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FORMULATION AND EVALUATION FLOATING DRUG DELIVERY MATRIX TABLETS OF PRAMIPEXOLE DIHYDROCHLORIDE

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ABSTRACT

The present research attempted for improving the gastric residence time of pramipexole dihydrochloride to release drug slowly for about 24 h. Various excipients with different ratios were used to formulate sustained FDDS in tablet dosage form. The tablets were formulated by direct compression method with different grades of Hydroxy propyl methyl cellulose (HPMC) and carbopol as rate retarding polymers and a combination of sodium bi-carbonate and citric acid as gas generating system. Floating lag time, floating time, swelling index and in vitro drug release were determined in 0.1N HCl at 37±0.5 °C. All formulations were evaluated for friability, weight variation, hardness, drug content uniformity, floating capacity and swelling index. The blend of HPMC K100 M and HPMC K15 M at 110 and 40 mg respectively shown excellent release upto 24h in F 9 and in F 8 containing HPMC K100 M and HPMC K15 M were 100 and 50 mg in the absence of MCC. The compatibility studies revealed by FTIR and DSC were also in good agreement; the accelerated stability studies have shown no significant change in drug release after 90 days. The increase in gastric residence time and prolonged drug release of a highly water-soluble drug like pramipexole could be achieved by formulating into matrix type floating drug delivery system.

INTRODUCTION

The prominent neuro-degradative disorder noted throughout world is Parkinson's disease (PD) characterized by rigidity, bradykinesia, tremor and unstable posture (Asquith, 1999). L-Dopa (levo-dopa) is the drug of choice in the treatment of PD, recently dopamine receptor agonists (nonergot agonists) second most widely used medications, pramipexole and ropinirole (Rosa et al., 2010) were introduced.

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United States recognized as monotherapy for treatment of early PD, further pramipexole recommended as adjuvant for therapy along with L-DOPA. Dopamine agonists effectively reduce dyskinesias through the droping of daily L-DOPA dose (Clarke et al., 2000). pramipexole is effective and safe as monotherapy in patients with motor symptoms of Parkinson's disease (PD) of mild to moderate severity, and in PD patients with motor fluctuations as an adjunctive therapy along with L-DOPA. The half-life of Pramipexole is 8 h, highly soluble in water and belongs to BCS class I. The drug release of highly water soluble drug is mainly modulated by polymeric matrix system. The drug release for extended duration, for highly water-soluble drugs, using a hydrophilic matrix system is restricted because of

rapid diffusion of the dissolved drug through the hydrophilic gel network. Immediate release dosage form of pramipexole using thrice a daily, once a day FDDS form offer patients a more convenient and alternative. Patient compliance with single daily dosing has been shown to be superior to thrice in a day dosing, chiefly the setting of poly pharmacy (Tarrants et al., 2010). The most common side effect of dopamine agonists is nausea and can be avoid by prolonged dose titration by designing of extended or prolonged dosage forms. Prolonged release preparations of pramipexole can show longer time to peak serum level (T_{max}) and a lower peak serum level (C_{max}) than their immediate release form tend to low incidence of nausea and relief of motor symptoms in a shorter period of time. So there is essential need to formulate extended release dosage form as it is highly soluble and high half-life, chose a floating drug delivery systems for pramipexole.

HPMC is a non ionic water soluble polymer and sodium bicarbonate is gas producing agent in floating matrix tablets only (Passerini and Apertini. 2002) widely used in pharmaceutical dosage forms. The present investigation is an attempt to design and *in vitro* evaluation of more promising pramipexole effervescent floating matrix tablets with: i) varying concentrations of HPMC K100 M:HPMC K15M; ii) varying the concentration of carbopol; iii) constant weight of sodium bicarbonate. HPMC K100M (high viscosity) with HPMC K15M (low viscosity) to get desired drug release and buoyancy time.

Materials and methods:

Pramipexole dihydrochloride was obtained as a gift sample from Cadila HealthCare Ltd., Ahmedabad. Glyceryl Behenate (Compritol 888 ATO) was obtained as a gift sample from Cadila HealthCare Ltd., Ahmedabad. Gum Rosin was procured from local market. All the other chemicals used were of analytical grade & were used as received. Sodium bicarbonate was received from B. D Pharmaceutical Works, Howrah, India. Citric acid and magnesium stearate were obtained from Loba Chemie Pvt Ltd., Mumbai, India. Talc was purchased from Nice Chemie Pvt. Ltd., Mumbai, India. Lactose was purchased from Reidel India Chemicals, Mumbai, India.

