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Formulation and optimization of carbamazepine floating tablets by 2^3 - factorial design employing Starch-Urea-Borate: A new floating polymer

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ABSTRACT

Several approaches are currently used to retain the dosage form in the stomach. These include bioadhesive systems, swelling and expanding systems, floating systems and other delayed gastric emptying devices. The principle of floating tablets offers a simple and practical approach to achieve increased gastric residence time to enhance the bioavailability and to obtain controlled release. Floating tablets are designed based on gas generating principle. Design of floating tablets needs a strong matrix forming polymer. Though several polymers are available for floating tablets, there is a continued need to develop new, effective and efficient polymers for controlled release floating tablets. The major objective of the investigation is to evaluate starch-urea-borate, a new modified starch as a floating matrix former in the design of controlled release floating tablets.

Keywords: Optimisation, Carbamazepine, Starch-Urea-Borate, Floating Tablets

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INTRODUCTION

Several approaches are currently used to retain the dosage form in the stomach. The principle of floating tablets is simple and practical approach to achieve increased gastric residence time to enhance the oral bioavailability and to obtain controlled release. Floating tablets designed based on gas generating principle needs a strong floating matrix former. Starch –urea-borate, a new modified starch was tried as floating matrix former in the design of floating tablets.

The present investigation deals with an attempt of systematic formulation approach for optimization of floating tablets of carbamazepine (a poorly soluble BCS-Class II drug) employing starch-urea-borate as new floating matrix former, sodium bicarbonate as gas generating agent, bees wax and ethyl cellulose as floating enhancers. A 2^3 - Factorial design was applied to investigate the main and interaction effects of the three formulation variables i.e, sodium bicarbonate (A), ethyl cellulose (B) and bees wax (C) in each case to develop a floating formulation with more floating time and to permit rational selection of a batch of floating tablets with controlled dissolution profile over a period of 24 h.

MATERIALS

Carbamazepine was a gift from M/s. Ranbaxy Research Labs., Gurgaon, Haryana.

Starch-urea-borate prepared in Potato starch (Loba Chemie)

Urea (Qualigens)

Borax (Qualigens)

Ethyl cellulose (viscosity of 5% w/w solution in 80 : 20 toluene : ethanol by weight at 25^0C in 18 cps, containing not less than 46.5% ethoxyl groups). (Loba-chemie).

Bees wax. I. P (Moksha life style products, New Delhi)

Sodium bicarbonate (SD Fine Chemie)

Magnesium stearate (Loba Chemie)

Talc I.P (Loba Chemie)

All other ingredients used were of analytical grade and used as received.

METHODS

Preparation of starch – urea – borate:

Starch–urea–borate was synthesized by gelatinizing potato starch in the presence of borax and urea.

Potato starch (50 g) was dispersed in 100 ml of purified water to form starch slurry. Borax (10.0 g) and urea (15.0 g) were dissolved separately in 400 ml of purified water and the solution was heated to boiling. While boiling, the starch slurry was added and mixed. Mixing while heating was

continued for 10 minutes to gelatinize starch to form starch–urea–borate polymer. The mass formed was spread on to a stainless steel plate and dried at 80^0C for 6 – 8 h. The dried polymer was powdered and passed through mesh no. 120.

Characterization of starch – urea – borate:

The starch – urea – borate prepared was characterized by microscopical examination, chemical and physical tests to determine its melting point, solubility, swelling index, pH, viscosity and various micromeritic properties namely bulk density, tap density, compressibility index and angle of repose and also by DSC and FTIR spectra.

1. Microscopic examination:

Slurry (1 %) of each of potato starch and starch – urea – borate in a mixture of equal volumes of glycerin and water were prepared. A smear of the slurry was made and examined under microscope. Photomicrographs of potato starch and starch – urea – borate are shown in Figs. 1A, 1B, 2A and 2B. The size of 100 particles was measured using a calibrated eye – piece micrometer. The particle size distribution of potato starch and starch – urea – borate (prepared) are given in Table 1.

2. Chemical test:

Iodine test:

Slurry of starch – urea – borate in water was treated with iodine test solution. A reddish violet colour was observed indicating the presence of α - amylose.

