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Development and Optimization of Gastroretentive drug delivery system for Oseltamivir

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Abstract

The objective of this research work was to formulate and optimize a floating drug delivery system of Oseltamivir using simple lattice design. Floating tablets were prepared by melt granulation method. In this design xanthan gum as matrix forming agent, sodium bicarbonate as gas generating agent and ethyl cellulose as floating enhancer were used as independent variables and floating lag time, t_{50} and t_{80} as responses. The optimization study reveals that optimum amounts of xanthan gum, sodium bicarbonate and ethylcellulose is required to develop a gastroretentive drug delivery system of oseltamivir with a desired release profile. Moreover, the studies indicate that the proper balance between floating enhancer and release rate retardant can produce formulations with desirable release and floating properties. Kinetics of the drug release from tablets followed Krosmeyer Peppas model by anomalous non-Fickian diffusion. It was concluded that the gastroretentive drug delivery system can be developed for Oseltamivir to increase the residence time of drug in the stomach and thereby increasing its absorption. The present study demonstrates the use of Simple lattice design in the development of floating tablets with minimum experimentation.

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Oseltamivir, Xanthan Gum, Gastroretentive drug delivery, In vitro buoyancy study.

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INTRODUCTION:

Oseltamivir is an anti-viral drug approved for the prophylaxis and treatment of Type A and B influenza

in adults and children aged one year and older. The current dosage forms of oseltamivir available are in the form of capsule and suspension. However there are some limitations to the current dosage forms. The absorption in the gastrointestinal tract of immediate release dosage form such as capsule and suspension in this case may be very short and highly variable in altered circumstances [1]. For antiviral treatment, maintenance of therapeutic concentration is of utmost importance as resistance of virus to the drug may develop quickly. Repeated dosing requires close monitoring of the pharmacokinetic profile of the drug. Limitations of conventional drug delivery can be overcome by modification and application of pharmaceutical technology by developing controlled release formulations [2]. However, these delivery systems have its own problems. One of the problems associated is rapid gastrointestinal transit time which could result in incomplete drug release in the absorption zone leading to diminished efficacy of the administered dose [3].

Different approaches are currently available to retain the dosage form in the stomach. These include bioadhesive systems [4], swelling and expanding systems [5, 6], floating systems [7, 8] and other delayed gastric emptying devices [9, 10]. The principle of buoyant preparations offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release. In this study floating drug delivery system (FDDS) is chosen as a method to obtain sufficient bioavailability and maintain therapeutic drug levels. The aim of the present research study is to develop gastroretentive drug delivery system for oseltamivir using simplex lattice design as an optimization technique.

MATERIALS AND METHODS:

Materials

Oseltamivir is a gift sample obtained from Aurobindo Pharmaceuticals Ltd, Hyderabad, India. Xanthan gum is purchased from CCM chemicals Sdn Bhd., Kuala Lumpur, Malaysia. Ethylcellulose (EC) is purchased from Hoe Pharmaceuticals Sdn Bhd., Kuala Lumpur, Malaysia. All other chemicals used were of analytical grade.

Methods

Preparation of oseltamivir gastroretentive tablets

Gastroretentive tablets of oseltamivir were prepared by melt granulation technique. A geometric mixture of xanthan gum, sodium bicarbonate and ethylcellulose was prepared using mortar and pestle. The weighed amount of beeswax was melted in a beaker using water bath. The required amount of oseltamvir was then added into the melted beeswax which forms a molten mass. Then, the geometric mixture was slowly added into the molten mass with continuous stirring allowing formation of a uniform mass. The mass was subjected to cooling at room temperature. The mass was then passed through a sieve to obtain the granules. Finally the granules were lubricated with 2% talc and 1% magnesium stearate and subjected to compression using and 9 mm round and flat tablet punch. Compression force was adjusted according to the required hardness.

In vitro buoyancy study

Each tablet was placed in a 250 ml beaker containing dissolution medium, USP simulated gastric fluid 0.1N HCl with pH1.2. The time taken for the tablet to float to the surface of the dissolution medium (Floating lag time, F_{lag}) and the floating duration is determined.

In vitro dissolution study

Dissolution studies of oseltamivir formulations were carried out in simulated gastric fluid 0.1N HCl with pH 1.2. Dissolution study was carried out using USP XXI dissolution rate test apparatus (TDT-08L) with rotating paddle in 900 ml of dissolution medium. The stirring speed was set at 50 rpm and the temperature was maintained at 37°C ± 0.5°C and the study was conducted for 24 hours. 5 ml of aliquot of dissolution medium was withdrawn at time intervals

of 1, 2, 3, 4, 6, 8, 10, 12, 18 and 24 hours by a syringe with Millipore filter with pore size of 0.45 µm. The volume withdrawn at each time was replaced with 5 ml of fresh dissolution medium. The sample was then assayed using spectrophotometer for absorbance at wavelength 208.5 nm. The drug concentration was then calculated using the standard calibration curve.