Preparation of floating tablets

Floating matrix tablets of pramipexole were prepared by direct compression method according to the formula given in Table 1. Pramipexole (3 mg) was mixed with the required quantity of polymer HPMC K100 M and HPMC K15M alone or in combination, sodium bicarbonate (50 mg), citric acid (15 mg), carbopol and MCC as diluents in mortar and pestle for 15 min. The powder blend was lubricated with magnesium stearate (10 mg) and talc (5 mg) for 5 min just prior to the compression; the powder blend was evaluated for precompression parameters. The blended powder was compressed into tablets on single punch tablet punching machine (Kilburns, Allahabad, India) using 6 mm standard flat punches.

Evaluation of powder blend

Bulk density and tapped density

Both poured (or fluff) bulk (Do) and tapped bulk densities (D_F) were determined, according to the method reported by Raghuram et al., (2003), whereby a quantity (3 g) of granules from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10 mL measuring cylinder. After the initial volume was observed, the cylinder allowed falling under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in the volume was noted. The value of bulk density and tapped density were calculated by using equation: Bulk density; Weight of powder; Volume of powder; Volume of powder after tapping; Tapped density

$$\text{Bulk density} = \frac{\text{Weight of powder}}{\text{Volume of powder}}$$

$$\text{Tapped density} = \frac{\text{Weight of powder}}{\text{Volume of powder after tapping}}$$

Compressibility index

The Carr's compressibility index and Hausner's ratio were calculated from the values of bulk density and tapped density (Lachman and Lieberman, 1987). Hausner's ratio

$$\text{Compressibility \%} = \frac{D_F - D_O}{D_F} \times 100$$

$$\text{Hausner's ratio} = \frac{D_F}{D_O}$$

Where 'D_F' is tapped density; 'D_O' is loose bulk density.

Drug-Excepients Compatibility Studies:

FTIR and DSC examined for the compatibility on pure drug and formulation for interactions in between drug and excepients.

Table. 1. Composition of various formulations of floating matrix tablets of pramipexole

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Pramipexole	3	3	3	3	3	3	3	3	3	3
HPMC K100 M	----	100	----	50	----	100	100	100	110	125
HPMC K15 M	100	----	----	100	100	----	50	50	40	40
Carbopol 934 P	----	----	100	----	50	50	----	50	50	35
MCC	100	100	100	50	50	50	50	----	----	----
$NaHCO_3$	30	30	30	30	30	30	30	30	30	30
Citric Acid	15	15	15	15	15	15	15	15	15	15
PVP	10	10	10	10	10	10	10	10	10	10
Mg.Stearate	10	10	10	10	10	10	10	10	10	10
Talc	5	5	5	5	5	5	5	5	5	5
Acrosil	7	7	7	7	7	7	7	7	7	7
Total weight(mg)	280	280	280	280	280	280	280	280	280	280

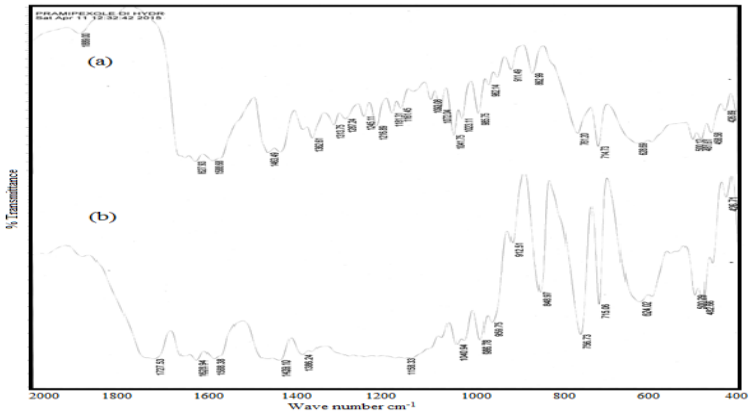

Fig. 1. FTIR Spectral comparison of (a) Pramipexol dihydrochloride (b) Pramipexole Floating formulation.

