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Research Article

PREPARATION OF HYDROPHILIC SWELLING CONTROLLED-RELEASE FLOATING MATRIX TABLETS CONTAINING HPMC AND CHITOSAN

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ABSTRACT

The research is aimed to investigate the methods and variables for the preparation of floating sustained release matrix tablets of furosemide. Different proportions of HPMC and Chitosan were taken for preparing successful sustained release matrix tablets. Sodium bicarbonate was incorporated in the matrix to make the matrix floatable. Effect of the different proportions of hydrophilic polymers on drug release was evaluated by fitting the data to various kinetic models. The buoyancy of the tablets depended on the viscosity of the HPMC grade. Greater the content of chitosan in matrix the greater was the release rate. The matrices containing lower viscosity HPMC grades showed increased release rates. Most of the formulations showed biphasic drug release i.e. initial slower release phase followed by faster release phase. The drug release was sustained for more than 8 h using higher viscosity HPMC grades. All the formulations followed zero order kinetics which indicates that the drug release was nearly independent of drug concentration in the matrices. Matrices followed non-Fickian diffusion mechanism indicating drug release through diffusion and relaxation. Drug release from most of the formulations was found to be similar with $t_{50\%}$ ranging from 316.6 to 533.7 and $t_{80\%}$ from 491.9 to 848.6.

Keywords: Controlled release, Floating, Chitosan, HPMC, Relaxation

INTRODUCTION

Chitosan [(1→4)-2-amino-2-deoxy-β-D-glucan] is obtained by the alkaline deacetylation of chitin. The N-acetyl-2-amino-2-deoxy-D-glucopyranose or (Glu-NH_2) units in chitosan molecules are linked by (1→4) - β-glycosidic bonds[1, 2]. Chitosan is currently receiving enormous interest for medical and pharmaceutical applications due to its nontoxic, odorless, biocompatibility in animal tissues and biodegradable properties[3].

The effects of chitosan on drug release rate[4, 5, 6] and the capacity of chitosan for mucoadhesion[7, 8] depend on properties such as molecular weight and degree of deacetylation of chitosan. High molecular weight chitosan function as matrix tablet retardants, whereas low molecular weight chitosan can function as drug release enhancers for poorly water-soluble drugs due to an improvement in wettability resulting from the solubility of low molecular weight chitosan in water (less than 10,000)[9, 10].

Chitosan salts are soluble in water, the solubility depending on the degree of deacetylation and the pH of solution. Chitosan with low degree of deacetylation (≤40%) are soluble up to a pH of 9, where as highly deacetylated chitosan (≥85%) is soluble only up to a pH of 6.5. Increasing the degree of deacetylation increases the viscosity. Highly deacetylated chitosan has an extended conformation with a more flexible chain because of charge repulsion in molecule. Low degree of deacetylated chitosan has a rod like or coiled shaped molecules due to low charge density in polymer chain[11, 12].

Due to its positive charges at physiological pH, chitosan is bioadhesive, which increases retention at the site of application[8, 13]. It is totally degraded by colonic bacteria but is not digested in the upper GI tract. These polysaccharides remain intact in the physiological environment of the stomach and the small intestine, but are degraded by the bacterial inhabitants of the human colon[14] and certain human enzymes, especially lysozyme[15, 16].

Blending of chitosan with other polymers[17, 18, 19] and crosslinking are both convenient and effective methods of improving the physical and mechanical properties of chitosan for practical applications.

The purpose of this research was to study the factors influencing the floatation capability and release kinetics and to optimize the formula in order to increase the bioavailability. The floating matrix tablets of furosemide were prepared using blends of HPMC (hydroxypropylmethylcellulose) and chitosan and were evaluated for in vitro floating behavior. HPMC was initially used because it is reputedly a mucoadhesive[20], and should control the release of materials incorporated into matrix. To aid in the floatation of matrix tablets, sodium bicarbonate was incorporated. The principle of floatation was used to restrict the floating tablets to the stomach.

