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Research Article

FORMULATION AND *IN VITRO* EVALUATION OF SIMETHICONE TABLETS AS GASRTO RETENTIVE DRUG DELIVERY SYSTEM

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ABSTARCT

The aim of the present study was to develop a delayed release formulation of Simethicone to maintain constant therapeutic levels of the drug for over 12 hrs. Various grades of HPMC polymers and accrual were employed as polymers. Simethicone dose was fixed at 62.5 mg. The total weight of the tablet was considered as 300 mg. Polymers were used in the concentration of 10, 20 and 30 mg concentration and accrual concentration used in the formulations were optimized according to the floating properties of the formulations. All the formulations were passed various physicochemical evaluation parameters like hardness, bulk density, friability, weight variation etc. and they were found to be within limits and also the drug and excipient studies showed that there is no incompatibility between pure drug and excipient. Whereas from the dissolution studies, it was evident that the optimized formulation (F_6) showed better and desired drug release pattern i.e.,98.17 % in 12 hours. The optimized formulation dissolution data were subjected to release kinetics; from the release kinetics data it was evident that the formulation followed Higuchi mechanism of drug release.

Keywords: Simethicone, Accrual, HPMC, Hardness, Bulk density, Friability, Weight variation, Incompatibility and Higuchi mechanism.

INTRODUCTION

The oral route is increasingly being used for the delivery of therapeutic agents because the low cost of the therapy and ease of administration lead to high levels of patient compliance. More than 50%of the Drug delivery systems available in the market are oral drug delivery systems[1]. Controlled-release drug delivery systems (CRDDS) provide drug release at a predetermined, predictable and controlled rate. Controlled-release drug delivery system is capable of achieving the benefits like maintenance of optimum therapeutic drug concentration in blood with predictable and reproducible release rates for extended time period [2], enhancement of activity of duration for short half-life drugs, elimination of side effects, reducing frequency of dosing and wastage of drugs, optimized therapy and better patient compliances[3].The successful development of oral controlled drug delivery systems requires an understanding of the three aspects of the system, namely.1.The physiochemical characteristics of the drug, 2.Anatomy and physiology of GIT and Characteristics of Dosage forms [4].Good fundamental understanding of the anatomic and physiological characteristics of the human GIT is required to modulate the gastrointestinal transit time of a drug through FDDS for maximal gastrointestinal absorption of drugs and site-specific delivery [5]. The aim of the study is to formulate and evaluate Simethicone non effervescent floating tablets using different polymers HPMC K100M, HPMC K15M, HPMC K4M and Magnesium Stearate, Talc in different ratios.

MATERIALS AND METHODS

Simethicone procured from Natco Laboratories Pvt Ltd, Hyderabad, and Telangana, India. HPMC K4M from Merck Pvt Ltd, Mumbai, India. HPMC K4M, HPMC K15M, K100M and Talc from SD fine chemical, Mumbai, India. Magnesium stearate and Micro crystalline cellulose from Heligent Pharma, Mumbai, India and other chemicals were consumed of laboratory grade.

Determination of Absorption maxima: A solution containing the concentration 10 µg/ ml drug was prepared in 0.1N HCl UV spectrum was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400 [6].

Preparation of calibration curve:100mg of the Simethicone pure drug was dissolved in 100ml of 0.1N HCl (stock solution)10ml of solution was taken and make up with100ml of 0.1N HCl (100µg/ml). From this 10ml was taken and make up with 100 ml of 0.1N HCl (10µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain a series of dilutions Containing 1,2,3,4 and 5µg/ml of Simethicone per ml of solution. The absorbance of the above dilutions was measured at 266 nm by using UV-Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of the correlation coefficient (R^2) which determined by least-square linear regression analysis [7].

Drug – excipient compatibility studies

Fourier transform infrared (FTIR) spectroscopy: The physical properties of the physical mixture were compared with those of plain drug. Samples were mixed thoroughly with 100mg

potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resulting disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the IR spectrum was recorded from 3500 cm to 500 cm. The resultant spectrum was compared for any spectrum changes [8].