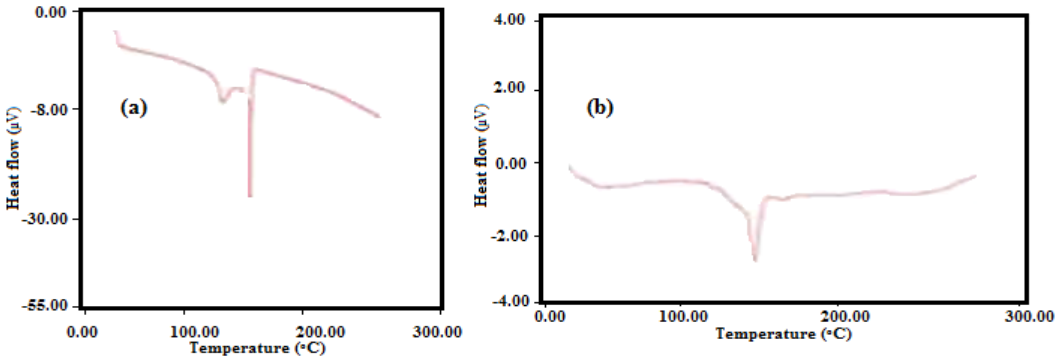

Fig. 2. DSC images of (a) Pramipexole dihydrochloride (b) Pramipexole Floating formulation.

Pramipexole analysis

Buffer preparation (pH 3): Weighed accurately 4.6 g of 1-octaned sulphonic acid sodium salt and 9.1 g of potassium dihydrogen phopshpate dissolved in 1000 mL of milli-Q water and pH was adjusted to 3.0±0.05 with orthphosphoric acid and mixed well.

Mobile phase: A mixture of pH 3 buffer and acetonitrile in the ratio of 72:28 (v/v) was prepared and filtered through 0.45µm nylon membrane filter and degassed for about 10 min.

Diluent: pH 3 buffer and methanol mixed in the ratio of 60:40 (v/v) mixed well and filtered through 0.45µm nylon membrane filter.

Standard preparation: 60 mg of pramipexole dihydrochloride monohydrate working standard was transferred in to a 100 mL volumetric flask and to that 70 mL of diluents was added and sonicated to dissolve and diluted to volume

with diluents. Solution was filtered through 0.45µm nylon membrane filter.

Chromatographic conditions: The chromatographic column is prontosil, C18 (150×4.6 mm; 5µm packing), the flow rate was 1.0 mL/min, the column temperature was 40°C, injection volume was 20 µL and at the wavelength of 264 nm.

Figure 3 revealed the peak areas of pure drug (a) and formulations as test sample (b), then calculated the drug concentrations.

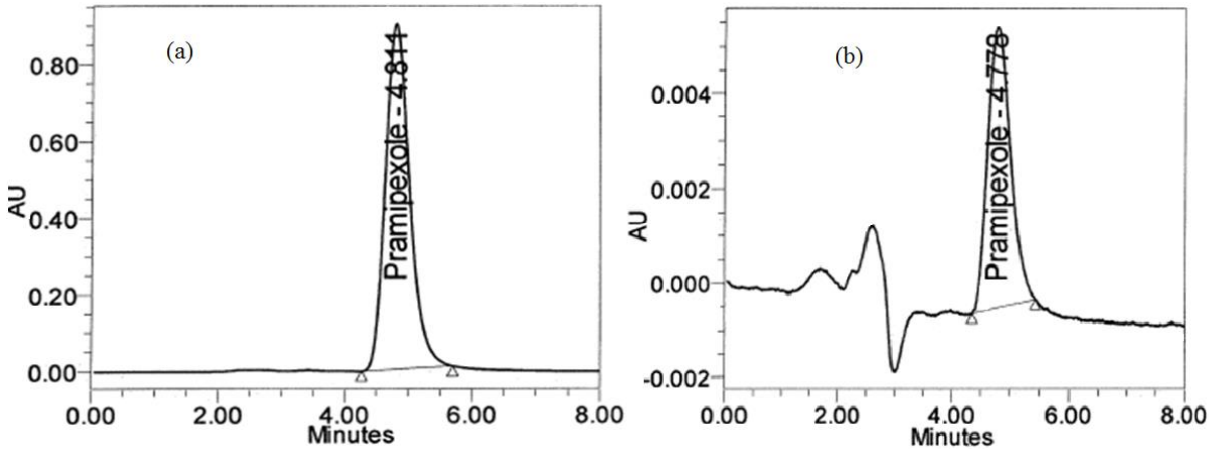

Fig. 3. HPLC analysis of (a) Pramipexol dihydrochloride standard; (b) Pramipexole Floating formulation as test sample.

