Formulation optimization of floating microbeads containing modified Chinese yam starch using factorial design.

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ABSTRACT

Controlled release floating metformin hydrochloride microbeads were prepared and optimized using a blend of varying concentrations of freeze-dried pregelatinized Chinese yam starch (*Dioscorea oppositifolia* L) and sodium alginate. Floating microbeads were prepared by the ionotropic gelation method using 10% w/v calcium chloride as the cross-linking agent and sodium bicarbonate as the gas releasing agent. A full 3^2 factorial design was used to investigate the influence of two variables: concentrations of starch (X_1) and sodium bicarbonate (X_2) on the swelling, floating lag time and amount of drug released after 1 hour (Q_1) and 10 hours (Q_{10}). Potential variables such as the concentrations of drug and total polymer were kept constant. The results showed that the properties of the floating microbeads were significantly ($p<0.01$) affected by the concentration of the modified Chinese yam starch. Buoyancy and drug release appeared to be facilitated by increased concentrations of both starch and sodium bicarbonate in the formulation. The results also show that an optimized formulation of metformin hydrochloride could be obtained with the potential for gastroretentive controlled drug delivery using a blend of freeze-dried pregelatinized Chinese yam starch and sodium alginate.

KEY WORDS: Excipients, floating microbeads, Chinese yam starch, metformin hydrochloride, controlled drug delivery

INTRODUCTION

During the last two decades tremendous advances have been made in the development of oral controlled drug delivery systems (1-3). Some of the advantages include improved therapeutic efficacy, ease of administration of dosing, flexibility when formulating a drug, and patient compliance (3). However, a major constraint of these delivery systems is that not all drug candidates are absorbed uniformly throughout the gastrointestinal tract. One of the approaches for achieving prolonged and predictable drug delivery profiles in the gastrointestinal tract is to control the gastric residence time using Gastroretentive Dosage Forms (GRDFs). With GRDFs, the dosage form is retained in the stomach for a prolonged period of time while the drug is released continuously, thus ensuring optimal bioavailability. One of the approaches to increase the retention of an oral dosage form in the stomach is to use a Floating Drug Delivery System (FDDS) (4). An FDDS has a lower bulk density than the gastric fluid, and without affecting the

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gastric emptying rate, remains buoyant in the stomach for a prolonged period of time (5). The drug is released slowly from the delivery system while the dosage form is floating on the gastric contents leading to reduced fluctuations in plasma drug concentrations (6). The FDDSs utilize matrices prepared with swellable polymers such as polysaccharides, e.g., sodium alginate, and an effervescent component, e.g., sodium bicarbonate, citric or tartaric acids or matrices containing chambers of liquid that gasify at body temperature. On arrival in the stomach, the carbon dioxide is liberated from the matrices by the acidity of the gastric contents and then entrapped in the gelatinous hydrocolloid which causes an upward motion of the dosage form to float on top of the chyme. The carbonates, in addition to imparting buoyancy to these formulations, also provide the initial alkaline microenvironment for the polymer to gel (6).

Drug formulation studies often involve a great number of experiments and much time and effort is usually expended, especially when developing complex formulations. The number of experiments can be reduced by the use of an experimental design which can be an efficient method for indicating the relative significance of a number of formulation variables and their interactions with each other (7). It also allows the formulation studies to be completed within the shortest possible time, resulting in cost savings and the reduction of raw materials used. Moreover, the effects of the independent variables and their interactions can be evaluated. One such experimental design is the 3^2 factorial statistical model which incorporates interactive and polynomial terms to evaluate the responses of the various formulation and process variables (7).

Starch is a well-known excipient but lately there has been a growing interest in starch microspheres for delivery of active substances via several different routes of administration. This is because starch is known to have low toxicity, is biodegradable and yet quite stable in a biological environment (8-10). Most studies have used a blend of proprietary starches such as corn, potato and rice starches (8, 9) and polymers, such as sodium alginate, to modulate drug release from mucoadhesive microbeads. Controlled release was achieved only when the microbeads were coated with HPMC (9). It has been shown that starches from different sources vary in their physicochemical and functional properties. Starches containing mainly amylopectin and traces of amylose have been shown to have great potential as novel mucoadhesive polymers. This is due to the free hydroxyl groups that open up the possibility for the starch to be crosslinked with other polymers for controlled drug release (11).