3. Melting point:

Melting point of starch – urea – borate was determined in a melting point apparatus and also by DSC.

4. Solubility:

Solubility was tested in water, aqueous buffers of pH 1.2 and 7.4, methanol, petroleum ether, dichloromethane, cyclohexane and chloroform.

5. Swelling index:

Starch – urea – borate (1 gm) was taken into two graduated 50 ml measuring cylinders, one containing petroleum ether and other containing water and stored for 24 h. Swelling index of starch – urea – borate was determined using the formula

$$\text{Swelling index (\%)} = \frac{Vw - Vo}{Vo} \times 100$$

Where, Vo is the volume of the sediment in petroleum ether and

Vw is the volume of sediment in water after 24 h

6. pH:

The pH of a 0.1 % w/v aqueous dispersion was measured.

7. Viscosity:

Viscosity of a 0.1 % w/v homogenized dispersion was determined using Ostwald Viscometer.

8. Density (g/cc):

Density was determined by liquid displacement method using petroleum ether as liquid.

9. Bulk and tap densities:

Bulk and tap densities were determined by 3 tap method in a graduated cylinder.

10. Compressibility index:

Compressibility index was determined by measuring the initial volume (Vo) and final volume (V) after 100 tappings of a sample of starch – urea – borate in a measuring cylinder.

Compressibility index was calculated using the equation,

$$\text{Compressibility index} = \frac{Vo - V}{Vo} \times 100$$

11. Angle of repose:

Angle of repose was determined by fixed funnel method.

The physical and micromeritic properties of starch – urea – borate prepared are summarized in Table 2.

Experimental Design:

Optimization of the Carbamazepine floating tablets was done using 2^3 factorial design in which 3 factors, each at two levels were evaluated. To evaluate the individual and combined effects of sodium bicarbonate (factor A), ethyl cellulose (factor B) and bees wax (factor C) on the *in vitro* buoyancy and drug release characteristics, the floating tablets were formulated using selected combinations of three factors as per 2^3 - factorial design. Formulae of carbamazepine floating tablets prepared as per 2^3 – factorial design are given in Table 3.

Drug – Excipient Compatibility Studies

The compatibility of starch-urea-borate with the selected drugs was evaluated by TLC studies.

TLC Study:

TLC was carried out on carbamazepine and its mixtures (1: 1) with starch-urea-borate as follows:

Stationary phase: Silica gel G (pre coated TLC plates).

Mobile phase:

Carbamazepine: Strong Ammonia Solution: Methanol (1.5: 100)

Diltiazem: Ethyl acetate: Methanol: Strong ammonia solution (80 : 10 : 10 v/v)

Procedure:

Mobile phase was prepared and taken in a TLC chamber. The chamber was allowed to saturate with solvent vapour for 24 h. Standard (pure drug) and test (drug – starch-urea-borate mixtures) sample were spotted on activated silica plates using narrow capillary tubes. The spotted plates were kept in the TLC chamber and allowed to run the mobile phase. The plates were dried and kept in iodine chamber to develop the spots. The R_f values of standard and test samples were determined by the following formula.

R_f = Distance travelled by sample / distance travelled by solvent front.

The R_f values are given in Table 3.

Preparation of Carbamazepine Floating Tablets:

The tablets were prepared by melt granulation method. Bees wax was melted in a large porcelain dish and previously prepared geometric mixture of carbamazepine, starch-urea-borate, ethyl cellulose and sodium bicarbonate was added to the molten bees wax and mixed thoroughly until it attained room temperature. The coherent mass was passed through mesh No 16 and the granules obtained were air dried. The lubricants talc (2%) and magnesium stearate (2%) were passed through mesh No.60 onto the dry granules and

blended in a closed polyethylene bag. The tablet granules were compressed into tablets on a 16 – station tablet punching machine (M/s Cadmach Machineries Pvt Ltd., Ahemedabad) to a hardness of 5-6 kg/sq.cm.

Evaluation of Carbamazepine Floating Tablets:

Estimation of Carbamazepine in tablets:

Five tablets were accurately weighed and powdered. Tablet powder equivalent to 25 mg of medicament was taken into a 150 ml conical flask and extracted with 3 X 25 ml methanol and the methonolic extracts were filtered and collected into a 100 ml volumetric flask. The solution was then made upto volume with methanol. The methanolic solution was subsequently diluted suitably with 0.1 N hydrochloric acid and assayed for carbamazepine at 288 nm. Four samples of tablet powder were analyzed in each case.