Table 2. Micromeritic properties of powder of different formulations

Formulation code	Parameters					
	Angle of repose (°)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Hausner's ratio	Carr's % Compressibility	Thickness (mm)
F1	22.1	0.541	0.592	1.094	8.614	3.9
F2	20.1	0.521	0.598	1.147	12.876	3.9
F3	21.7	0.502	0.588	1.171	14.625	3.9
F4	22.5	0.497	0.539	1.084	7.792	3.9
F5	23.2	0.473	0.509	1.076	7.072	3.9
F6	24.4	0.465	0.513	1.103	9.356	3.9
F7	21.3	0.432	0.499	1.155	13.426	3.9
F8	19.3	0.402	0.489	1.216	17.79	3.9
F9	19.2	0.413	0.501	1.213	17.56	3.9
F10	19.9	0.475	0.521	1.077	8.829	3.9

Table 3. Physicochemical and buoyancy properties of the tablets of various formulations

Formulation code	Parameters (mean±S.D)					
	Hardness (kg/m^2)	Friability (%)	Weight variation (mg)	Drug content (%)	Floating lag time (min)	Floating time (h)
F1	4.22±0.12	0.98±0.02	277±0.76	97.02±0.22	2.5±0.45	8.02±0.11
F2	4.68±0.55	0.92±0.03	276±0.95	96.56±0.78	3.2±0.32	8.24±0.03
F3	5.03±0.78	0.97±0.01	282±1.12	95.45±0.56	2.9±0.56	9.12±0.06
F4	6.67±0.45	0.76±0.02	283±0.95	93.43±0.33	2.3±0.36	10.33±0.23
F5	5.98±0.66	0.67±0.06	282±1.11	98.44±0.21	4.5±0.58	10.89±0.16
F6	6.76±0.55	0.57±0.04	284±1.76	94.25±0.98	5.7±0.54	12.06±0.14
F7	5.43±0.23	0.55±0.05	282±1.83	97.08±0.64	4.9±0.36	15.08±0.46
F8	7.89±0.62	0.24±0.01	280±0.97	99.33±0.12	1.02±0.76	24.55±0.26
F9	7.02±0.48	0.12±0.02	281±1.21	98.08±0.16	1.24±0.56	24.35±0.66
F10	5.76±0.32	0.62±0.03	282±1.46	96.23±0.18	3.23±0.22	13.09±0.88