MATERIALS AND METHODS

Materials

Furosemide was obtained as gift sample from Modimundi Pharma Ltd, Modipuram, India. Hydroxypropylmethylcellulose 4000, 15000 and 100000 cps (HPMC K4 M, K15M and K100M respectively) were procured from Colorcon Company, Mumbai, India. Chitosan was obtained as a generous gift by Central Institute of Fisheries Technology, Kochi (Chennai, India). The other ingredients used were spray dried lactose (Vardhman Healthcare, Haryana, India) as a diluent and sodium bicarbonate (Ranbaxy Laboratories Ltd., India) as an effervescent agent. All other chemicals used were of analytical grade.

Methods

Preparation of matrix tablets

The weights of the matrix tablets prepared was kept 200 mg. Blends of the appropriate proportions of furosemide, relevant grades of HPMC, chitosan and spray dried lactose was prepared in a pestle and mortar. Magnesium stearate was then added to the final blend. To aid floatation, an effervescent agent i.e. sodium bicarbonate was added in the formulation. The ingredients were passed through sieve #80 before processing. The drug blend powder was compressed using a single punch R&D tablet compressing machine equipped with concave punches of 8 mm diameter. Each tablet contains 20 mg of furosemide and other ingredients as listed in table 1. The tablet hardness was kept in the range of 5-10 kg/cm^2 and the dwell time after target pressure achieved was 10 sec.

Evaluation of matrix tablets

The prepared floating matrix tablets were evaluated for hardness, weight variation, thickness, friability and drug content. The hardness of the tablets was determined using Monsanto tablet hardness tester. The friability of the tablets was determined in a Roche friabilator. The tablet thickness was measured using vernier calipers and weight variation test was performed according to official

method. For the determination of drug content five randomly selected tablets were weighed and powdered. The powdered tablet equivalent to 20 mg drug in one tablet was taken and transferred in a 250 mL flask containing 100 mL of 0.1N HCl (pH 1.2). The flask was shaken on a flask shaker for 24 hours and was kept for 12 hours for the sedimentation of undissolved materials. The solution was filtered through Whatman filter paper. 10 mL of this filtrate was taken and appropriate dilution was made. The samples were analyzed at 273 nm using UV visible spectrophotometer. The drug content was determined from the standard curve prepared at λ max 273 nm.

Table 1: Composition of matrix tablets

Ingredients	Quantity (mg)					
	A	B	C	D	E	F
Furosemide	20.0	20.0	20.0	20.0	20.0	20.0
HPMC K_4M	25.0	40.0	25.0	40.0	-	-
HPMC $K_{15}M$	25.0	40.0	-	-	25.0	40.0
HPMC $K_{100}M$	-	-	25.0	40.0	25.0	40.0
Chitosan	80.0	50.0	80.0	50.0	80.0	50.0
$NaHCO_3$	20.0	20.0	20.0	20.0	20.0	20.0
Lactose	29.0	29.0	29.0	29.0	29.0	29.0
Mag. Stearate	1.0	1.0	1.0	1.0	1.0	1.0
Total	200.0	200.0	200.0	200.0	200.0	200.0

Differential scanning calorimetry (DSC)

Differential scanning calorimetry (DSC) was used to characterize the thermal properties and possibility of any interaction between the excipients and with the drug in matrix. DSC analysis was conducted using a differential scanning calorimeter (Universal V4.1D TA Instruments (Q10), Waters Asia Ltd., USA). 10 mg of samples were accurately weighed and hermetically sealed in aluminium pans. Inert atmosphere was maintained by purging nitrogen gas (flow rate, 150 mL/min). The thermographs of the samples (figure 3) were obtained at a scanning rate of 10°C/min conducted over a temperature range of 40 to 400 °C.

In-vitro drug release and Buoyancy studies

A test of drug release from floating matrix tablets was performed in triplicate using USP type II dissolution apparatus (Scientific Instruments, USP-II, Grovers Enterprises, New Delhi) under sink condition. The dissolution medium was 900 mL, 0.1 N HCl (pH 1.2, enzyme free) at 35±0.5ºC with a stirring speed of 50 rpm for 8hrs. The samples (10 mL) were withdrawn at predetermined intervals and replaced by an equivalent volume of fresh medium. The dissolution data were corrected for this dilution effect. The samples were filtered through a 0.45µ membrane filter (Millipore, USA) and analyzed for furosemide concentration using spectrophotometrically (UV-Vis/NIR Spectrophotometer, Cary 5000, Varian, Australia Pty Ltd.) at 273 nm. Cumulative percentage drug release was calculated using an equation obtained from the standard curve. The times for 50, 80 and 100% drug release were calculated.