Pre formulation studies

Angle of repose: The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully poured through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula[9]:

$$\tan\theta = h / r \quad \tan\theta = \text{Angle of repose}$$

h = Height of the cone, r = Radius of the cone base

Bulk density: 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read.The bulk density was calculated using the formula[10]:

$$\text{Bulk Density} = M / V_o$$

Where, M = weight of the sample, V_o = apparent volume of powder

Tapped density: After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until the difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula[11]:

$$\text{Tap} = M / V$$

Where, Tap= Tapped Density, M = Weight of the sample, V= Tapped volume of powder

Measures of powder compressibility: It is determined from the bulk and tapped densities. As such, it is measures of the relative importance of inter particulate interactions. In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter particle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index, which is calculated using the following formulas[12]:

$$\text{Carr's Index} = [(\text{tap} - b) / \text{tap}] \times 100$$

Where, b = Bulk Density, Tap = Tapped Density

Formulation of tablets: All the formulations were prepared by direct compression. The compressions of different formulations are given in Table 1. The tablets were prepared as per the procedure given below and the aim is to prolong the release of Simethicone. Total weight of the tablet was considered as 500mg.Simethicone and all other ingredients were individually passed through sieve no ≠ 60. All the ingredients were mixed thoroughly by triturating up to 15 min. The powder mixture was lubricated with talc. The tablets were prepared by using direct compression method [13].

Optimization of accrual concentration: Accrual was employed as effervescent gas generating agent. It helps the formulation to float. Various concentrations of accrual were employed; floating lag time and floating duration were observed. Based on that the concentration of accrual was finalized and preceded for further formulations as shown in table 1.

Evaluation of tablets

Weight variation test: Twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage. The mean and deviation was determined. The percent deviation was calculated using the following formula[14].

$$\% \text{ Deviation} = (\text{Individual weight} - \text{Average weight} / \text{Average weight}) \times 100$$

Hardness: For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation[15].

Thickness: Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in reproducing appearance. Average thickness of the core and coated tablets is calculated and presented with deviation[16].

Friability: It measures of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Preweighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were re weighed, loss in the weight of the tablet is the measure of friability and is expressed in percentage as[17]:

$$\% \text{ Friability} = [(W1-W2) / W] \times 100$$

Where, W1 = Initial weight of three tablets, W2 = Weight of the three tablets after testing

Determination of drug content: Both compression-coated tablets were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of Simethicone were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with water. The solution was suitably diluted and the absorption was determined by UV – Visible spectrophotometer. The drug concentration was calculated from the calibration curve[18].

In *vitro* buoyancy studies: The tablets were placed in a 100ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined at the floating lag time (FLT) and duration of time the tablet constantly floats on the dissolution medium was noted as Total Floating Time respectively (TFT) [19].

***In vitro* drug release studies:** 900ml 0f 0.1 HCl was placed on the vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c $\pm$ 0.5°c. The tablet was placed in the vessel and the vessel was covered the apparatus was operated for 12 hours and then

the medium 0.1 N HCl was taken and the process was continued from 0 to 12 hrs at 50 rpm. At defined time intervals of 5 ml of the receptor fluid were withdrawn, filtered and again 5ml receptor fluid was replaced. Suitable dilutions were done with receptor fluid and analyzed by spectrophotometrically at 244 nm using UV-spectrophotometer[20].

Application of release rate kinetics to dissolution data[21-25]: Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted in zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Zero order release rate kinetics: To study the zero–order release kinetics the release rate data are fitted to the following equation.

$$F = K_o t$$

Where, 'F' is the drug release at time't', and 'K_o' is the zero order release rate constant. The plot of % drug release versus time is linear.

First order release rate kinetics: The release rate data are fitted to the following equation

$$\text{Log } (100\text{-}F) = kt$$

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

Higuchi release model: To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

$$F = k\, t_{1/2}$$

Where, 'k' is the Higuchi constant.

In Higuchi model, a plot of % drug release versus the square root of time is linear.