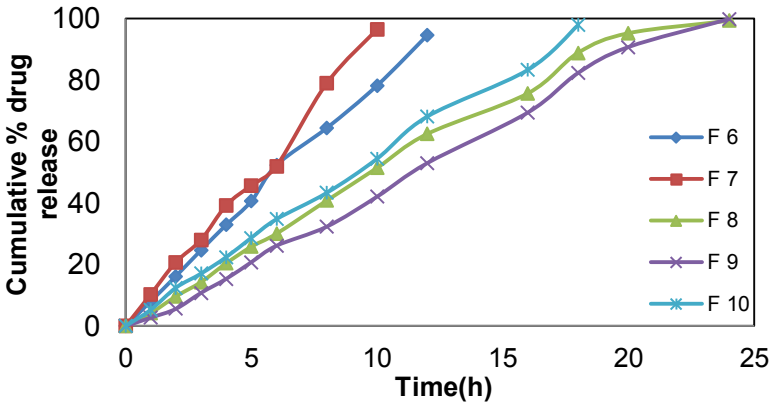

Fig. 4. Cumulative % drug release vs time profiles of F6 to F10 formulations

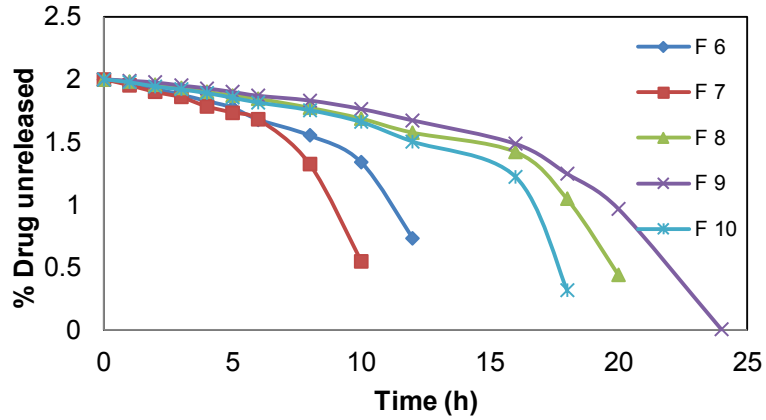

Fig. 5. First order plot for FDDS of Pramipexole

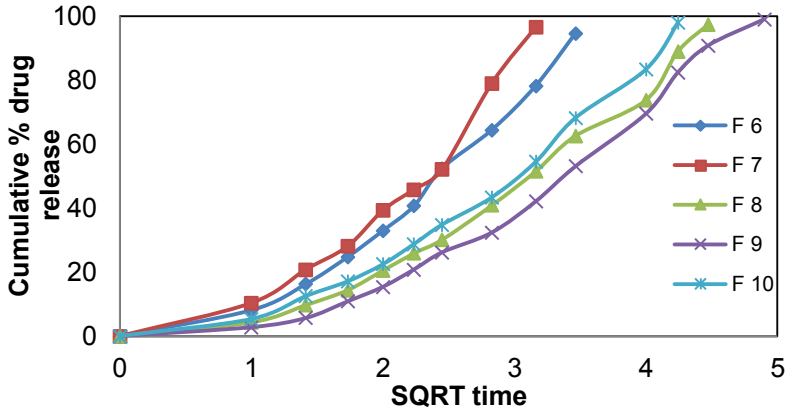

Fig. 6. Higuchi plot for FDDS of Pramipexole

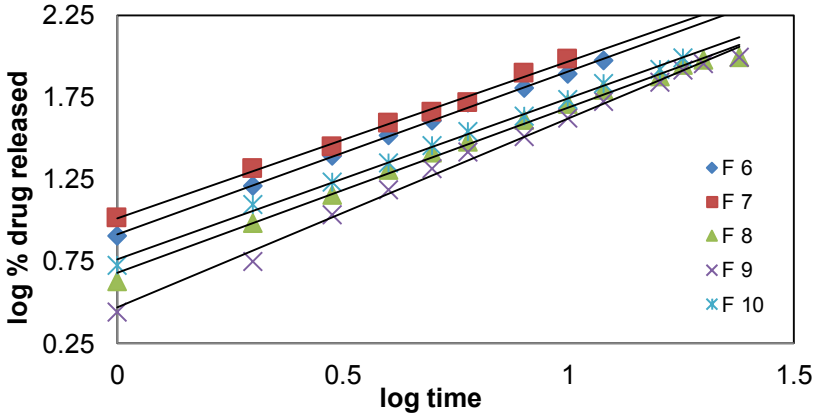

Fig. 7. Korsemeyer- peppas plot for FDDS of Pramipexole

Table 4. *In-vitro* release kinetic parameters of pramipexole floating tablets

Formulation code	Zero order		First order		Higuchi		Koresmeyer-peppas	
	k_0	R^2	k_1	R^2	k_H	R^2	N	R^2
F1	13.89	0.959	2.27	0.887	39.68	0.889	0.456	0.938
F2	14.11	0.96	2.2	0.894	39.81	0.878	0.462	0.933
F3	11.65	0.985	1.18	0.861	31.99	0.844	0.543	0.984
F4	10.44	0.991	1.1	0.909	33.99	0.922	0.589	0.973
F5	8.003	0.982	1.05	0.876	29.6	0.953	0.678	0.956
F6	7.878	0.997	0.91	0.869	28.4	0.92	0.698	0.998
F7	9.534	0.994	1.25	0.808	30.48	0.893	0.706	0.995
F8	4.507	0.981	0.62	0.836	23.49	0.93	0.789	0.994
F9	4.449	0.995	0.65	0.808	22.98	0.921	0.804	0.994
F10	5.341	0.997	0.72	0.793	24.09	0.924	0.79	0.997

Table 5. Effect of time on optimized formulations of F8 and F9 at accelerated stability storage conditions (42±2°; RH-75±5°C)

