FORMULATION DEVELOPMENT OF BUOYANT CONTROLLED RELEASE TABLETS CONTAINING CHITOSAN: OPTIMIZATION OF *IN-VITRO* DISSOLUTION AND RELEASE KINETICS

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ABSTRACT

The present study deals with formulation and evaluation of floating matrix tablets of Chitosan and HPMC using furosemide as model drug. Floating matrix tablets using Chitosan and HPMC in various concentrations were formulated and investigation of in vitro dissolution, floating capability, drug release kinetics and mechanism, similarity factor analysis were performed along with Differential Scanning Calorimetry to determine the physiochemical properties of the prepared tablets and the excipients. Effect of Chitosan and HPMC concentration on drug release kinetics and buoyancy was also determined. Formulations showed 78.53, 63.72, 50.19, 46.67, 74.95 and 76.52% of drug released in 8 hrs respectively. The values of $t_{50\%}$ and $t_{80\%}$ were found to be between 293.78 to 513.13 minutes for 50% of drug release and 488.72 to 826.69 minutes for 80% of drug release. In vitro drug release of furosemide in all the formulations was best explained by zero order equation and followed mechanism typical of non-Fickian diffusion. Most of the formulations showed floatation lag time of less <1 min and floated throughout the dissolution process. By combining HPMC with Chitosan in various blends we obtained formulations following zero order kinetics with floatation period of more than 8hrs and suitable for oral control release of furosemide.

Keywords: Floating drug delivery system, Release kinetics, Gastroretentive, HPMC, Chitosan.

INTRODUCTION

Furosemide (4-chloro-N-furfuryl-5-sulphamoylanthranilic acid) is a diuretic and has a highly variable bioavailability (<60%) when administered as commercially available tablets[1]. The bioavailability studies carried out on animals have pointed out that there may be regions in the stomach and/or upper part of the small intestine in which furosemide is specifically absorbed and it has been thought that the short stay of controlled release preparations in this specific region of absorption leads to bioavailability problems[2]. Passive diffusion is the major mechanism of transport of the drug across the gastrointestinal tract. Furosemide has a pKa of 4.6 and since the stomach environment is acidic, there is an increase in the unionized moiety of the drug with subsequent increase in the absorption[3]. A high peak diuresis is observed after the administration of a conventional tablet of furosemide. Due to this, it is only administered experimentally in the therapy for ascites, and edema due to liver cirrhosis.

To eliminate such an effect, various efforts have been made to formulate furosemide in prolonged release forms. A previous study has shown that the bioavailability of furosemide was excessively increased compared to conventional forms and that absorption of furosemide taken place vastly in stomach and upper parts of small intestine when administered as a floating tablet formulation[4]. Buoyant preparations offer a simple and practical approach to not only achieve increased gastric residence time for the dosage form but also modify the drug release profile. The present study involved the design of furosemide floating matrix tablets and the investigation of in vitro dissolution; buoyancy studies and drug release modeling were performed along with Differential Scanning Calorimetry to determine the physiochemical properties of the prepared tablets and the excipients.

MATERIALS AND METHODS

Furosemide and Chitosan were obtained as a generous gift by ModiMundi Pharma Pvt. Ltd. (U.P, India) and Central Institute of Fisheries Technology, Kochi (Chennai, India) respectively. HPMC K4 M, K15M and K100M (hydroxypropylmethylcellulose [HPMC] 4000, 15000, 100000 cps respectively) were procured from Colorcon Company, (Mumbai, India). Spray dried lactose from Vardhman Healthcare, Haryana, India, and sodium bicarbonate from Ranbaxy Laboratories Ltd., India. All other materials/solvents used were of analytical grade.