Korsmeyer and Peppas release model: The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer- Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

$$M_t / M_\infty = K\, t^n$$

Where, M_t / M_∞ is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case I I transport), n=1; and for supercase II transport, n > 1. In this model, a plot of log (M_t / M_∞) versus log (time) is linear.

Hixson-Crowell release model: Hixson-Crowell model describes the release of drugs from an insoluble matrix through mainly erosion. (Where there is a change in surface area and diameter of particles or tablets).

$$(100\text{-}Q_t)^{1/3} = 100^{1/3} - K_{HC}.t$$

Where, k is the Hixson-Crowell rate constant.

Table 1: Formulation composition for floating tablets

Formulation Code	Simethicone	HPMC K4M	HPMC K15M	HPMC K100M	Accrual	Mag. Stearate	Talc	MCC
F1	62.5	10	-----	-----	120	6	6	QS
F2	62.5	20	-----	-----	120	6	6	QS
F3	62.5	30	-----	-----	120	6	6	QS
F4	62.5	-----	10	-----	120	6	6	QS
F5	62.5	-----	20	-----	120	6	6	QS
F6	62.5	-----	30	-----	120	6	6	QS
F7	62.5	-----	-----	10	120	6	6	QS
F8	62.5	-----	-----	20	120	6	6	QS
F9	62.5	-----	-----	30	120	6	6	QS

All the quantities were in mg, Total weight is 300 mg.

Table 2: Observations for graph of Simethicone in 0.1N HCl (244 nm)

Concentration	Absorbance
0	0
0.1	0.038
0.2	0.14
0.3	0.199
0.4	0.289
0.5	0.385
0.60	0.459

Table 3: Pre-formulation parameters of blend

Formulation Code	Angle of Repose	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Index (%)	Hausner's Ratio
F1	26.01	0.49±0.07	0.57±0.01	16.21±0.06	0.86±0.06
F2	24.8	0.56±0.06	0.62±0.05	16.87±0.05	0.98±0.05
F3	22.74	0.52±0.03	0.68±0.07	17.11±0.01	0.64±0.03
F4	25.33	0.54±0.04	0.64±0.08	17.67±0.08	1.12±0.04
F5	26.24	0.53±0.06	0.67±0.03	16.92±0.04	1.2±0.08
F6	26.12	0.56±0.05	0.66±0.06	17.65±0.09	1.06±0.09
F7	27.08	0.58±0.06	0.69±0.04	16.43±0.05	0.76±0.03
F8	25.12	0.48±0.05	0.57±0.02	17.97±0.02	1.15±0.09
F9	25.45	0.54±0.08	0.62±0.03	17.54±0.09	1.17±0.02

Table 4: Quality Control parameters for tablets

Formulation code	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Floating lag time (min)
F1	302.5	4.5	0.52	4.8	99.76	4.0
F2	305.4	4.2	0.54	4.9	99.45	4.2
F3	298.6	4.4	0.51	4.9	99.34	4.5
F4	300.6	4.5	0.55	4.9	99.87	4.1
F5	299.4	4.4	0.56	4.7	99.14	4.0
F6	300.7	4.2	0.45	4.5	98.56	4.4
F7	302.3	4.1	0.51	4.4	98.42	4.5
F8	301.2	4.3	0.49	4.7	99.65	4.6
F9	308.3	4.5	0.55	4.6	99.12	4.7

Table 5: Dissolution Data of Simethicone Tablets

Time(h)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	30.22	33.26	25.02	59.21	24.66	15.12	51.10	19.80	14.54
2	69.88	70.65	75.55	97.52	38.44	22.05	97.73	31.58	32.23
3	96.25	94.82	98.69		72.85	31.29		59.28	44.85
4	-	-	-	-	96.66	42.83	-	71.01	51.31
5	-	-	-	-	-	59.26	-	98.06	60.86
6	-	-	-	-	-	61.70	-	-	78.98
7	-	-	-	-	-	74.33	-	-	94.26
8	-	-	-	-	-	87.26	-	-	-
9	-	-	-	-	-	98.17	-	-	-