Days Interval	F8				F9			
	Hard ness (kg/cm^2)	Friability (%)	Weight variation (mg)	Drug release (%)	Hard ness (kg/cm^2)	Friability (%)	Weight variation (mg)	Drug release (%)
0	7.89±0.6	0.24±0.01	280.06±0.9	99.9±0.1	7.02±0.48	0.124±0.02	280.21±0.9	99.6±0.54
15	7.69±0.5	0.23±0.02	280.06±0.1	99.9±0.1	7.02±0.42	0.136±0.03	280.12±0.2	99.2±0.64
30	7.58±0.2	0.24±0.03	280.12±0.5	98.9±0.7	7.06±0.09	0.122±0.03	279.6±0.32	98.7±0.14
45	7.49±0.1	0.22±0.06	280.15±0.0	98.7±64	7.1±0.02	0.134±0.04	278.9±0.56	98.66±0.42
60	7.4±0.28	0.23±0.02	280.09±0.6	99.6±0.5	7.05±0.12	0.126±0.02	279.3±0.43	98.78±0.68
75	7.42±0.1	0.23±0.04	279.6±0.59	99.2±0.3	7.5±0.22	0.128±0.03	270.16±0.4	99.5±0.46
90	7.39±0.5	0.24±0.05	280.08±0.8	99.1±0.7	7.1±0.11	0.127±0.04	279.5±0.76	99.8±0.18

Evaluation of tablets

Prepared tablets were evaluated for quality control tests like weight variation, hardness, friability, content uniformity and *in vitro* release study.

Weight variation test

To study weight variation, tablets from each formulation were selected at random and average weight was determined using an electronic balance. Then individual tablets were weighed and compared with an average weight (mg), mean and SD were calculated.

Hardness test

From each formulation, the hardness of six tablets was determined using a hardness tester (Monsanto, Mumbai, India). Hardness values were reported in kg/cm^2, mean and standard deviation were calculated.

Friability test

For each formulation, six tablets were weighed initially and were placed in a Roche friabilator (Labotech, Mumbai, India) and subjected to 100 rotations in 4 min. The tablets were then dedusted and reweighed. The friability was calculated as the percent weight loss.

$$\text{Friability} = 100 \times \left(1 - \frac{W}{W_O}\right)$$

Where, W_O is initial weight; W is final weight.

Swelling index

The swelling index of tablets was determined in 0.1 N HCl (pH 1.2) at room temperature. The swollen weight of the tablets was determined after predefined time

$$\text{Swelling index} = \left(\frac{W_T - W_O}{W_O}\right) \times 100$$

Where, W_O is initial weight of the tablet; W_T is final weight of the tablet at time 't'.

Drug content uniformity study

Five tablets were weighed individually, then placed in a mortar and powdered with a pestle. An amount equivalent to 25 mg drug (100 mg) was extracted with 100 mL of 0.1N HCl (pH 1.2), stirred for 15 min using magnetic

stirrer (REMI 2M). The solution was filtered through a filter (0.22 µm pore size), properly diluted with 0.1 M hydrochloric acid and the drug content was measured using HPLC at 264 nm.

***In vitro* buoyancy study**

The *in vitro* buoyancy was characterized by floating lag time and total floating time. The method described by Chaudhri et al., (2005) was used to carry out *In vitro* buoyancy studies. The test was performed using USP 24 type II apparatus (Timestan, Kolkata, India) at 100 rpm in 900 mL of 0.1N HCl (pH 1.2) maintained at 37±0.5°C. The time required for tablet to rise to the surface of dissolution medium and duration of time the tablet constantly float on dissolution medium were noted as floating lag time and total floating time, respectively (n = 3) (Patel and Patel, 2005).

***In vitro* drug release study**

The *in vitro* drug release study was performed using USP 24 type II apparatus (Timestan, Kolkata, India) at 50 rpm in 900 mL of 0.1N HCl (pH 1.2) maintained at 37±0.5°C. The samples were withdrawn at predetermined time intervals for period of 24 h and replaced with the fresh medium. The samples were filtered through 0.22 µm membrane filter, suitably diluted and analysed at 264 nm using HPLC (Waters, Mumbai, India). The percent drug release was calculated using equation generated from calibration curve. The test was performed in triplicate and the mean value was used to construct the release profile.

Determination of release kinetics and release mechanism

The rate and mechanism of release of pramipexole from the prepared floating tablets were analyzed by fitting the dissolution data into following equations:

Zero order kinetics: $F = k_0 t_{(5)}$

First order kinetics: $1n(1-F) = -k_1 t$

To describe the drug release behavior from polymeric systems, the dissolution data were also fitted according to the well-known exponential Korsmeyer-Peppas equation (Korsmeyer et al., 1983) as.

$$\frac{M_t}{M_\infty} = kt^a$$

Where $\frac{M_t}{M_\infty}$ is the fraction of drug release at time 't', and 'k' is the kinetic constant, 'a' is the release exponent (indicating the general operating release mechanism). For tablets, depending on the aspect ratios, 'a' value between 0.43 and 0.5 indicating Fickian (case I) diffusion-mediated release, non-Fickian (Anomalous) release, coupled diffusion and polymer matrix relaxation, occurs if 0.5<n <0.89, purely matrix relaxation or erosion-mediated release occurs for n=1 (zero-order kinetics), and super case II type of release for n>0.89.