METHODS

Matrix preparation

The blend of polymers HPMC K4M, K15M, K100M, and chitosan were employed in the formulations to control the delivery of active material and for the matrix formation. To aid floatation, an effervescent agent i.e. sodium bicarbonate was added in the formulation. All the ingredients were passed through sieve #80 before processing. For each formulation, preweighed quantity of furosemide, blend of HPMC, chitosan, lactose, sodium bicarbonate, and magnesium stearate were manually blended homogenously using a pestle mortar. The homogenous blend was then directly compressed into tablet on a single punch R&D tablet compressing machine equipped with concave punches of 8mm diameter to produce tablets. The tablet weight was adjusted to 200mg. The tablet hardness was kept in the range of 5-6 kg/cm² and was measured on Monsanto tablet hardness tester.

Table 1: Composition of matrix tablets of Furosemide*

Ingredients (%)	A	B	C	D	E	F
Furosemide	10	10	10	10	10	10
HPMC** K₄M	26	6.5	26	6.5	-	-
HPMC K₁₅M	6.5	26	-	-	26	6.5
HPMC K₁₀₀M	-	-	6.5	26	6.5	26
Chitosan	32.5	32.5	32.5	32.5	32.5	32.5
NaHCO₃	10	10	10	10	10	10
Lactose	14.5	14.5	14.5	14.5	14.5	14.5
Mag. Stearate	0.5	0.5	0.5	0.5	0.5	0.5

*The weight of each matrix tablet is 200 mg; **HPMC indicates hydroxypropylmethylcellulose.

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 physical mixtures. DSC analysis was conducted using a Universal V4.1D TA Instruments (Q10) (Waters Asia Ltd., USA). Ultrahigh purity nitrogen was used as the purge gas at a flow rate of 150 ml/min. 10 mg samples were accurately weighed into aluminium pans and then hermetically sealed with aluminium lids. 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. Differential Scanning Calorimetry (DSC) studies of the prepared matrix tablet, the drug and the excipients showed that no polymorphic changes occurred during manufacturing of tablets as all the peaks were present in the DSC graph (figure 3) of tablet sample.

Dissolution methodology

The release of furosemide from different floating matrix tablets was carried out in triplicate using USP type II apparatus (Scientific Instruments, USP-II, Grover Enterprises, New Delhi) under sink condition. The dissolution medium was 900ml, 0.1 N HCl (pH 1.2, enzyme free) at $35±0.5°C$ with a stirring speed of 50 rpm for 8hrs. The samples were withdrawn at 0.5, 1, 2, 3, 4, 5, 6, 7, and 8hrs. 10ml of samples were withdrawn at intervals and replaced by an equivalent volume of fresh solvent. The dissolution data were corrected for this dilution effect. The samples were filtered through a 0.45µ membrane filter. The filtered samples were measured for furosemide concentration using UV Spectrophotometer at $\lambda=273$ nm (UV-Vis/NIR Spectrophotometer, Cary 5000, Varian, Australia Pty Ltd.). 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.

Floating capability

Floating time was determined by using the USP type II dissolution apparatus with 900 ml of 0.1N HCl solution at $37°C±0.5°C$ used as a testing medium. Both the time needed to go upward and float on the surface of the fluid and the floating durations were determined.

Kinetic modeling

The release profile obtained from each batch was fitted to Zero order (equation 1), First order (equation 2), Higuchi (equation 3), Korsmeyer & Peppas (equation 4) and Hixon-Crowell (equation 5) models to ascertain the kinetic modeling of drug release. 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 [5, 6, 7].

$$M_t = M_0 + k_0 t \tag{1}$$

$$\log M_t = \log M_0 + \frac{k_0 t}{2.303} \tag{2}$$

$$M_t = M_0 + k_H \sqrt{t} \tag{3}$$

$$\frac{M_t}{M_0} = k_k t^n \tag{4}$$

$$M_0^{1/3} - M_t^{1/3} = k_s t \tag{5}$$

The applicability of the Higuchi model is diminished due to some of the factors like it does not considers the edge effect and assumes the release to be one dimensional diffusion and fails to allow for the influence of swelling of the matrix (upon hydration) and gradual erosion of the matrix. The power law gives only a limited insight into the release mechanism of the drug however it is more comprehensive than Higuchi[7]. Hixon Crowel equation assumes that the release rate is limited by the drug particle dissolution and not by the diffusion occurring through the polymeric matrix[5]. This model was used by Neibergall et al.[8] and Prista et al.[9] to describe the release profile keeping in mind the diminishing surface of the drug particles during the dissolution.