Table 6: Release kinetics data for optimized formulation (F6)

Cumulative (%) release Q	Time (T)	Log (%) release	Log T	Log (%) remain	Cumulative % release / t)	1/Cum% release	Peppas log Q/100	% Drug Remaining
0	0			2.00	0	0	0	100
19.62	0.5	1.293	-0.301	1.905	39.240	0.0510	-0.707	80.38
27.86	1	1.445	0.000	1.858	27.860	0.0359	-0.555	72.14
36.35	2	1.561	0.301	1.804	18.175	0.0275	-0.439	63.65
41.45	3	1.618	0.477	1.768	13.817	0.0241	-0.382	58.55
47.8	4	1.679	0.602	1.718	11.950	0.0209	-0.321	52.2
55.25	5	1.742	0.699	1.651	11.050	0.0181	-0.258	44.75
60.24	6	1.780	0.778	1.599	10.040	0.0166	-0.220	39.76
66.73	7	1.824	0.845	1.522	9.533	0.0150	-0.176	33.27
71.34	8	1.853	0.903	1.457	8.918	0.0140	-0.147	28.66
78.52	9	1.895	0.954	1.332	8.724	0.0127	-0.105	21.48
80.17	10	1.904	1.000	1.297	8.017	0.0125	-0.096	19.83
88.75	11	1.948	1.041	1.051	8.068	0.0113	-0.052	11.25
96.33	12	1.984	1.079	0.565	8.028	0.0104	-0.016	3.67