Hardness:

Hardness of the tablets was tested using a Monsanto Hardness Tester.

Friability:

Friability of the tablets was determined in a Roche Friabilator.

***In Vitro* Buoyancy Studies:**

In Vitro buoyancy was determined by floating time as per the method described by Dave B.S *et al*[1]. The tablets were placed in a 250 ml glass beaker containing simulated gastric fluid (SGF), pH 1.2 as per USP. The time required for the tablet to rise to the surface and float was determined as floating lag time. The time period during which the tablet remains floating was determined as floating time.

Dissolution Rate Study:

The *in vitro* dissolution rate study of carbamazepine floating tablet was performed using 8-station dissolution test apparatus (Labindia Disso 2000) fitted with paddles (50 rpm) at 37 ± 0.5^0 C, using simulated gastric fluid (pH 1.2; 900 ml) as a dissolution media. At the predetermined time intervals, 5 ml samples were withdrawn, filtered through 0.45 µ membrane filter, diluted, and assayed at 288 nm using a Elico UV/Visible Double beam spectrophotometer. Cumulative percentage drug release was calculated.

Kinetic modeling of drug release:

The dissolution profiles of all the batches was fitted to various models like zero-order, first order[2], Korsmeyer and Peppas[3-5], and Higuchi[6] models to ascertain the kinetic modeling of drug release.

Optimization:

The percentages of sodium bicarbonate (A), ethyl cellulose (B) and bees wax (C) were selected as independent variables. The floating time and percent released at the end of 24 h were selected as dependent variables.

RESULTS AND DISCUSSION

Table 1: Particle Size Distribution of Potato Starch and Starch – urea – borate Prepared

Size Range (µm)	Number of Particles	
	Potato Starch	Starch – urea – borate
0 – 50	27	--
50 – 100	60	20
100 – 150	13	53
150 – 200	--	27
$\bar{x}$ ± s.d (µm)	67.5 ± 29.54	128.0 ± 33.21

Table 2: Physical and Micromeritic Properties of Starch – urea – borate Prepared

S. N.	Property	Result
1.	Iodine test	Positive indicates the presence of α - amylose
2.	Melting Point	Charred at 210^{0}C
3.	Solubility	Insoluble in water, aqueous fluids of acidic and alkaline pHs and in organic solvents
4.	Swelling index	Swells in water with a swelling index of 614.28 %
5.	pH of 0.1 % aqueous dispersion	9.01
6.	Viscosity of a 0.1 % aqueous dispersion	1.011 cps
7.	Density	0.511 g/cc
8.	Tap density	0.721 g/cc
9.	Compressibility index	12.91 %
10.	Angle of repose	22^0 76^1

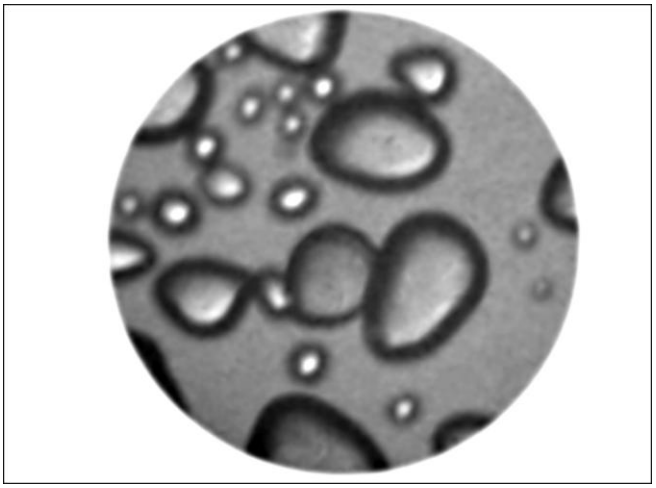


Figure 1A: Photomicrographs of Potato Starch (unstained)

