

FORMULATION AND EVALUATION OF GASTRORETENTIVE FLOATING TABLET OF BROMOCRIPTINE MESILATE

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ABSTRACT

Bromocriptine is a semisynthetic ergot alkaloid that has inhibitory effect on D₂ dopamine receptors, it has wide applications in the treatment of hyperprolactinemia, parkinson's disease, type 2 diabetes mellitus and other diseases.

Objective: The objective of this study was to formulate an oral controlled release floating tablet of bromocriptine, this dosage form is associated with many advantages especially reduction in dosing frequency and possible increased bioavailability.

Methods: The effervescent floating tablets was prepared using the hydrophilic polymer hydroxy propyl methyl cellulose (HPMC) with sodium bicarbonate as gas generating agent . Eight formulas were prepared by different methods(direct compression and wet granulation) employing different polymer viscosity and concentrations in an attempt to achieve optimum floating and dissolution behavior.

The floating formulations were evaluated for angle of repose, Carr's Index, uniformity of weight , hardness, friability, drug content, *in vitro* buoyancy, dissolution and stability studies.

Results: The best formula (F8) that contain 60% HPMC K100M with 10 % NaHCO₃ prepared by direct compression shows good physical properties and the highest similarity factor (f_2 , 67.07) in comparison to the release profile of reference . Floating lag time of F8 was 200 sec and remained buoyant for 24 hrs. The diffusion exponent (n) of Krosmeier Peppas for best formulation was found to be 0.65 which indicates the mechanism of drug release was anomalous transport. Optimized formulation was checked for stability which was found to be stable with expired date about 2.7 years.

Conclusion: It can be concluded that that the selected formula (F8) can be a promising formula for preparation of gastroretentive floating drug delivery systems of bromocriptine mesilate

Keywords: Bromocriptine mesilate, Floating matrix, Gastroretentive, Sustained release

INTRODUCTION

Gastroretentive systems are modified release dosage forms that can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs .

Various approaches have been pursued to increase the retention of an oral dosage forms in the stomach, including floating drug delivery systems (FDDS) [1,2], expandable, unfoldable and swellable systems [3], superporous hydrogel composite system [4,5], mucoadhesive systems [6], high-density systems [7], and magnetic systems [8].

Many advantages are offered by gastroretentive drug delivery systems such as the improvement of bioavailability as that for cefpodoxime gastroretentive tablet which has an improved oral bioavailability in rat significantly by about 75% [9], also it can be used to achieve local effect for eradication of *Helicobacter pylori* [10], in addition to improving patient compliance, reduction in the incidence and severity of localized and systemic side effects, and others. [11,12]

The effervescent buoyant systems utilize matrices prepared with swellable polymers such as methocel, polysaccharides (e.g., chitosan), and effervescent components (e.g., sodium bicarbonate, citric acid or tartaric acid). The system is so prepared that upon arrival in the stomach, carbon dioxide is released, causing the formulation to float in the stomach. [13]

Bromocriptine is a semisynthetic ergot alkaloid that interacts with D₂ dopamine receptors to inhibit spontaneous and TRH-induced release of prolactin. [14] It is used in neuroleptic malignant syndrome, acromegaly, infertility, hyperprolactinemia, prolactinoma, parkinson's disease [15], and type 2 diabetes mellitus (it was approved by the Food and Drug Administration (FDA) in May 2009, for the treatment of type 2 diabetes). [16] it is rapidly absorbed after oral administration and has low systemic bioavailability about 28%. [17] Bromocriptine has a relatively short

elimination half-life (2-8 hours). The aim of this study is to prepare sustained release bromocriptine mesilate tablets utilizing the gastroretentive floating drug delivery system by effervescent technique.

MATERIALS AND METHODS

Bromocriptine mesilate powder was purchased from Asia company, Syria. Hydroxypropyl methylcellulose (HPMC) K15 M, K100 M and E15 were purchased from Shin-Etsu Chemicals Co. Ltd., Japan. Sodium bicarbonate was purchased from Riedel-deltaen, Germany and talc was purchased from Afco , India.

