6mm,biconvex tab.	3.37±0.04	5.8±0.6	99±1.8	0.513	98.73±1.2
F3	Off white, circular, 6mm,biconvex tab.	3.42±0.06	5.9±0.7	101±1.7	0.414	99.43±1.3
F4	Off-white, circular, 6mm, biconvex tab.	3.38±0.05	6.11±0.4	97±1.8	0.212	100.2±1.1
F5	Off-white, circular, 6mm, biconvex tab.	3.32±0.06	6.8±0.3	98±1.3	0.190	99.68±1.4
F6	Off-white, circular, 6mm, biconvex tab.	3.35±0.05	6.9±0.2	99±2.2	0.170	98.55±1.6
F7	Off-white, circular, 6mm, biconvex tab.	3.38±0.06	6.2±0.4	100±2.2	0.182	99.62±1.6
F8	Off-white, circular, 6mm, biconvex tab.	3.35±0.04	6.9±0.6	101±1.8	0.196	98.87±1.2
F9	Off-white, circular, 6mm, biconvex tab.	3.35±0.05	6.6±0.7	99±2.1	0.214	98.78±1.3

All values are expressed as mean ± SD, n=5# All values are expressed as mean ± SD, n=10 **

All values are expressed as mean ± SD, n=20 Where n is a number of tablets taken for the test.

Table11: Evaluation data of Factorial Design Batches

Formulation Code	Code Values		Floating lag time FLT secs ± SD	Swelling Index %	Total Floating Time (hours)	Tablet Integrity
	X_1	X_2				
F1	-1	-1	27±2.2	286.41±0.62	17	Poor
F2	-1	0	30±1.5	291.23±0.31	18	Poor
F3	-1	1	35±2.3	278.61±0.91	19	Fair
F4	0	-1	35±2.1	302.91±0.84	22	Good
F5	0	0	39±1.2	314.7±0.07	24	Excellent
F6	0	1	45± 2	306.72±0.27	24	Excellent
F7	1	-1	72±3	310.32±0.63	>24	Excellent
F8	1	0	81± 3	303.44±0.31	>24	Excellent
F9	1	1	90± 4	312.63±0.51	>24	Excellent

Table 12: Percentage Cumulative Drug Release of Formulations F1 to F9

Limits	Time (Hrs)	Percent Cumulative Drug Release								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
	0	0	0	0	0	0	0	0	0	0
Below 20%	1	23.32 ± 0.27	19.32 ± 0.33	15.12 ± 0.21	18.81 ± 0.29	17.24 ± 0.47	13.11 ± 0.31	18.62 ± 0.39	15.71 ± 0.27	12.70 ± 0.71
20-30%	2	29.54 ± 0.61	32.31 ± 0.44	22.45 ± 0.38	33.13 ± 0.31	23.72 ± 0.33	22.45 ± 0.49	27.17 ± 0.35	21.92 ± 0.21	22.92 ± 0.36
30-40%	4	43.25 ± 0.31	39.10 ± 0.51	32.21 ± 0.31	43.10 ± 0.43	34.22 ± 0.54	31.51 ± 0.16	41.77 ± 0.35	36.42 ± 0.39	31.20 ± 0.32
50-60%	8	51.60± 0.32	59.62 ± 0.51	55.12 ± 0.54	47.92 ± 0.55	62.20 ± 0.39	55.41 ± 0.49	47.76 ± 0.23	62.24 ± 0.58	52.15 ± 0.41
60-70%	12	60.12± 0.72	72.17 ± 0.72	72.40 ± 0.27	58.23 ± 0.47	71.30 ± 0.51	67.22 ± 0.27	62.21 ± 0.37	69.71 ± 0.55	74.29 ± 0.52
70-80%	16	70.36± 0.80	82.23 ± 0.44	77.15 ± 0.61	67.64 ± 0.51	84.51 ± 0.67	76.14 ± 0.61	72.20 ± 0.35	83.33 ± 0.11	80.23 ± 0.44
80-90%	20	80.22± 0.80	94.81 ± 0.34	91.61 ± 0.35	78.76 ± 0.57	97.24 ± 0.49	88.41 ± 0.70	82.31 ± 0.49	89.87 ± 0.17	91.72 ± 0.67
NLT 95%	24	NLT 95%	99.47 ± 0.61	97.42 ±0.50	88.84 ± 0.61	99.30 ± 0.78	97.83 ± 0.42	91.12 ± 0.77	95.39 ± 0.72	95.89 ± 0.18