Simplex lattice design

A simplex lattice design [12] was adopted to optimize the formulation variables. In this design, three factors were evaluated by changing their concentrations simultaneously and keeping their total concentration constant. The simplex lattice design for a 3-component system is represented by an equilateral triangle in 2-dimensional space (Figure 1). Seven batches (S1-S7) were prepared: one at each vertex (A, B, C), one at the halfway point between vertices (AB, BC, AC), and one at the center point (ABC). Each vertex represents a formulation containing the maximum amount of 1 component, with the other 2 components at a minimum level. The halfway point between the 2 vertices represents a formulation containing the average of the minimum and maximum amounts of the 2 ingredients represented by 2 vertices. The center point represents a formulation containing one third of each ingredient. The amounts of matrixing agent (Xanthan gum, X1), gas-generating agent (Sodium bicarbonate, X2), and floating enhancer (Ethyl cellulose, X3) were selected as independent variables. The floating lag time (Flag) and the time required for 50% (t_{50}) and 80% (t_{80}) drug dissolution were taken as responses.

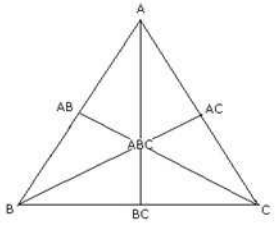

Figure 1: Equilateral triangle representing simplex lattice design for 3 components (A, B, and C)

Kinetics of drug release

The dissolution of all the batches of floating tablets of oseltamivir was carried out. Model-dependent approach was used to study the release kinetics. The dissolution profile of all the batches was fitted into various models which include zero order, first order, Higuchi's and Korsemeyer- Peppas models to ascertain the kinetic modeling of drug release. The best fit model was determined using the correlation coefficient, R^2 which was obtained from the respective plots.

Stability Studies

Short term stability studies were carried out as per ICH guidelines [13]. The tablets were stored at 40°C /75% RH for 3 months. The samples were withdrawn at monthly intervals and checked for physical appearance, floating properties and *in vitro* drug release studies.

RESULTS AND DISCUSSION:

The major objective of the present study was to develop a gastroretentive drug delivery system for oseltamivir using simplex lattice design as an optimization technique. In this study, tablets were prepared using xanthan gum as the matrix forming agent, beeswax as a meltable polymer, ethyl cellulose (EC) as floating enhancer and sodium bicarbonate as gas generating agent. Initially, five trial batches (T1-T5) were prepared using the fixed amounts of sodium bicarbonate and beeswax but different amounts of xanthan gum and EC. The amount of xanthan gum was decreased, while the amount of EC was increased from batch T1 to T5. From the evaluation results (Table 1), it was observed that as the amount of EC was increased from 0% to 20%, the F_{lag} decreased, and this effect was significant on reducing F_{lag} up to 10% of EC and beyond that there is no significant decrease in F_{lag}. Hence, it was decided to optimize the amount of EC between 0% and 10%. As the amount of xanthan gum was increased from 20% to 40%, the F_{lag} increased, indicating that a high amount of

xanthan gum is undesirable to achieve low F_{lag}. Below 25%, xanthan gum could not give sufficient strength to the matrix as the tablets ruptured within 6 hours. Hence, it was decided to optimize xanthan gum between 25% and 35%. Formulations T1 to T5 were subjected to *in vitro* dissolution study. All the tablets ruptured within 14 hours with more than 80% drug release. This result might be due to poor strength of tablets or to insufficient binding provided by beeswax, which failed to keep the matrix intact. Therefore, two more formulations were prepared (T6 and T7) using 15% and 20% of beeswax, respectively, and were found to remain intact for more than 24 hours under stirring at 50 rpm in the dissolution studies. Formulation T7 exhibited floating lag time of 234 seconds. This result might be due to poor penetration of SGF in a tablet core owing to a high amount of beeswax. Hence, it was decided to keep the beeswax at 15%. In order to optimize the formulation for acceptance criteria (ie, Flag, less than 180 seconds; t_{50}, between 11 and 13 hours; and t_{80}, between 18 and 20 hours), a simplex lattice design was used in the present investigation.