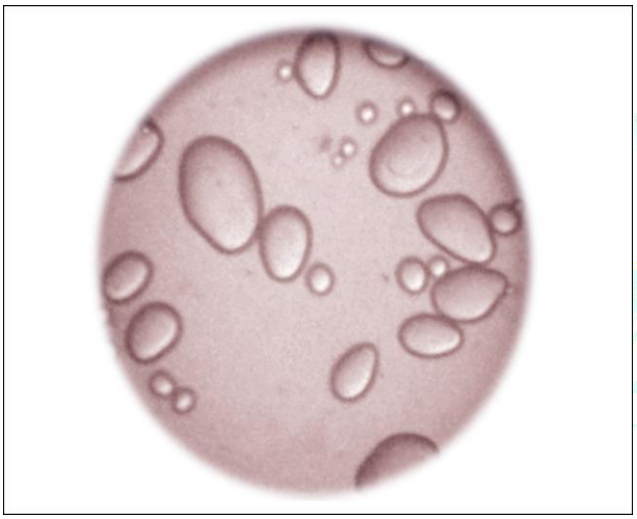


Figure 1B: Photomicrographs of Potato Starch (stained with Saffranin)

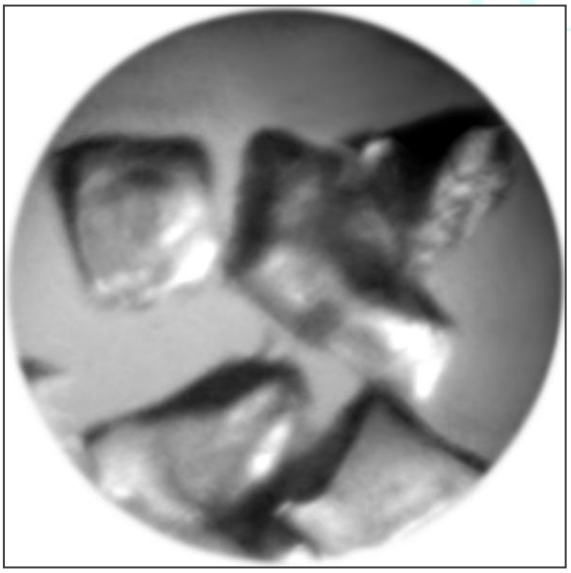


Figure 2A: Photomicrographs of Starch-urea-borate (unstained)

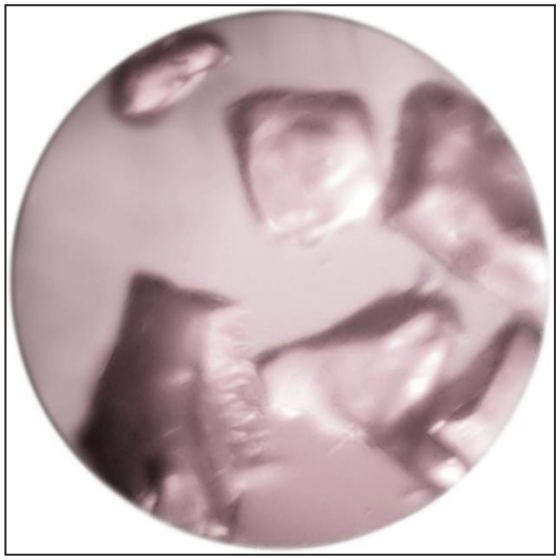


Figure 2b: Photomicrographs of Starch-urea-borate (stained)

Starch – urea – borate was prepared by gelatinizing potato starch in the presence of borax and urea. It is known[1, 2] that starch reacts with urea to form starch carbamate, a starch – urea cross linked polymer. Khalil *et al.* investigated the reactions between starch and urea resulting in the formation of starch cross linked with urea. The reactions involved are as follows