Similarity factor (f₂) analysis

The similarity factor between the formulations was determined using the data obtained from their drug release studies. The data were analyzed by the formula shown in equations 8 and 9.

The difference factor (f_1) (equation 6) measures the percent error between two curves over all time points and similarity factor (f_2) (equation 7) is a logarithmic transformation of the sum squared error of differences between the test T_j and reference products R_j over all time points[6]. The values of 0-15 for (f_1) and the values of 50-100 for (f_2) are acceptable[10]. The difference factor (f_1) and the similarity factor (f_2) provide a simple measure of similarity between pairs of dissolution profile but do not provide information on individual batches[11].

$$f_1 = \frac{\sum_{j=1}^n |R_j - T_j|}{\sum_{j=1}^n R_j} \times 100 \tag{6}$$

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{j=1}^n (R_j - T_j)^2 \right]^{1/2} \times 100 \right\} \tag{7}$$

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

In vitro release drug release

Figure 1 shows the mean in vitro release profiles of the six different batches. The various dissolution parameters for the different matrix types are given in table 2. Also listed in the table are the respective values of $t_{50\%}$ and $t_{80\%}$ that is the time for release of 50 % and 80% of the dose. The data are average of three individual measurements of random tablets. There is a distinct difference in the furosemide release pattern between the formulations. As soon as the tablet came in contact with the dissolution medium, acid in the test medium reacted with sodium bicarbonate in the matrix resulting in CO_2 formation. The gas generated got entrapped in the sticky gel formed by the hydration of HPMC and prevents the air bubble from rupture. This decreases the density of the tablet below 1.0 and keeps the whole tablet buoyant on the surface of the test medium for as long as 8 hrs. The drug release from these matrices is controlled by the rate of formation of a partially hydrated gel layer formed on the tablet surface.
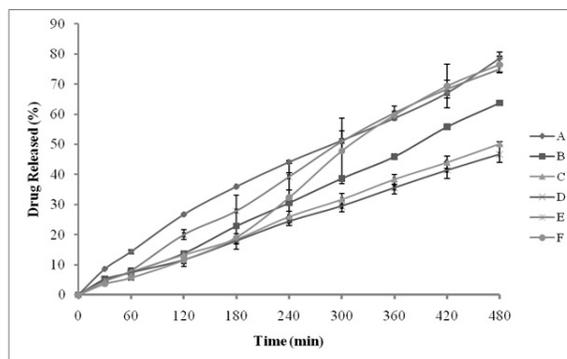

Fig. 1: Dissolution of Furosemide from HPMC-Chitosan matrix tablets (n=3)

All the batches were formulated using varying quantities of HPMC K_4M, $K_{15}M$, $K_{100}M$ and Chitosan. Varying ratios of HPMC K_4M, $K_{15}M$ and $K_{100}M$ were incorporated in the formulations but the chitosan

content was kept constant in order to study the viscosity effect of HPMC on release profile. Batches A, B, C, D, E and F showed 78.53, 63.72, 50.19, 46.67, 74.95 and 76.52% of drug released in 8 hrs respectively (table 2). The values of $t_{50\%}$ and $t_{80\%}$ were found to be between 293.78 to 513.13 minutes for 50% of drug release and 488.72 to 826.69 minutes for 80% of drug release for the floating tablets at varying polymer viscosities. This finding indicates the considerable release-retarding potential of the polymer blend for furosemide. An increase in polymer blend viscosity decreases the rate of swelling of polymer and increases the gel strength of swelled polymer. The time required traversing the thick viscous gel increases; thus, slower release from matrices prepared from high viscosity polymers occurs. All of these formulations showed sustained release. The percentage immediate release[12] part for sustained release furosemide was calculated using equation 8 and was found to be 2.7 to 7.5%.