Table13: Model fitting data of Floating Controlled Release Tablets of Mosapride

S. No.	Formulation	Models	r	n	k
1	F1	Zero order	0.8642		
		First order	0.9921		
		Matrix	0.9992	0.4716	20.0585
		Korsmeyer peppas	0.9978		
		Hixson Crowell	0.9782		
2	F2	Zero-order	0.8820		
		First order	0.9902		
		Matrix	0.9981	0.4839	18.4204
		Korsmeyer Peppas	0.9955		
		Hixson Crowell	0.9761		
3	F3	Zero-order	0.9292		
		First order	0.9911		
		Matrix	0.9972	0.5589	13.2276
		Korsmeyer Peppas	0.9984		
		Hixson Crowell	0.9826		
4	F4	Zero-order	0.8698		
		First order	0.9919		
		Matrix	0.9986	0.4939	19.0857
		Korsmeyer Peppas	0.9970		
		Hixson Crowell	0.9763		
5	F5	Zero-order	0.9261		
		First order	0.9902		
		Matrix	0.9978	0.5612	14.8229
		Korsmeyer Peppas	0.9996		
		Hixson Crowell	0.9881		
6	F6	Zero-order	0.9432		
		First order	0.9936		
		Matrix	0.9944	0.5937	12.3823
		Korsmeyer Peppas	0.9983		
		Hixson Crowell	0.9890		
7	F7	Zero-order	0.8627		
		First order	0.9902		
		Matrix	0.9971	0.5189	17.3822
		Korsmeyer Peppas	0.9970		
		Hixson Crowell	0.9681		
8	F8	Zero-order	0.9278		
		First order	0.9983		
		Matrix	0.9954	0.5894	13.9814
		Korsmeyer Peppas	0.9979		
		Hixson Crowell	0.9900		
9	F9	Zero-order	0.8971		
		First order	0.9663		
		Matrix	0.9942	0.5968	11.6853
		Korsmeyer Peppas	0.9938		
		Hixson Crowell	0.9577		

In the present study, a Floating Matrix Drug Delivery System of Mosapride Citrate (using dihydrate form) was formulated using the nonaqueous wet granulation technique and compression of the granules to result in a sustained release gastroretentive drug delivery system (GRDDS).The drug excipients compatibility was studied using a novel approach of $3^4//3^2$ Factorial design module details of which are described under 5.4, 5.5, and 5.6.The results of the compatibility study showed which excipients have the least or no interaction with the drug and the polymer and excipients were selected based on these observations. The selection of the polymer was done after evaluating the Floating time, Floating lag time and Matrix integrity on the tablets made by the 4 different polymer ready mixes, The tablets of the 9 formulations were prepared using a uniform process and with the same process parameters and all the 9 batches were evaluated for the different physical and chemical properties. Out of the 9 set of the results, the formulation F5 complied with all the parameters.

The dissolution profile showed that the formulation F5 followed the Korsmeyer Peppas kinetics of drug release as the „r" value for F5 is 0.9996 and the „n" value of 0.5612i.e. $0.5 < n < 1$, indicating anomalous diffusion or non-fickian diffusion. Thus, the release from F5 is by anomalous diffusion and erosion. This study reveals successful application of Factorial design and optimization technique for the development of GRDDS.

CONCLUSION

It can be concluded that a one daily GRDDS matrix tablet of Mosapride Citrate Dihydrate, having a short half-life was found to exhibit a satisfactory sustained release profile which may result in improved bioavailability, increased therapeutic efficacy and better patient compliance. The tablets prepared by the formulation F5 were selected for *In-vivo* studies and evaluation.

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