Buoyancy test

The tablets were placed in USP type II dissolution apparatus with 900 mL of 0.1N HCl solution at 37°C±0.5°C used as a testing medium. The medium was agitated with a paddle rotating at 50 rpm for 8 h. Both the time needed to go upward and float on the surface of the fluid and the floating durations were determined.

Table 2: Formulation Evaluation Parameters (n=3)

Code	Tablet Avg. Wt. (mg)	Tablet Avg. Hardness (Kg/cm_2)	Friability (%)	Average Thickness (mm)	Drug Content (%)
A	200.6	4.5	0.48	4.5	99.4
B	199.4	5.6	0.24	4.8	96.9
C	200.1	4.6	0.40	4.5	100.2
D	202.0	4.9	0.29	5.0	99.7
E	198.7	5.1	0.36	5.2	97.2
F	203.0	5.8	0.20	4.7	98.1

Dissolution profile fitting

The mechanism of drug release from floating matrix tablets during dissolution investigations in 0.1N HCl was determined using Zero order (eq. 1), First order (eq. 2), Higuchi (eq. 3), Korsmeyer & Peppas (eq. 4), Hixon-Crowell (eq. 5)[21, 22, 23] and Peppas and Sahlin (eq. 6) models:

$$M_t = M_0 + k_0 t \quad (1)$$

$$\log M_t = \log M_0 + \frac{k_1 t}{2.303} \quad (2)$$

$$M_t = M_0 + k_H \sqrt{t} \quad (3)$$

$$\frac{M_t}{M_0} = k_k t^n \quad (4)$$

$$M_0^{1/3} - M_t^{1/3} = k_s t \quad (5)$$

$$\frac{R}{F} = \frac{k_2}{k_1} t^m \quad (6)$$

In all mathematical expressions, M_t is the amount of the drug dissolved in time t; M_o is the initial amount of drug in the solution; M_t/M_0 is the fractional release of the drug; K_o is the zero-order release constant; k_H is the Higuchi rate constant; k_k is the release constant; k_s is a constant incorporating the surface-volume relation; and n is the release exponent, which characterizes the mechanism of drug release. Drug release data where M_t/M_0 is ≤0.6 were employed for determination of the release exponent.The similarity factor and dissimilarity factors between the formulations was determined using the data obtained from their drug release studies. The data were analyzed by the formula shown in equations 7 and 8.

$$f_1 = \frac{\sum_{j=1}^{n} |R_j - T_j|}{\sum_{j=1}^{n} R_j} \times 100 \quad (7)$$

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{j=1}^{n} (R_j - T_j)^2 \right]^{1/2} \times 100 \right\} \quad (8)$$

Where n = number of time points, R_j and T_j = dissolution of reference and test products at each time point j.

RESULTS AND DISCUSSION

Tablets prepared were obtained of uniform weight due to uniform die fill, with acceptable weight variation as per Pharmacopoeial specification. The drug content was found in the range of 96.9-100.2% (acceptable limit) and the hardness of the tablet was found between 4.5 – 5.8 Kg/cm^2. The hardness of the tablets containing higher chitosan content was found low with respect to tablets with low chitosan content. Similarly pattern was also observed during friability testing.

The tablet thickness was found to be around 3.0 mm and friability of tablet was found below 1% indicating good mechanical resistance. The formulated matrix tablets have content uniformity 95.68 to 104.63 % (table 2).

The Differential Scanning Calorimetry study of the tablet samples showed all the characteristic peaks of the excipients present and indicates that no polymorphic changes occurred during manufacturing of tablets (figure 3).