A new starch that could be explored commercially in the food and pharmaceutical industries is the starch from the Chinese yam found in the tubers of *Dioscorea oppositifolia* L, Family Dioscoreaceae, a staple root crop found in China and parts of Africa (12). The tubers have a starch content of 64% w/w (dry weight basis) and the starch has shown promising potential as a disintegrant or binder in tablet formulations (13). Native Chinese starch which consists of 78.4% amylopectin (12) has been modified by pregelatinization followed by freeze drying and characterized as a pharmaceutical excipient (14). The modified Chinese yam starch has been used in combination with sodium alginate for the formulation of floating gastroretentive microbeads for the controlled delivery of metformin hydrochloride (hereafter referred to as MET) (10). The spherical, discrete and free flowing floating microbeads were prepared using a blend of the modified Chinese yam starch and sodium alginate at different concentrations using sodium bicarbonate as a gas-generating agent. The beads provided controlled release of MET, buoyancy was maintained for up to 12 hours. The formulations released the drug by diffusion and erosion controlled mechanisms of drug release which appeared to be controlled by varying the starch to alginate polymer ratio. However, the

effects of important formulation variables on these novel microbeads have not been fully evaluated. Thus in the present study, a full 3^2 factorial experimental design has been used to evaluate the influence of two variables: concentrations of starch (X_1) and sodium bicarbonate (X_2) on the floating lag time, swelling and drug release properties of MET microbeads.

The metformin hydrochloride, used as the model drug, is an orally administered biguanide derivative widely used in the treatment of non-insulin dependent diabetes mellitus. It has a half-life of approximately 4-6 hours (15). The immediate release formulations are administered 2-3 times daily and are associated with a high incidence of side effects (16). Various controlled release formulations of MET have been developed in order to optimize therapy and patient compliance. However, burst release which is undesirable has been reported for the controlled release tablets (15). Floating controlled release microbeads could offer a better means of delivering the drug in a controlled manner, thus avoiding low and erratic bioavailability and optimizing therapy.

MATERIALS AND METHODS

Materials

The materials used were Metformin hydrochloride USP ($C_4H_{11}N_5.HCl$, *MW = 165.62*) which was kindly provided by Zydus Cadila Healthcare Ltd. (Ahmedabad, India)

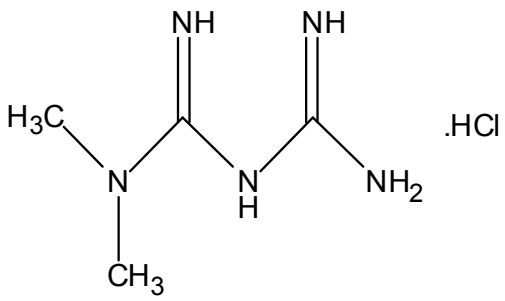

Figure 1 Metformin Hydrochloride USP

(shown in Figure 1) sodium alginate ($C_6H_9O_7Na$, *MW = 40,000)* which was obtained from S.D. Fine Chemicals (Mumbai, India) and calcium carbonate and sodium bicarbonate which were obtained from Finar Chemicals Ltd. (Ahmedabad, India). Tubers of *Dioscorea oppositifolia* L (Chinese yam) were obtained from local farmers in Ibadan, Nigeria and authenticated. The description of the extraction and modification procedures and the properties of the starch have been reported elsewhere (12, 13). All other reagents used were of analytical grade.