Table 1: Results of tablet formulation and evaluation of preliminary trials*

Formulation Ingredients/ Evaluation Parameters	T1	T2	T3	T4	T5	T6	T7
Beeswax (%)	10	10	10	10	10	15	20
Xanthan gum (%)	40	35	30	25	20	30	30
Sodium bicarbonate (%)	10	10	10	10	10	10	10
Ethylcellulose (%)	0	5	10	15	20	10	10
Floating lag time (seconds)	265	213	172	168	162	149	234
Floating time without rupture of tablets (hrs)	<14	<14	<12	<6	<4	>24	>24

*All batches contained 150mg oseltamivir, 2% w/w talc and 1% w/w magnesium stearate; the average weight of each tablet was 385mg.

Simplex Lattice Design

The amounts of matrix forming agent (xanthan gum, X_1), gas generating agent (sodium bicarbonate, X_2), and floating enhancer (EC, X_3) were selected as independent variables in a simplex lattice design. The floating lag time (F_{lag}) and times required for 50% (t_{50}) and 80% (t_{80}) drug release were taken as responses. A statistical model incorporating 7 interactive terms was used to evaluate the responses.

$$Y= b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{123}X_1X_2X_3 \ldots\ldots \textbf{(1)}$$

where Y is the dependent variable, bi is the estimated coefficient for the factor Xi. The main effects (X_1, X_2, and X_3) represent the average result of changing 1 factor at a time from its low to high value. The interaction terms (X_1X_2, X_2X_3, X_1X_3, and $X_1X_2X_3$) show how the response changes when 2 or more factors are simultaneously changed.

The dissolution profile of the simplex lattice design batches (S1-S7) are shown in Figure 2. The values for F_{lag}, t_{50}, and t_{80} for all 7 batches (S1-S7) showed a wide variation (ie, 104 to 212 seconds, 6 to 12 hours, and 13 to 23 hours, respectively) (Table 2). The data clearly indicate that the values of F_{lag}, t_{50}, and t_{80} are strongly dependent on the selected independent variables.

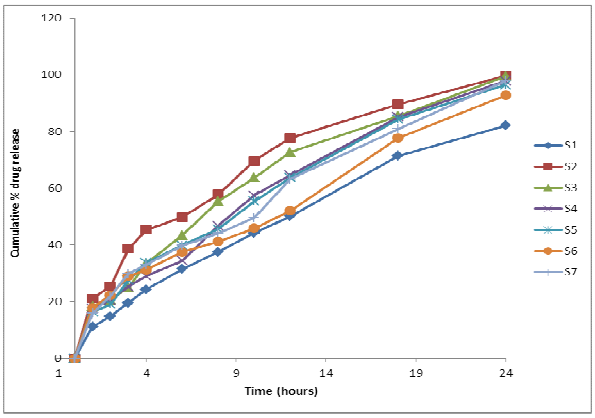

Figure 2: Dissolution profiles of the simplex lattice design batches

The fitted equations relating the responses F_{lag}, t_{50}, and t_{80} to the transformed factor are shown in Equation 2, Equation 3, and Equation 4, respectively.

$$F_{lag} = 212.43\ X_1 + 104.43\ X_2 + 126.44\ X_3 - 52.8\ X_1X_2 - 236.71\ X_1X_3 + 191.29\ X_2X_3 \quad \textbf{....(2)}$$

$$t_{50} = 11.86\ X_1 + 5.96\ X_2 + 7.06\ X_3 - 0.56\ X_1X_2 + 8.03\ X_1X_3 + 5.439\ X_2X_3 \quad \textbf{.... (3)}$$

$$t_{80} = 22.64\ X_1 + 12.94\ X_2 + 15.14\ X_3 - 4.56\ X_1X_2 + 0.62\ X_1X_3 + 5.22\ X_2X_3 \quad \textbf{....(4)}$$

Table 2: Formulation and Evaluation of Batches in Simplex Lattice Design*

Formulation code	Transformed Fractions of Variables			F_{lag} ± SD (seconds)	t_{50} ± SD (hours)	t_{80} ± SD (hours)
	X_1	X_2	X_3			
S1	1	0	0	212	11.9	22.7
S2	0	1	0	104	6	13
S3	0	0	1	126	7.1	15.2
S4	0.5	0.5	0	147	8.6	16.4
S5	0	0.5	0.5	165	7.7	15.1
S6	0.5	0	0.5	112	11.3	18.8
S7	0.33	0.33	0.33	133	10.1	17.6

Code values	Actual values**		
	X_1	X_2	X_3
0	90	15	0
1	120	45	30

*F_{lag} indicates floating lag time; SD, standard deviation, t_{50} and t_{80}, time required for 50% and 80% drug dissolution, respectively. All batches contained 150 mg of oseltamivir, 50 mg of beeswax, 2% w/w talc, and 1% w/w magnesium stearate. Average weight of each tablet was 385 mg.