In-vitro drug release and buoyancy

As shown in the figure 1, there is a distinct difference in drug release profile of the different floating matrix tablets. Once in contact with the dissolution medium the matrices showed no visible disintegration but rather, they showed an apparent volume increase, due to water absorption, which was sensibly more marked for the matrices containing higher chitosan content.The highest percent of drug release was obtained from the formulation A (75.93%) followed by E (72.76%), F (56.98%), C (55.86%), B (50.17%), and D (48.37%) respectively in 8 h. The higher content of chitosan affected the extent of drug release whereas the type and quantity of HPMC in the matrices affected the pattern of drug release. All the formulations except formulation A exhibited buoyancy throughout the dissolution studies. The failure of formulation A to float for more than 1 hours may be due to presence of low viscosity grade HPMC along with high content of chitosan which could not retain the air bubbles liberated and also the tablet eroded very rapidly and sank in the dissolution medium.

Table 3: Drug Release Parameters of the Prepared Formulations (n=3)

Model	A	B	C	D	E	F
Zero Order	0.992	0.994	0.988	0.988	0.979	0.997
First order	0.820	0.842	0.888	0.857	0.870	0.697
Higuchi	0.902	0.920	0.863	0.891	0.875	0.920
Korsmeyer Peppas	0.943	0.896	0.894	0.929	0.841	0.974
N	0.690	0.632	0.612	0.589	0.715	0.611
K	0.718	0.651	0.656	0.727	0.531	1.022
Hixon Crowel	0.932	0.963	0.929	0.941	0.934	0.925
$t_{50\%}$	316.6	475.2	460.3	533.7	316.6	429.3
$t_{80\%}$	500.2	757.5	722.5	848.6	491.9	706.4
%Release (8hr)	75.94	50.17	55.86	48.37	72.76	56.98

Effect of Chitosan on Drug Release

The batches A, C, E the chitosan content was kept 40% and in batches B, D and F it was kept to 25%. In a study it was found that chitosan decreases rate of release of drugs from tablets during dissolution tests at acidic and slightly acidic pH levels[24, 25]. Similar results were also confirmed by Mi *et al*[5]. The results obtained by a study conducted by Ritger and Peppas[26], it was found that hydration & gel formation by chitosan in formulations takes place more readily at acidic pH levels (pH 1.2) than at pH levels close to neutral. It is due to the cationic nature of chitosan. The rate at which a drug is released from a hydrophilic chitosan matrix depends on the amount of chitosan involved and on the nature of the drug. Increasing the amount of chitosan in tablets decreases the release rate[5, 24]. Drugs with low solubility in water and/or high molecular weights were released most slowly[27, 28]. Formulations which contained 40% chitosan gave larger release rate in their last phase as compared to formulations containing 25%. It may be attributed to the fact that matrices containing chitosan become more porous as dissolution proceeds and release drug by diffusion[29]. Drug release profile of formulation F was unexpectedly faster in the initial phase. This may be due to rapid rate of surface erosion before a stable gel layer was formed. As sufficient water entered into the tablets, gel layer formed controlled the release of drug from the matrix.

Table 4: Results of Fitting Drug Release Data to Peppas-Sahlin Equation and Floating Parameters (n=3)

Code	K1	K2	K2/K1	M	R^2	Difference factor (f_1)	Similarity factor (f_2)	Buoyancy lag time (min)	Duration of Buoyancy (hr)
A	0.0035	0.00011	0.0311	0.69	0.994	-	-	< 1.0	8.0
B	0.003	0.00015	0.0504	0.632	0.993	41.20	50.18	10-12	8.0
C	0.0042	0.0002	0.0502	0.612	0.998	41.86	51.45	5-8	8.0
D	0.0008	0.0003	0.378	0.589	0.996	37.04	58.54	8-10	8.0
E	0.0024	0.000093	0.0381	0.715	0.975	76.53	5.94	6-8	6.5
F	0.0055	0.00018	0.0320	0.611	0.984	48.33	32.59	8-15	7.5

Effect of HPMC concentration

The batches A, B, C, D, E and F were prepared using similar blends in the ratio 0.5:0.5, but the percent content of the HPMC blend was increased. Therefore, the drug release will only depend on the content of HPMC blend. The effect of the content of HPMC blend on drug release is illustrated in figure 1. The rate of drug release from formulation A and B was greater than C & D. This may be due to the increased viscosity of HPMC blend in formulations C & D.