Preparation of floating microbeads

The microbeads were prepared by the ionotropic gelation method using a gel blend of freeze dried pregelatinized Chinese yam starch and sodium alginate (17, 18). The concentration of the drug (2% w/v) and total polymer (2% w/v) was kept constant. The required amount of drug was dispersed in 100 ml solution of modified Chinese yam starch (1.0, 1.3 and 1.60% w/v) by stirring with a magnetic stirrer for 60 minutes. Varying quantities of sodium bicarbonate (1.0, 1.5, 2.0% w/v solution) were added to the sodium alginate solution. The two gels were blended and homogenized to obtain a suitable starch-sodium alginate blend. The resulting dispersion was extruded into calcium chloride solution (10% w/v), maintained under gentle agitation (400 rpm) using a syringe with 0.90 mm needle at a dropping rate of 2 ml/minute. The velocity and height of extrusion were kept constant to ensure uniformity of bead size. After curing for 15 minutes, the beads were collected by decantation, washed in ethanol and, then dried for 10 hours at room temperature followed by 6 hours in a hot-air oven at 40°C. The content of MET in the microbeads was determined using a UV spectrophotometer (UV-1700 Schimadzu, Japan) at 233 nm. The calibration curve was linear based on Equation (1):

$$y = 0.087 - 0.09,\ r^2 = 0.999 \qquad \text{Eq. 1}$$

Size and morphology

The particle size of the microbeads were determined using optical microscopy while the morphology and surface characteristics of the microbeads were analyzed using scanning electron microscopy (XL 30 ESEM, Philips, Eindhoven, Netherlands) at an accelerating voltage of 30 KV.

Floating ability and Swelling Index

The floating ability of the microbeads was determined by placing the beads in a dissolution apparatus containing 0.1N HCl (900 ml). The time taken for the beads to rise to the surface and float was taken as the floating lag time (FLT) (19).

The swelling index was determined by soaking 0.5 ml of the microbeads in 5 ml of 0.1 N HCl in a 10 ml measuring cylinder. The volume of the microsphere beads was determined after 12 hours. Swelling index was calculated using Equation 2 (20).

$$\text{Swelling Index} = \frac{\text{Volume after 12 hours (ml)}}{\text{Original volume (ml)}} \quad \text{Eq. 2}$$

Drug release study

The *in vitro* dissolution studies were carried out using the USP XXI paddle method at 50 rpm in 900 ml of 0.1 N Hydrochloric acid (pH 1.2) maintained at 37 ± 0.5°C. The quantity of microbeads containing 200 mg of MET was used and samples (10 ml) were withdrawn at different intervals and replaced with equal amounts of fresh medium. The sample was diluted and the amount of MET released was determined at a wavelength of 233 nm, using a UV/VIS spectrophotometer (Schimadzu 1700, Japan). Determinations were carried out in triplicate.

Factorial experimental design

A full 3^2 factorial experimental design was performed using two factors, each at three levels (21). The nine possible combinations are shown in Table 1. The concentration of starch (X_1) and sodium bicarbonate (X_2) were chosen as independent variables while the swelling index (S), floating lag time (FLT) and quantities of drug released in 1 hour (Q_1) and 10 hours (Q_{10}) were selected as dependent variables. The data were subjected to multiple regression analysis using statistical software (Systat®, Systat Software Inc., Chicago, IL.). The model incorporating first order polynomial terms was used to evaluate the responses and the Equation (3) used was:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2 \quad \text{Eq. 3}$$

where, Y is the dependent variable, b_0 is the arithmetic mean response of the 9 runs and b_1 is the estimated coefficients for the related factor X_1.

The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction term "X_1X_2"shows how the response changes when the two factors change simultaneously. The polynomial terms (X_1^2 and X_2^2) are included to investigate non-linearity. Each experiment was conducted in triplicate and the mean determined.

Data analysis

To compare the differences between the formulations, statistical analysis was carried out using the analysis of variance (ANOVA) using GraphPad Prism© 4 (Graphpad Software Inc. San Diego, CA). At the 95% confidence interval, p values, less than or equal to 0.05 were considered significant.