Percentage immediate release part = $\dfrac{C_{ss} \times V_d}{F} \times 100$ **(8)**

Where, Css is steady state plasma concentration, Vd is volume of distribution, and F is fraction bioavailability.

Drug release kinetics and mechanism

Dissolution data from the batches was fitted to zero order, first order, Higuchi, Korsmeyer and Peppas and Hixon-Crowell models and the results are shown in table 2. The value of the release exponent (n) was found to be a function of polymer used and the physico-chemical property of the drug molecule itself. It was found that in vitro drug release of furosemide in all the formulations was best explained by zero order equation, as the plots showed the highest regression coefficient followed by Korsmeyer-Peppas and Hixon Crowel models.

A good compliance with zero order equation (average=0.99±0.013) indicates that the drug release was nearly independent of drug concentration in the matrix. The next best fit was Korsmeyer-Peppas model (average=0.958±0.0420) and Hixon Crowel (average=0.943±0.218). The calculated diffusion exponents (n) were found between 0.5 and 1 (average=0.724±0.056), which indicates a combination of diffusion and swelling controlled release mechanism, and drug release was highly influenced by swelling and gradual erosion of the matrix. It was concluded in a study that chitosan forms swellable and erodible gel[13] which resulted in release mechanism typical of non-Fickian diffusion[14].

In order to determine the contributions of the diffusional and relaxation mechanisms during the non-Fickian release process, a model proposed by Hopfenberg[15] and developed by Peppas and Sahlin[16] was used (equation 10):

$$\frac{M_t}{M_\infty} = k_1 t^m + k_2 t^{2m} \qquad \textbf{(10)}$$

Where k_1, k_2 and m are constants, the first term on the right hand side represents the Fickian diffusional contribution, F, whereas the second term the case-II relaxation contribution, R. The ratio of the two contributions is calculated by the following equation:

$$\frac{R}{F} = \frac{k_2 t^m}{k_1} \qquad \textbf{(11)}$$

The release data of formulations were analyzed according to this equation and the graph of ratio of R/F Vs fraction released is presented in figure 2. As shown in this figure, the contribution of the two mechanisms for the drug release seems to be almost equal for formulations A, C, D and E. For these formulations, the Fickian diffusion mechanism seems to be more effective on drug release as evident from their values of "n" (table 2). The higher R/F values for formulation F may be due to its biphasic release pattern in which the factor controlling the drug release is relaxation of the polymer network and erosion of the matrix. Diffusion seems to be more pronounced on drug release from rest of the formulations. The R/F contribution in formulation A seems to be balanced with respect to other formulations and also justifies its higher rate and extent of drug release.
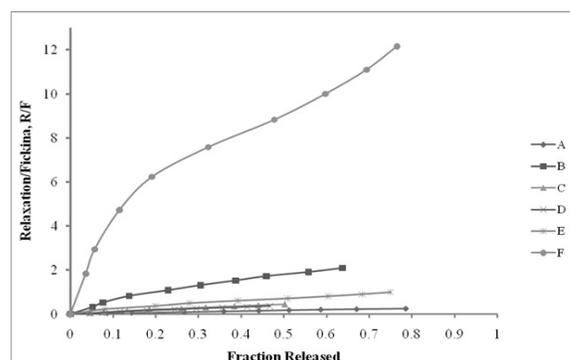

Fig. 2: Peppas-Sahlin model to investigate the release rate of Furosemide from matrix tablets.
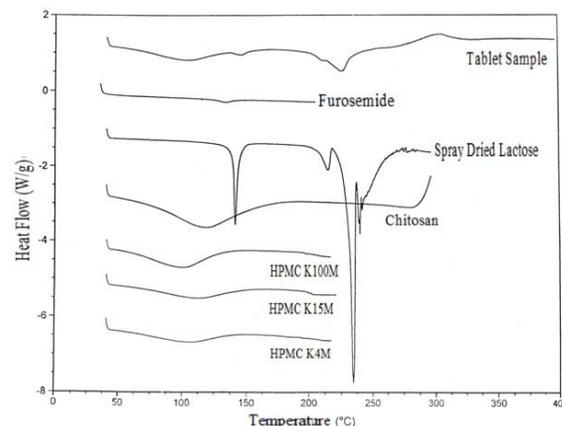

Fig. 3: Differential scanning calorimetry thermogram.