Formulation A released drug faster than B and similarly formulation C showed faster drug release than D. This effect may be attributed to the percentage content of HPMC blend in these matrices. Formulation E showed very fast drug release in second stage as compared to F.

The drug release from formulation F was in a controlled manner throughout the dissolution process. All of the formulations showed biphasic drug release i.e. initial slower release phase followed by faster release phase except formulation F. This behavior is unexpected corresponding to the composition of the matrix and is beyond the scope of this literature. This may be due to rapid erosion of the matrix initially followed by a stable gel layer formation which released the drug in a controlled manner[30].

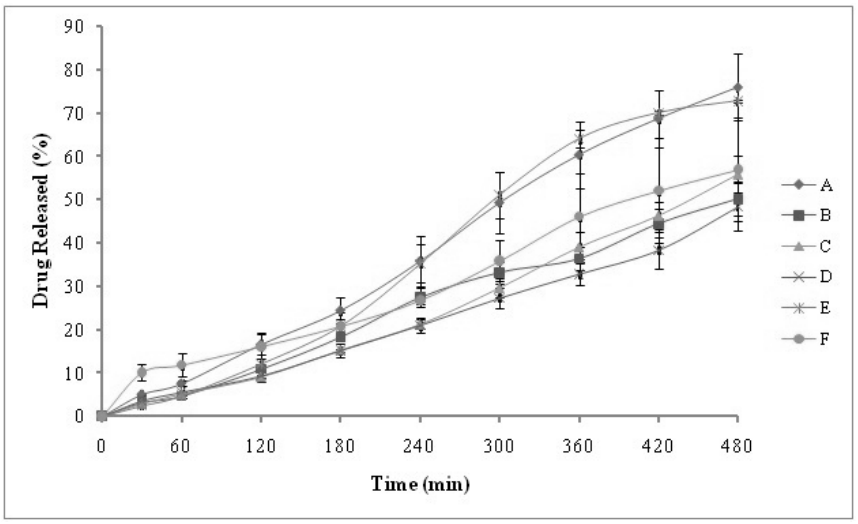

Fig. 1: Comparative drug dissolution profile mean±SD (n=3)