Preparation of bromocriptine floating sustained release tablet

All formulas of bromocriptine floating sustained release tablet (Table 1) were prepared by non aqueous wet granulation method using polyvinyl pyrrolidone (PVP K30) solution in ethanol as a binder except formulas (F6, 7 and 8) were prepared by direct compression method. The compression to tablet was done using 9mm flat face punch tablet machine. [18]

Evaluation of precompression formulas mixture

Flow properties

The tablet blend were evaluated for their bulk density, tapped density, compressibility index and flow properties. The tapping method was used to determine the bulk density, tapped density and percent compressibility index.

$$\text{Compressibility index} = \left[\frac{\rho_t - \rho_b}{\rho_t} \right] \times 100$$

Where ρ_t = tapped density

ρ_b = initial bulk density of tablet blend.

Angle of repose θ of the tablet blend measures the resistance to particle flow and was determined by fixed funnel method. [19]

Table 1: Different Formulas of Bromocriptine Sustained Release floating Tablets

Materials (mg)	Formula No							
	F1	F2	F3	F4	F5	F6*	F7*	F8*
Bromocriptine mesilate	5.74	5.74	5.74	5.74	5.74	5.74	5.74	5.74
HPMC K15				120			120	
HPMC K100M	60	90	120					120
HPMC E15					120	120		
NaHCO ₃	20	20	20	20	20	20	20	20
Talc	4	4	4	4	4	4	4	4
Polyvinyl pyrrolidone(PVP)	13	13	13	13	13			
Avecil 101 up to	200	200	200	200	200	200	200	200

Note: Formulas with star * were prepared by direct compression

Evaluation of post compressed bromocriptine floating tablet

Hardness

The Monsanto hardness tester was used to determine the tablet hardness. The tablet was held between affixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of the hardness of the tablet which was expressed in kg/cm².

Friability Test

Tablet strength was tested by Roche friabilator. Pre weighed tablets were allowed for 100 revolutions in 4 min and were dedusted. The percentage weight loss was calculated by reweighing the tablets. The % friability was then calculated by the following equation.[20]

$$\% \text{ Friability} = (\text{initial weight} - \text{final weight}) / \text{initial weight}$$

Weight variation

Randomly selected 20 tablets were weighed individually and together. The average weight was recorded. The variation limit is $\pm 7.5\%$ according to British pharmacopeia.

Content Uniformity Test

The procedure described in United States Pharmacopoeia (USP XXX) for determination of bromocriptine in tablets was used in which the accepted range of drug content is 90-110% of the labeled.[21]

In vitro buoyancy study

The floating lag time (FLT; time period between placing the tablet in the dissolution medium and tablet floating) and floating duration of the tablets (FD) were determined by visual observation of tablets placed in a 100ml beaker containing 0.1NHCl at 37°C.[22]

Dissolution study

In vitro drug release of the formulation was carried out by USP type II paddle type apparatus under sink condition with rotating speed of 50 rpm and at temperature of 37 \pm 0.5°C. The dissolution medium used was 300ml 0.1NHCl. The samples were withdrawn at predetermined time intervals for period of 6 hrs and replaced with the fresh medium, suitably diluted and were analyzed using

UV/Visible spectrophotometer (Cary UV, Varian, Australia) at λ max 306 nm. The test was performed in triplicate.

Selection of best formula

The similarity factor (f_2) introduced by Moore and Flanner was used as criterion for assessment of the best formula in comparison to release of drug from reference (controlled release bromocriptine tablet, parlovel SRO®) utilizing the following equation .

$$f_2 = 50 \times \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^n |R_t - T_t|^2 \right]^{-0.5} \times 100 \right\}$$

Where, n is the number of dissolution time points, R_t and T_t are the reference and test dissolution values at time t .

Kinetic analysis of Release

The release kinetics of bromocriptine from the prepared floating tablets was determined by fitting the dissolution data to mathematical Korsmeyer- Peppas model using the following equation. [23]

$Q_t / Q_\infty = kt^n$ where, Q_t : amount of drug released in time t ; Q_∞ : total amount of drug dissolved ; K : release rate constants; n : release exponent

Stability Study

The study was done to assess the selected formula stability according to Arrhenius method and to determine the expired date. The tablets were stored at different storage conditions at elevated temperatures of 40, 50, and 60°C for 4 months.

The samples were withdrawn at monthly intervals and checked for physical appearance, drug content, floating properties and *in vitro* drug release studies.[24]

RESULTS AND DISCUSSION

The results of flowability studies reveal that all the formulations are meeting the official pharmacopeia requirements (Table 2).

Table 2: The Precompression parameters for the bromocriptine floating formulas.