Similarity factor (f₂) analysis

Formulation A was considered as reference formulation for the comparison of difference (f₁) and similarity (f₂) factors due to its higher rate and extent of drug release with highest zero order release kinetics compliance. The data is tabulated in table 3 which reveals that formulations B and E (f₁= 7.98 and f₂= 66.58) showed the similarity of release profiles. Release profiles of other formulations were significantly different.

Table 2: Kinetic values obtained from different plots of formulations*

Model	A	B	C	D	E	F
Zero Order	0.995	0.998	0.994	0.999	0.990	0.964
First order	0.684	0.810	0.795	0.800	0.793	0.878
Higuchi	0.963	0.912	0.930	0.932	0.925	0.853
Korsmeyer Peppas	0.996	0.966	0.980	0.986	0.941	0.882
n	0.699	0.668	0.784	0.804	0.708	0.682
k	0.920	0.356	0.436	0.386	0.700	0.622
Hixon Crowel	0.951	0.951	0.956	0.961	0.943	0.901
t₅₀% (min)	293.78	383.11	477.05	513.13	308.79	322.29
t₈₀% (min)	488.72	611.09	768.24	826.69	493.45	499.39
% Release	78.53	63.72	50.19	46.67	74.95	76.52

*All values represent mean (n = 3). t_{50} and t_{80} indicates time required for 50% and 80% drug dissolution, respectively.

In vitro buoyancy

On contact with the dissolution medium, hydrochloride in the test medium reacts with sodium bicarbonate in the matrix inducing CO_2 formation in the floating section, thereby decreasing the density of the matrix system and aid in floatation. The swelling properties of HPMC[17] and chitosan[14] supported the system reaching a lower density as long as the volume expansion was faster than the weight gain. Blends of various grades of HPMC and chitosan[18, 19] were found good candidates for the floating delivery system. It sufficiently expanded in contact with dissolution media and was flexible enough to encapsulate the CO_2 formed and did not release it rapidly, which made the formulation to float almost throughout the dissolution process.

Formulations A, B, C and D showed lag time of less <1 min. whereas formulations E and F showed lag time of approximately 3-5 and 5-8 minutes respectively. High lag time may be due to the content of low swelling high viscosity HPMC K100M in these formulations. The Content of lactose did not play any significant role in swelling of these matrices. Dissolution media could not easily penetrate through these formulations resulting in lower rate of formation of CO_2. The floatation time of formulations E & F were approximately 5.5 and 7.0 h respectively. This may be due to large rate of erosion, which significantly reduced the volume of these matrices, and they sank in the dissolution medium. All the formulations except E and F floated throughout the dissolution process.

Table 3: Evaluation parameters of floating matrix tablets*

Code	Peppas-Sahlin model					Difference factor (f_1)	Similarity factor (f_2)	Buoyancy lag Time (min)	Duration of Buoyancy (hr)
	K1	K2	K2/K1	m	R^2				
A	0.008181	0.0000272	0.00332	0.699	0.9977	-	-	< 1	T
B	0.003352	0.000113	0.0338	0.668	0.9992	26.22	47.56	< 1	T
C	0.002759	0.00000974	0.00353	0.784	0.9992	39.15	38.05	< 1	T
D	0.002411	0.00000614	0.00255	0.804	0.9989	43.10	35.83	< 1	T
E	0.004954	0.0000622	0.0126	0.708	0.9944	7.98	66.58	3-5	5.5
F	0.000913	0.000165	0.181	0.682	0.9901	15.41	52.65	5-8	7.0

*I= Immediate floatation within 1 min., T= Throughout the dissolution studies. Formulation A has been taken as reference in determining f_1 and f_2.