RESULTS AND DISCUSSION

The composition of the modified Chinese yam starch-alginate blends used for the formulation of the floating microbeads is presented in Table 1.

Table 1 Composition of polymers for the floating microbeads

CONTENT	B1	B2	B3	B4	B5	B6	B7	B8	B9
Sodium Alginate (% w/v)	1.00	1.00	1.00	0.70	0.70	0.70	0.40	0.40	0.40
Starch (% w/v)	1.00	1.00	1.00	1.30	1.30	1.30	1.60	1.60	1.60

Table 2 The 3^2 Factorial Design for the formulation (the independent variables are starch concentration (X_1) and sodium bicarbonate concentration (X_2)).

BATCH CODE	VARIABLE LEVEL IN CODED FORM		REAL VALUES		DEPENDENT VARIABLES			
	X_1	X_2	X_1 (% w/v)	X_2 (% w/v)	FLOATING LAG TIME (s)	SWELLING	Q_1 (%)	Q_{10} (%)
B_1	-1	-1	1.00	1.00	40.00	1.55	1.82	40.82
B_2	-1	0	1.00	1.50	30.50	1.60	1.94	42.68
B_3	-1	+1	1.00	2.00	21.00	1.62	2.96	51.84
B_4	0	-1	1.30	1.00	22.10	2.12	5.15	63.78
B_5	0	0	1.30	1.50	20.22	2.32	7.12	65.37
B_6	0	+1	1.30	2.00	15.50	2.35	8.14	70.11
B_7	+1	-1	1.60	1.00	10.00	2.60	9.15	71.78
B_8	+1	0	1.60	1.50	8.35	2.65	9.32	74.37
B_9	+1	+1	1.60	2.00	6.50	2.68	10.09	75.99

The properties of the prepared microbeads used for the factorial design are shown in Table 2, while the results of the multiple regression analysis are summarized in Table 3.

Table 3 Summary of regression outputs of significant factors for measured response

COEFFICIENTS OF PARAMETERS	RESPONSES			
	FLH	Swelling	*Q1*	*Q10*
b_o	19.33	2.13	5.97	61.86
b_1	-11.11	0.53	3.64	14.47
b_2	-4.85	0.06	0.85	3.59
b_{12}	-1.38	0.04	0.30	1.79
b_{11}	0.12	0.15	-0.92	-6.84
b_{22}	-0.51	-0.04	0.09	1.58
R^2	0.928	0.968	0.962	0.920

The results were found to fit the polynomial regression equation with a correlation coefficient, $r \geq 0.920$ for all the dependent variables. The drug entrapment efficiency of the microbeads increased with an increase in the concentration of the polymer and ranged from 30.55±4.40 to 55.20±5.45%. Floating microbeads are expected to remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. The time taken for the beads to rise from the bottom of the flask to the surface and float is regarded as floating lag time (FLT). The factors X_1 and X_2 showed negative effects on the FLT indicating that the time taken for the formulation to float to the surface of the medium decreased with increase in the concentration of starch and sodium bicarbonate. When the beads come in contact with an acidic medium, sodium bicarbonate effervesces, releasing carbon dioxide which imparts buoyancy to the microbeads while providing an alkaline environment for gelation and crosslinking of the polymer to provide a gel barrier at the surface of the formulation (22). The released carbon dioxide lowers the density of the beads making them more buoyant for a prolonged period of time. The effect of starch concentration on the floating properties of the microbeads was significantly ($p<0.01$) higher than those of sodium bicarbonate. This indi-