Formulas	Angle of Repose	Carr's Index	Formulas	Angle of Repose	Carr's Index
F1	31.6	27	F5	33.0	26
F2	28.3	25	F6	35.8	27
F3	27.4	23	F7	35.7	28
F4	28.6	16	F8	36.4	32

The results of the formulated tablets characterization indicate that the hardness of prepared tablets was close to 5Kg for all formulas, while the variations in weight of randomly sampled tablets from each formulation are within accepted official limit. The assay results were found between 91.3-100.5% and friability is less than 1% for all formulation as listed in table (3), and these results are comply with BP specification. [25]

Most of the prepared formulas had acceptable (FLT) due to the presence of the gas generating agent which is in the acidic dissolution media generates carbon dioxide gas that would be entrapped within the gelling layer of the hydrophilic polymer and also due to the swelling of the hydrocolloid particle on surface following exposure to the aqueous gastric fluids, which in turn results in an increase in the bulk volume that lead to an internal void space in the dry center of the tablet.

Table 3: The evaluation parameters of the bromocriptine floating formulas

Formulas no	Friability (%)	Drug content(%)	Floating lag time(sec)	Total floating duration(hrs)	f ₂ value
F1	0.20	98.6	10	12	18.62
F2	0.32	99.2	17	>24	29.70
F3	0.16	91.3	21	>24	38.78
F4	0.20	94.8	12	11	24.61
F5	0.20	92.9	7	2	14.40
F6	0.32	99.2	2	5	18.28
F7	0.16	97.3	7	14	30.23
F8	0.20	100.5	200	>24	67.07

Figure (1) shows the effect of polymer concentration using formula F1,F2, and F3 on the drug release which indicates that as there is increase in the polymer concentration, the rate of drug release

decreases significantly (p<0.05), and this may be due to decrease the porosity of matrix [26] leads to retard the drug to diffuse from the matrix.[27]

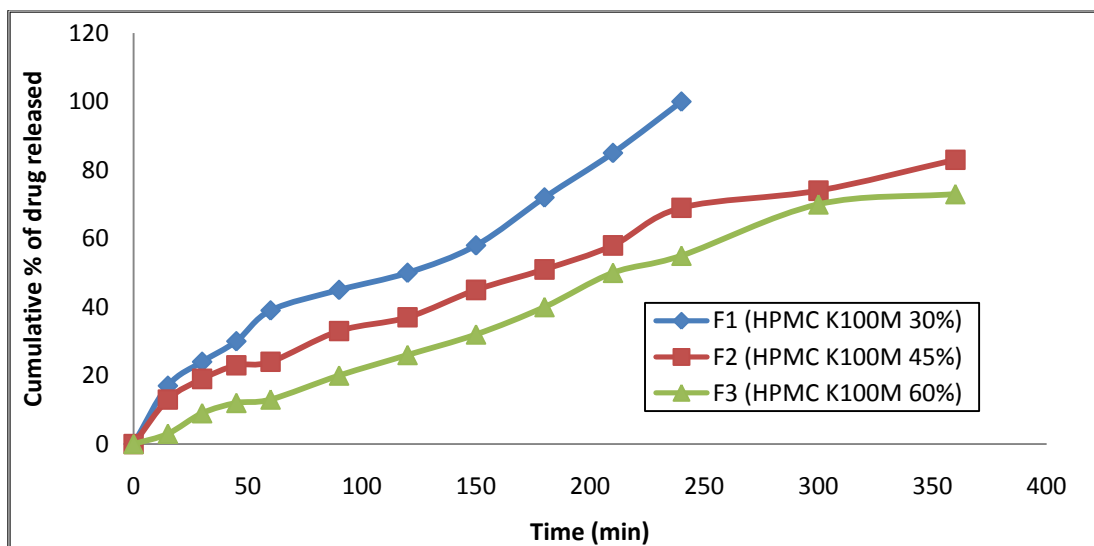


Fig. 1: The effect of HPMC K100M polymer concentration on the release of bromocriptine in 0.1N HCl at 37°C

Formula F3,F4, and F5 were used to study the effect of polymer viscosity and molecular weight on the floating and release behavior. It was observed that replacement of HPMC K15M polymer with HPMC K100M will result in prolongation in FLT and FD while a reverse trend was observed on replacement with HPMC E15 polymer which has lower viscosity and molecular weight.