Accelerated Stability Studies

In order to access the long term stability and shelf life, the optimized tablets of drug were packed in wide mouth air tight glass container and stored at (40±2°C/75±5% RH) for a period of 3 months. The samples were withdrawn at predetermined time intervals (0, 30, 60 and 90 days) and characterized for parameters like physical appearance, drug content and dissolution profile (Table 5).

Statistical analysis

To evaluate contribution of each factor with different levels on responses, two way analysis of variance (ANOVA) was performed using Sigma Stat software (Sigma Stat 6.0, USA).

RESULTS AND DISCUSSION

Compatibility studies

The major peaks obtained in the FTIR studies of pure drug Pramipexole dihydrochloride monohydrate like benzothiazole, C=C, N-H and aromatic C-H stretching's remained unchanged when mixed with the polymers and in the formulation (Fig. 1). DSC thermo grams of pure drug and formulation revealed that there is no considerable change observed in melting endotherm of Pramipexole dihydrochloride monohydrate pure drug and drug in optimized formulation which are shown in Figure 2. It indicates that there is no interaction takes place between pure drug and excipients used in the formulation.

Evaluation of flow properties

The micromeritic parameters of the powder blend of different formulation batches are shown in Table 2. Angle of repose and compressibility index was found to be in the

range of 19.2° to 24.4° and 7.07 to 17.79 respectively. The bulk density and tapped density of the prepared powder blend was fond to be in the range of 0.402 to 0.541 gm/cm^3 and 0.489 to 0.598 gm/cm^3, respectively. The result of angle of repose indicates good flow property of the granules and the value of compressibility index further support for the good flow property.

Evaluation of physicochemical properties of tablets

The tablets of all formulations was found to be off white, smooth, flat faced circular with no visible cracks. The physicochemical properties of all the formulations are shown in Table 3. The hardness of the tablets was measured by Monsanto hardness tester and was found in between 4.22±0.12 to 7.89±0.62 kg/cm^2. The friability was measured by Roche friabilator and was found to be within acceptable range. The weight variation of the tablet formulations was found to be in the range of 276.12±0.95 to 284.08±1.76 mg. The drug content estimations showed values in the range of 93.43±0.33% to 99.33±0.12%, which reflects good uniformity in drug content among different formulations. All the formulations showed values within the prescribed limits for tests like hardness, friability and weight variation which indicate that the prepared tablets are of standard quality.

***In vitro* drug release study**

All the tablets were prepared by effervescent approach. Sodium bicarbonate was added as a gas-generating agent. The combination of sodium bicarbonate and citric acid provided desired floating ability and therefore this combination was selected for the formulation of the floating tablets. Pramipexole release profiles of the floating tablets formulated are summarized in figures 4-7. Drug release from the prepared tablets was slow, and spread over more than 24 h and depended on the polymer used and its strength and concentration of sodium bicarbonate in the tablets. The *In vitro* drug release data was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equation, Higuchi's and Korsmeyer's models in order to determine the mechanism of drug release. The correlation coefficient (r2) values were higher in zero order model than those in the first order model (Table 4) in all the cases. The release rate constants are given in Table 4. It is notable that the 'r' values of the linear regression for Higuchi's plot were found to be in the range of 0.844 to 0.953 indicating that the data fits the Higuchi's model well and the drug release was found to be predominantly controlled by diffusion process. When the release data was analysed as per Peppas equation, the release exponent 'n' was found to be in the range 0.456-0.804 indicating 'non-Fickian diffusion' as the release mechanism from all the floating tablets prepared.

CONCLUSION

In the present study, gastro-retentive floating tablets of pramipexole were prepared successfully by direct compression method using HPMC K 100M and HPMC K 15M and Carbopol. Fabricated tablets showed acceptable weight variation, hardness, and uniformity of drug content. Thus with proper selection of the ratio of HPMC K 100M and HPMC K 15M, desired drug release was achievable. Extensive studies on similar formulations are essential to establish a successful formulation from the biopharmaceutical viewpoint.

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