Table 4 Results of the two-way ANOVA for the dependent variables

Dependent variable	Source	Degree of Freedom	Sum of Squares	Mean Square	F-value	P-value
Swelling	X_1	2	1.707	0.854	329.03	0.000
	X_2	2	0.027	0.013	5.16	0.078
	Residual	4	0.010	0.003		
	Total	8	1.744			
Floating lag time	X_1	2	740.398	370.199	21.74	0.007
	X_2	2	141.648	70.824	4.16	0.105
	Residual	4	68.108	17.027		
	Total	8	950.154			
Q_1	X_1	2	81.203	40.601	101.12	0.000
	X_2	2	4.301	2.150	5.36	0.074
	Residual	4	1.606	0.402		
	Total	8	87.110			
Q_{10}	X_1	2	1349.28	674.639	151.23	0.000
	X_2	2	82.47	41.233	9.24	0.032
	Residual	4	17.84	4.461		
	Total	8	1449.59			

cates that the modified starch conferred a higher degree of buoyancy to the microbeads than sodium bicarbonate which could probably be due to the nature of the starch (14). The results of the two-way ANOVA presented in Table 4, indicates that the concentration of starch significantly (p<0.01) affected the FLT while the effects of sodium bicarbonate was not statistically significant (p>0.05) over the range of the investigation. The interactive terms X_1 and X_2 also showed negative values indicating that both variables interact to decrease the floating lag time of the microbeads.

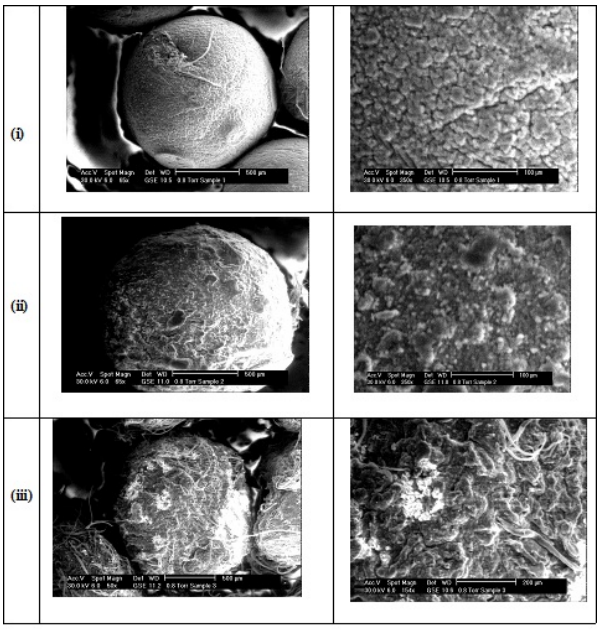

Figure 2 SEM images showing shapes and the surface characteristics of floating microbeads (i) B3, (ii) B6 and (iii) B9.

SEMs of the microbeads containing different concentrations of the modified starch are presented in Figure 2. They show that the microbeads were spherical in shape and their surfaces appeared to be coated by the starch, thus making the beads more porous. The porosity appeared to increase as the amount of starch increased producing more buoyant beads and thus reducing the FLT. The average particle size of the beads also increased (from 1.10 mm to 1.50 mm) with the increase in the concentration of starch.

Both factors X_1 and X_2 showed positive effects on the swelling index indicating that increasing the concentrations of starch and sodium bicarbonate led to an increase in the swelling properties of the beads. This could be due to the high water sorption capacity of the starch and the surface characteristics of the microbeads. The results of the two-way ANOVA also indicate that the swelling property of the microbeads was significantly (p< 0.001) dependent on the concentration of starch present is the formulation. The positive value of X_1^2 indicates positive linearity in the effectiveness of starch to aid swelling as the concentration increased. The interactive terms

X_1 and X_2 showed positive effects on swelling, thus indicating that swelling increased when both variables were simultaneously increased.