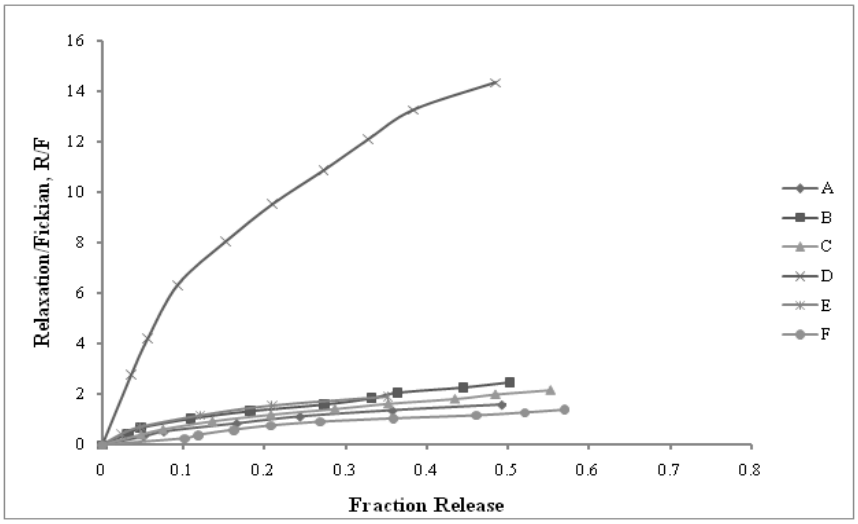

Fig. 2: Dissolution data fitting to Peppas Sahlin model

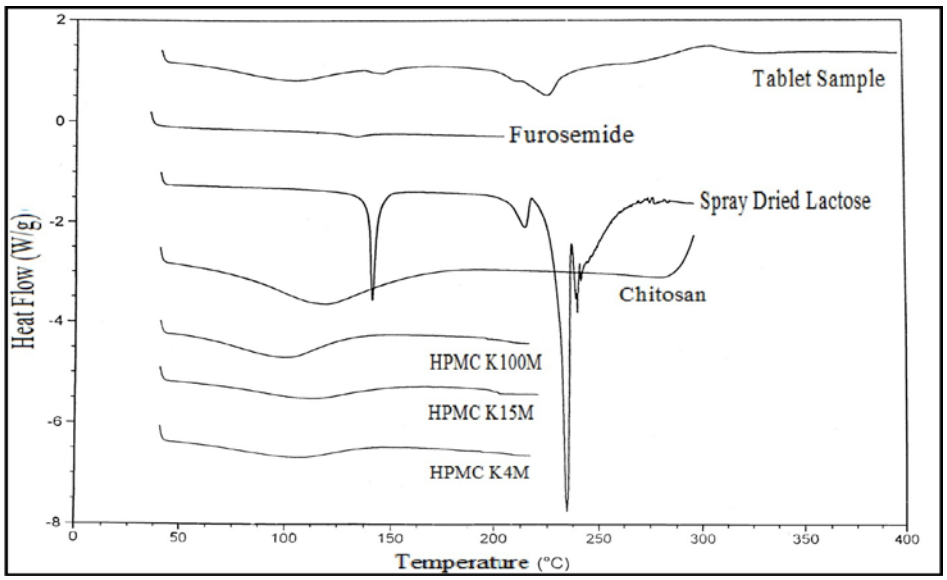

Fig. 3: Differential scanning calorimetry thermogram

Determination of Kinetics

In order to investigate the release mechanism, the data were fitted to various models and from the table 3, it is concluded that all the fabricated tablets followed zero order kinetics which indicates that the drug release was nearly independent of its concentration in the matrices (0.992, 0.994, 0.988, 0.988, 0.979, 0.997 respectively), however the second best kinetic model followed by the formulations A, C, D, E, F was Korsmeyer Peppas model (0.943, 0.894, 0.929, 0.974 respectively) and for formulations B and E was Higuchi model (0.920, 0.875). This explains why the drug diffuses at a comparatively slower rate as the distance for diffusion increases, which is referred to as square root kinetics (or Higuchi's kinetics).

In order to further understand the drug release mechanism, the data were fitted to Peppas exponential equation (equation 4) in which the diffusional exponent n characterizes the drug transport mechanism[31]. When n = 0.5, it indicates quasi-Fickian diffusion mechanism. For n > 0.5, an anomalous non-Fickian diffusion and the special case of n = 1 that has gained importance due to its potential application in the development of swelling controlled drug delivery systems with zero-order kinetics indicate pseudo-case-II transport mechanism[32]. From the kinetics data (table 3), it was observed that all the fabricated tablets followed non-Fickian diffusion mechanism, which indicates the drug release through diffusion and relaxation.

Contribution of the diffusional and relaxational mechanisms during the non-Fickian release process was carried out by fitting the data to the heuristic model proposed by Peppas and Sahlin (equation 6)[33]. From fitting of the data to this equation the ratio of relaxational (R) and Fickian (F) contributions can be calculated. The ratios of relaxation to diffusional contributions vs. fraction released of drug are presented in figure 2. As shown in this figure, the contributions of the two mechanisms for the fractional release of drug seem to be almost equal for A, B, C, E and F formulations, corresponding to the non-Fickian transport mechanism. For the other formulations D, the Fickian diffusion mechanism seems to be more effective on drug release as evident from their values of n (table 4). All these formulations exhibited the R/F profiles as expected from their values of 'n'.

CONCLUSION

It was concluded from the above study that the floating matrix tablets of furosemide was successfully developed in order to sustain the drug release rate by using combination of chitosan and HPMC as effective hydrophilic polymers. Chitosan was found to have profound influence on the in-vitro release profile of furosemide from the hydrophilic matrices. The buoyancy of tablets depends on the content of sodium bicarbonate and swelling property of the polymers. The tablets released the drug by non-Fickian diffusion following zero order release mechanism. The difference in the HPMC viscosity did influenced the drug release profiles.

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