Also a significant (p<0.05) retardation effect of the polymer viscosity on the drug release as shown in figure (2). This behavior may be attributed to that the higher viscosity polymer produces thicker gel layer which not permit the rapid drug diffusion from matrix. [28,29]

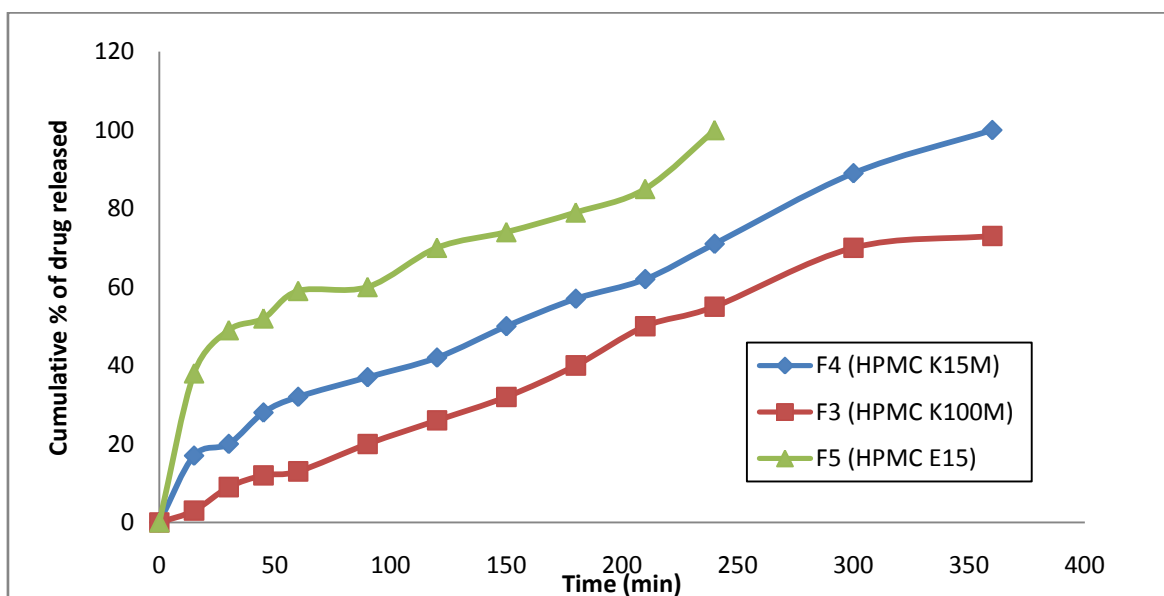


Fig. 2: The effect of polymer viscosity on the release of bromocriptine in 0.1N HCl at 37°C

Figure (3) shows the effect of method of tablet preparation which reveals that a significant ($p < 0.05$) decrease in the drug release rate was observed for formulas prepared by direct compression in comparison to that prepared by wet granulation method. This is due

to the fact that PVP-K30, which is hydrophilic in nature, absorb water rapidly and dissolve without gel formation allowing easy penetration of the medium into the matrix and a more rapid release.[30]