The drug dissolution profiles of the microbead formulations are shown in Figure 3, while the percentage of drug released after 1 hour (Q_1) and 10 hours (Q_{10}) are also shown in Table 2. The drug release profiles show that the beads did not exhibit burst release. This suggests that the drug was not loosely bound to the surface of the microbeads but embedded into the bead structure (8). The drug was released at a controlled rate from the beads probably as a result of the combined effects of the cross-linked polymer network of sodium alginate and the swollen starch. The percentage of drug released after 1 hour (Q_1) and 10 hours (Q_{10}) shown in Table 2 appeared to be dependent on the concentration of starch in the microbeads (23). The values of the coefficients calculated from the multiple regression analysis clearly indicate that the responses were strongly dependent on the two factors studied. The effect of the concentration of starch on the amount of drug release after 1 hour and 10 hours was significantly (p<0.05) higher than the effects of the concentration of sodium bicarbonate. The results from the two-way ANOVA indicate that the concentration of starch significantly (p<0.001) increased the amount of drug release while the effects of the concentration of sodium bicarbonate was only significant (p<0.05) on the amount released after 10 hours. This is in agreement with previous studies (23, 24) and may be attributed to the fact that the presence of starch renders the gel matrix more porous as shown in Figure 2, thereby facilitating drug release. The interactive terms X_1 and X_2 showed positive values for the amount of drug release, indicating that the two variables interact synergistically to increase the amount of drug released from the floating microbeads.

Surface plots which can assist in understanding the influence of the variables on the properties of the floating microbeads were generated for

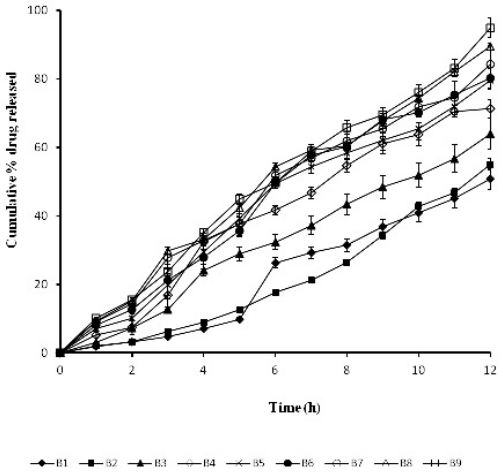

Figure 3 In vitro dissolution profiles of the floating microbeads.

all dependent variables as shown in Figure 4. Surface plots have been used to describe the influence of the variables on the properties of the floating microbead (7, 8). Generally, the steeper the slope, the stronger the interaction between the variables. The surface plots showed that while the starch and sodium bicarbonate interact strongly to decrease the floating time, they also increase the swelling properties of the microbeads. On the other hand, the two variables interact strongly to increase the amount of drug released after 1 hour and 10 hours. This indicates that the concentration of the modified starch could be used to modulate the drug release properties of the floating microbeads.

CONCLUSION

This study investigated the preparation of optimized floating metformin hydrochloride microbeads using freeze-dried pregelatinized Chinese yam starch and sodium alginate polymer blends. The results of the 3^2 factorial design revealed that the concentrations of the modified Chinese yam starch significantly (p<0.01) affected the swelling, floating lag time and drug release properties of the beads. The concentration of the modified starch can be

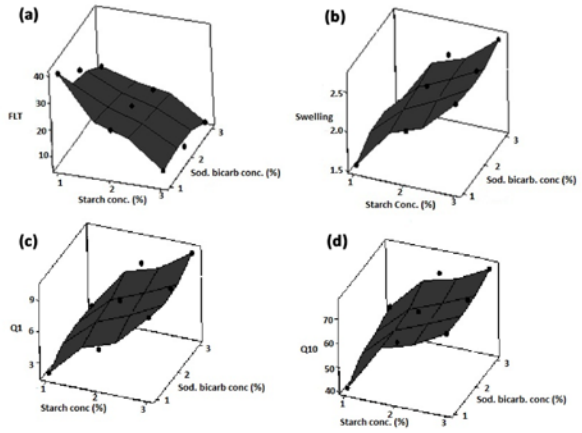

Figure 4 Surface graphs showing effect of variables on (a), floating lag time, (b) swelling, (c) percent drug released in 1 hour (Q_1) and percent drug released in 10 hours (Q_{10}).

altered to control the floating lag time and the drug release properties of the microbeads depending on the desired drug release rate. Thus, an optimized formulation of metformin hydrochloride microbeads could be developed for controlled drug delivery.

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