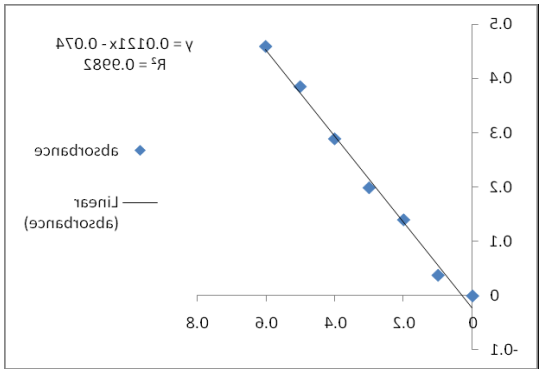

Figure 1: Standard graph of Simethicone in 0.1N HCl

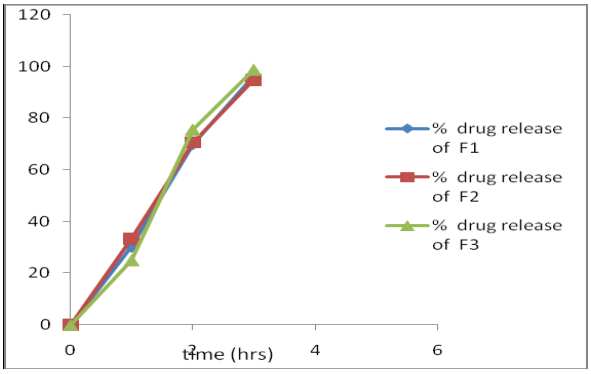

Figure 2: Dissolution profiles of formulations F1-F3

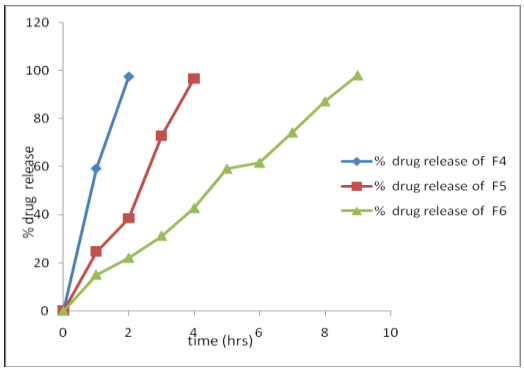

Figure 3: Dissolution profiles of formulations F4-F6

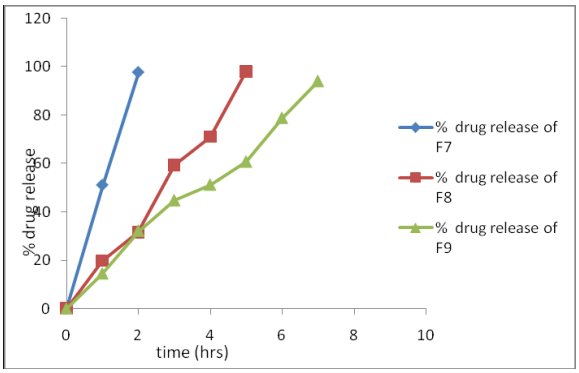

Figure 4: Dissolution profiles of formulations F7-F9

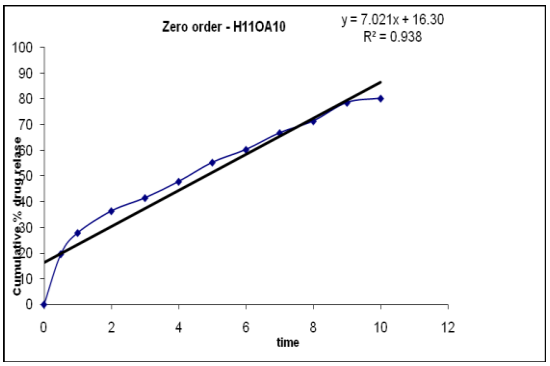

Figure 5: Zero order release kinetics graph

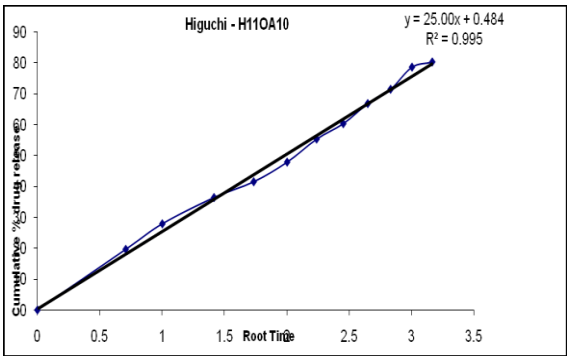

Figure 6: Higuchi release kinetics graph

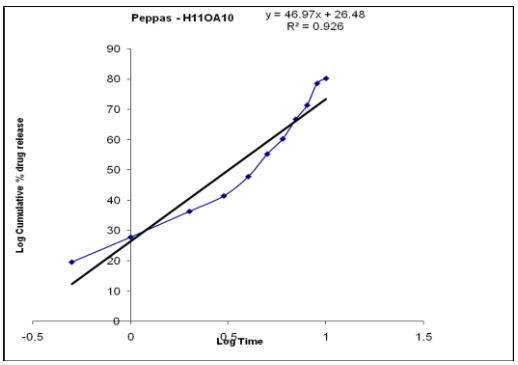

Figure 7: Karr's Meyers Peppas graph

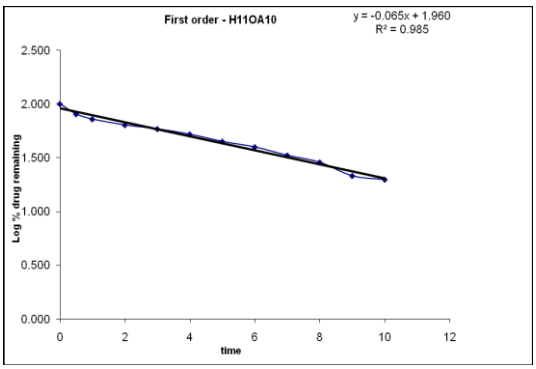

Figure 8: First order release kinetics graph

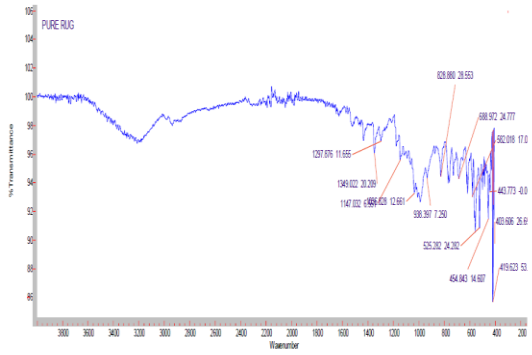

Figure 9: FT-TR Spectrum of Simethicone pure drug

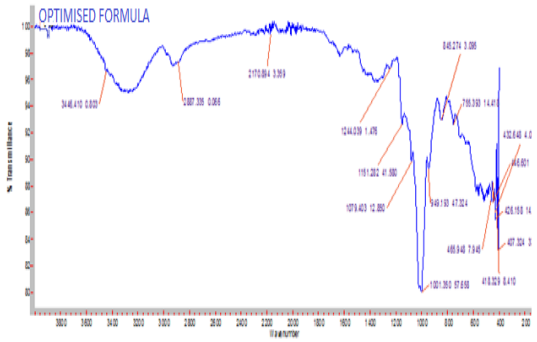

Figure 10: FT-IR Spectrum of Optimized Formulation

RESULTS AND DISCUSSION

The present study was aimed at developing gastro retentive floating tablets of Simethicone using various polymers. All the formulations were evaluated for physicochemical properties and *in vitro* drug release studies.

Analytical method: Graphs of Simethicone were taken with Simulated Gastric fluid (pH 1.2) at 244 nm.

Pre formulation parameters of powder blend: Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.43±0.07 to 0.58±0.06 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.57 to 0.69 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 16 to 18 which show that the powder has good flow properties. All the formulations have shown the Hausner ratio ranging between 0 to 1.2 indicating the powder has good flow properties as shown in Table 3.

Optimization of accrual concentration: Three formulations were prepared with varying concentrations of sodium bicarbonate. The formulation containing sodium bicarbonate in 50mg concentration showed less floating lag time of 4 min and the tablet was in floating condition for more than 12 hours.

Quality control parameters for tablets: Tablet quality control tests such as weight variation, hardness, and friability, thickness and drug release studies in different media were performed on the tablets. All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits as shown in Table 4.