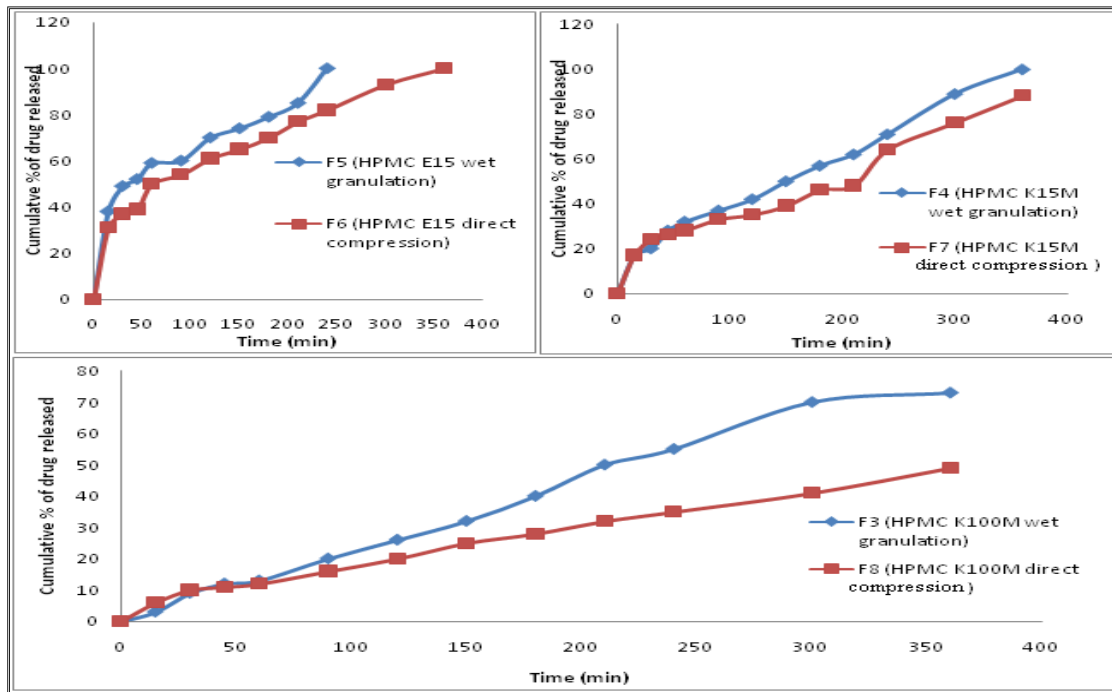


Fig. 3: The effect of preparation method on the release of bromocriptine from HPMC matrix tablet in 0.1N HCl at 37°C

The overall results of floating and dissolution studies indicate that formula F8 with good buoyancy has the highest similarity ($f_2, 67.07$) to the release profile of reference controlled release tablet (Parlodel SRO®) as shown in figure (4), thus selected as best formula and subjected for further studies

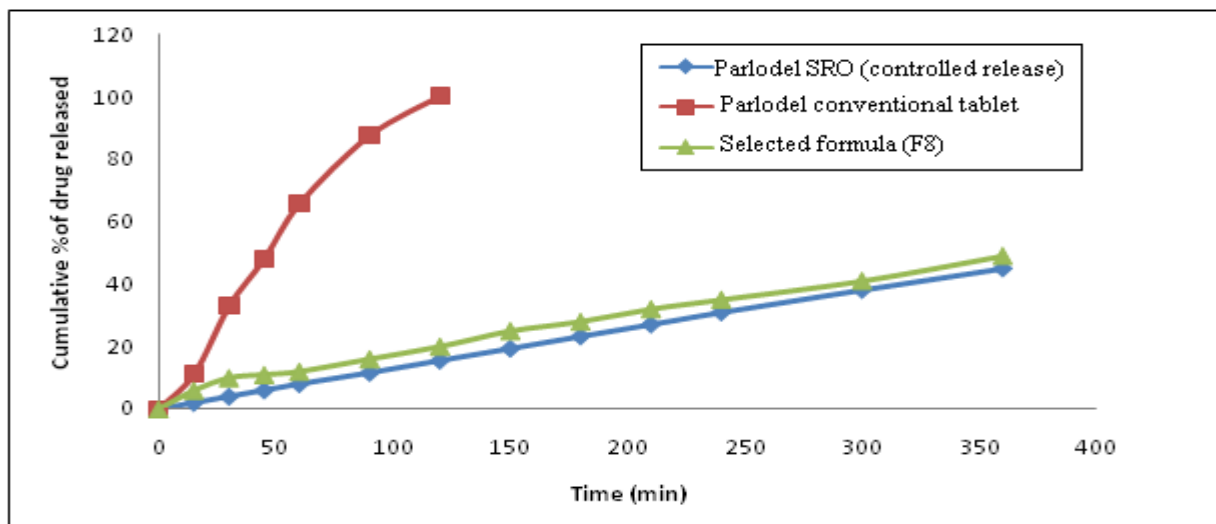


Fig. 4: Comparison the release profile of bromocriptine from the best formula (F8) with reference controlled release and conventional tablet in 0.1N HCl at 37°C

The fitting of release data of selected formula F8 to Korsmeier-Peppas model shows high correlation coefficient of 0.983 with n value equals 0.65 which indicates that the mechanism of drug release was non-fickian diffusion anomalous transport.

The stability study of the selected formula (F8) shows non significant change ($p > 0.05$) in physical properties, floating and dissolution behavior at the end of 4 months with calculated expired date equals 2.7 years.

Thus from the whole research work it can be concluded that the objective of the proposed project has been fulfilled and selected formula (F8) might be a promising gastroretentive drug delivery system for bromocriptine.

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