**X_1 is the amount of xanthan gum (mg); X_2 amount of sodium bicarbonate (mg); X_3 is the amount of ethyl cellulose (mg).

The high values of correlation coefficients for F_{lag} (R^2 = 0.9969), t_{50} (R^2 = 0.9921), and t_{80} (R^2 = 0.9916) indicate a good fit (i.e., good agreement between the dependent and independent variables). The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (i.e., positive or negative). The equation for F_{lag} suggests that the factor X_1 has more significant effect on floating lag time, followed by factors X_3 and X_2. Therefore, a high level of factor X_1 should not be selected for lowering floating lag time. From Equations 3 and 4, it can be concluded that factor X_1 has a more important role in prolonging both the t_{50} and t_{80}. The magnitude of coefficients indicates that the factor X_3 has a more favorable effect on both the dependent variables (t_{50} and t_{80}) than factor X_2. The negative coefficient of X_1X_2 in case of all the three equations implies that the interaction between X_1 and X_2 has an insignificant effect on F_{lag}, t_{50} and t_{80}. From the results of multiple linear regression analysis, it can be concluded that the drug release pattern may be changed by appropriate selection of the X_1, X_2, and X_3 levels.

The promising formulation was selected on the basis of the acceptance criteria for F_{lag}, t_{50}, and t_{80} as mentioned earlier. All the formulations have passed the criteria for F_{lag} except S1. Formulations S1 and S6 passed the criteria for t_{50}. The criterion for t_{80} was passed only by Formulation S6. Hence, Formulation S6 was selected as a promising formulation from the simplex lattice design batches.

Kinetics of Drug Release

The dissolution data of batches S1 to S7 were fitted to zero order, first-order, Higuchi, and Korsmeyer-Peppas models. The correlation coefficient (R^2) values of the plots "percentage drug release vs. time" and "log percentage drug remaining vs. time" are compared. The R^2 values for zero order kinetics of the drug release data are found to be higher (0.8865 to 0.9723) compared to that of the R^2 values for first order kinetics plain matrix tablets (0.7896 to 0.9297) as shown in Table 3 indicating that the drug release

from the formulations follow zero order kinetics. Moreover, the release profile of promising batch, S6, fitted best to zero-order model. Thus, it may be concluded that drug release from gastroretentive oseltamivir tablets is best explained by the zero-order model. The other simplex lattice design batches also followed the zero-order model.

Table 3: In vitro dissolution kinetics of oseltamivir floating tablets

Formulation	Correlation coefficient (R^2)			n
	Zero Order	First Order	Higuchi	Release exponent
S1	0.9723	0.8699	0.973	0.6533
S2	0.8865	0.7896	0.9907	0.513
S3	0.934	0.8346	0.9854	0.594
S4	0.9658	0.8981	0.9733	0.588
S5	0.96	0.8639	0.9841	0.589
S6	0.962	0.9297	0.9621	0.508
S7	0.9591	0.8811	0.9848	0.562

To evaluate drug release mechanism from the matrix tablets, plots of cumulative percentage release vs square root of time as per Higuchi's equation were constructed. These plots were found to be linear with all the formulations (R^2: 0.9621 to 0.9907) indicating that the drug release from the different formulations was diffusion controlled. To confirm the diffusion mechanism the data were fit into Korsmeyer equation. Release exponent value varied from 0.508 to 0.653 indicating release mechanism was anomalous non-Fickian or anomalous release ($0.45 < n < 0.89$).

The factorial batches were subjected to short-term stability studies at 40°C and 75% relative humidity (RH) for 3 months. Samples withdrawn after 3 months showed no significant change in appearance of the tablets, floating lag time, and *in vitro* drug release.

Conclusions:

The study was aimed at preparation of gastroretentive tablets of oseltamivir using xanthan gum, sodium bicarbonate and ethyl cellulose as matrixing agent, gas generating agent and floating enhancer respectively. A simplex lattice design was applied to investigate the combined effect of three formulation variables (i.e., amount of xanthan gum, sodium bicarbonate and ethyl cellulose). Results of the multiple regression analysis indicated that the optimum levels of the three variables should be used to manufacture the tablet formulation with desired *in vitro* floating time and dissolution. Formulation S6 was selected as a promising formulation and was found stable at 40°C temperature and 75% RH for 3 months.

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