***In-vitro* drug release studies:** From the dissolution data it was evident that the formulations prepared with HPMCK15M as polymer were unable to retard the drug release up to the desired time period i.e., 12 hours. Whereas the formulations prepared with hpmck100m retarded the drug release in the concentration of 30 mg showed required release pattern i.e., retarded the drug release up to 12 hours and showed a maximum of 96.33 % in 12 hours (Formulation F6) with good floating lag time and floating buoyancy time. The formulations prepared with Guar gum showed more retardation even after 12 hours they were not shown total drug release. Hence, they were not considered as shown Table 5 and Figures 2-4.

Application of release rate kinetics to dissolution data: Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted in zero-order, first order, Higuchi, and Korsmeyer-Peppas release model From this the graphs were evident that the formulation F6 was followed Higuchi mechanism as shown Table 6 and Figures 5-8.

Drug – excipient compatibility studies

Fourier transform infrared (FTIR) spectroscopy: For this study, there is no interactions between drug and polymers as shown in figures 9-10.

CONCLUSION

In the present research work, gastro retentive non effervescent floating matrix formulation of Simethicone by using various hydrophilic polymers. Initially analytical method developments were done for the drug molecule. Absorption maxima was determined based on that calibration curve was developed by using different concentrations. Gas generating agent accrual concentration was optimized. Then the formulation was developed by using different concentrations of polymers of various natural polymers. The formulations blend was subjected to various preformualation studies, flow properties and all the formulations were found to be good indicating that the powder blend has good flow properties. Among all the formulations the formulations prepared by using HPMC K100M were unable to produce desired drug release, they were unable to retard drug release up to 12 hours. The formulations prepared with HPMC K15M retarded the drug release up to 12 hours in the concentration of 30 mg (F6). The formulations prepared with HPMC K4M were also retarded the drug release for more than 12 hours. Hence, they were not considered. The optimized formulation dissolution data were subjected to release kinetics, from the release kinetics data it was evident that the formulation followed Higuchi mechanism of drug release.

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