Effect of polymer concentration

Instead of using only a single viscosity grade of HPMC polymer, blends of different viscosity grade of HPMC were used to prepare the matrix tablets. A broad range of drug release behavior was obtained from matrix tablets prepared with blends of HPMC K4M, K15M, and K100M. Streubel et al.[20] had also used blends of HPMC and reported similar results. The viscosity of the blends of HPMC grades could be obtained by empirical equation presented as follows;

$$V_b^{1/8} = F_1 V_1^{1/8} + F_2 V_2^{1/8} \qquad (9)$$

Where, V_b = viscosity of polymeric blend, F_1 and F_2 = fraction of polymers, and V_1 and V_2 = viscosity of two polymers respectively[21].

The batches A & B were prepared using blend of HPMC K4M/K15M, C & D using blend of HPMC K4M/K100M and E & F using blend of HPMC K15M/K100M respectively. The content of chitosan in all the formulations was kept constant (table 1).

The effect of varying the blend ratio on drug release is illustrated in figure 1. By the calculation of apparent viscosity of the HPMC blends, it was revealed that the viscosity of the mixture increased while the percent content of polymer blend in the tablets was kept constant. So, the effect on the drug release mainly depends on the viscosity of the HPMC blend[21]. The rate of drug release from the matrices was in the order A>F>E>B>C>D respectively.

Formulation A showed highest % drug release because when the viscosity of the blend is low the tablets show a fast controlled release phase, and as the viscosity of the HPMC blend increases, the drug release occurs in a slow controlled manner throughout. Similar results were reported by Wan et al.[22] and Dortunc et al.[23] in which they demonstrated that HPMC with higher viscosity resulted in thicker gel layer formulation. The presence of lactose also contributes its part in faster drug release due to its higher water solubility and osmotic activity, resulting in a faster uptake of the medium into the core by diffusion[17]. It may also be attributed that matrices containing chitosan become more porous as dissolution proceeds and release drug by diffusion[24]. The rate at which a drug is released from the hydrophilic matrix depends on the amount of polymer involved and on the nature of the drug. Increasing the amount of hydrophilic polymer in tablets decreases the release rate[13, 25]. On the other hand drugs with low solubilities in water and/or high molecular weights are released very slowly[26, 27]. Formulation C gave release nearer to that of D. A possible explanation is the existence of a limiting HPMC viscosity above which no further decrease in drug release is seen[28, 29, 30], and higher viscosity HPMC resulted in thicker gel formation and corresponding decrease in the drug release[31]. Matrix E and F (more distinct in F) showed a biphasic release pattern, that is, an initial polymer controlled slower release followed by rapid drug release in the second phase. These biphasic release patterns were caused by an apparent change in the matrix structure i.e. formation of a stable gel layer[32]. Over the first phase, hydrated HPMC remained at the surface of the matrix and the matrix swelled and disentangled, the density and strength of gel layer weakened, resulting in rapid erosion. The results comply with the findings of Krogel and Bodmeier[30]. They stated that the decreased drug release is probably because of the formation of a denser gel and slower erosion at the higher HPMC content.

CONCLUSION

The current studies are aimed at successful development and optimization of floating matrix tablets of furosemide with high regulation of the release rate. Differential Scanning Calorimetry (DSC) studies of the prepared matrix tablets and the drug and the excipients showed that no polymorphic changes occurred during manufacturing of tablets as all the peaks were present in the DSC graph of tablet sample. All the batches showed immediate floatation and floatation period of more than 8hrs. Furosemide release through the matrices includes the combination of diffusion and swelling controlled drug release. Release from these matrix tablets mostly complied with zero order kinetics and extended over longer period of time and depends on the composition of polymer blend. Incorporation of chitosan in the formulation included an initial burst effect followed by a controlled release phase. By increasing the viscosity of the polymer blend, the rate and extent of drug release form the tablets decreases. Regulated drug release in zero-order manner attained in the current study indicates that the floating matrix tablets of furosemide, prepared using blend of HPMC-Chitosan are thus suitable for oral control release of furosemide.

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