$$St\ OH + CO(NH_2)_2 \xleftrightarrow{heat} St\ OCONH_2 + NH_3$$

$$2\ St\ OCONH_2 \xrightarrow{heat} St\ OCONHCOOSt + NH_3$$

$$St\ OH + StOCONH_2 \xrightarrow{heat} St\ OCOOSt + NH_3$$

Where St OH is starch

Sodium borate serves as a catalyst in the cross linking reaction between starch and urea. Literature on pharmaceutical applications of starch-urea-borate polymer is scanty. In one study[4] it has been used in the controlled release formulation of insecticide acetamiprid. In another patent[5]a controlled release pesticide formulation was developed encapsulating the pesticide (deltamethrin) in a polymer matrix of starch-borax-urea. Chowdary K.P.R and Murali Krishna M.N used starch-urea-borate in the controlled release of gliclazde and diclofenac. In the present investigation starch-urea-borate was evaluated for its application as buoyant release retardant and rate controlling polymer in the design of floating controlled release formulations of selected drugs. The starch-urea-borate prepared was found to be fine, hard and free flowing crystalline powder. The density of Starch-urea-borate was found to be 0.511 g/cc (less than the density of water), so it can be used in the formulation of floating drug delivery systems. The compressibility index of Starch-urea-borate was found to be 12.91% and the angle of repose was found to be $22^0 76^1$. Both compressibility index and angle of repose of Starch-urea-borate indicates that the polymer has

excellent flow properties, so the polymer can be used in the formulation of tablets. It gave a positive iodine test indicating the presence of α- amylose.

Microscopic examination indicated that potato starch consists oval shaped grains (Fig. 1A and 1B). Whereas starch-urea-borate consists of rectangular, transparent crystals (Fig. 2A and 2B). The particle size in each case was determined by microscopy. The results are given in Table 1. The average size of the potato starch grains was 66.5 ± 30.87 µm. The average size of starch-urea-borate crystals was 127.0 ± 34.58 µm.

The physical and micromeritic properties of starch-urea-borate prepared are summarized in Table 2. It was insoluble in water, aqueous fluids of acidic and alkaline pHs. It was also insoluble in organic solvents like methanol, petroleum ether, dichloromethane, cyclohexane and chloroform. The pH of a 0.1 % aqueous dispersion was 9.01.

Starch-urea-borate exhibited good swelling in water. The swelling index was 614.28 %. The swelling of starch-urea-borate matrix tablets in water is shown in Fig. 5. All micromeritic properties indicated good flow and compressibility needed for solid dosage form manufacturing.

Table 3: R_f Values of Selected Drugs and their Mixtures (1: 1) with

Starch-urea-borate

S. No.	Product	R_f Value
1.	Carbamazepine	0.740
2.	Carbamazepine – Starch-urea-borate	0.735

As starch-urea-borate has density of 0.511 g/cc (less than the density of water), excellent flow properties, good swelling property in water, it is considered as suitable buoyant release retarding and rate controlling polymer in floating tablets for obtaining the formulations that remain in the gastric region for prolonged period with controlled release of drug.

(1)

Figure 3: 1 (A) Carbamazepine pure drug (B) Carbamazepine and starch-urea-borate

In the TLC study, single spots were observed in the case of pure drugs as well as their mixtures with starch-urea-borate. The close agreement of the R_f values of the drugs and their mixtures with starch-urea-borate (Table 3) indicated no interaction between the drugs and starch-urea-borate.

Thus the results of TLC indicated no interaction between the selected drugs and starch-urea-borate, the new starch based polymer developed. Hence, starch-urea-borate could be used as a floating matrix former in the design of floating drug delivery systems of the selected drugs.

Table 4: Tablet Formulations as per 2^3 – Factorial Design

Ingredient (mg/tablet)	CFF1	CFF2	CFF3	CFF4	CFF5	CFF6	CFF7	CFF8
Carbamazepine	50	50	50	50	50	50	50	50
Bees wax	33	33	33	33	44	44	44	44
SUB Polymer	85	63	74	52	74	52	63	41
Sodium bicarbonate	22	44	22	44	22	44	22	44
Ethyl Cellulose	22	22	33	33	22	22	33	33
Talc	4	4	4	4	4	4	4	4
Magnesium stearate	4	4	4	4	4	4	4	4
Total Weight (mg)	220	220	220	220	220	220	220	220

Table 5: Physical Properties: Hardness, Friability, Drug content, Floating lag time and Floating time of Carbamazepine Floating Tablets.

Formulation	Hardness (Kg/Cm²) ± S.D	Friability (%) ± S.D	Drug Content (mg/tab) ± S.D	Floating Lag Time (m) ± S.D	Floating Time (h) ± S.D
CFF1	5.5 ± 0.05	0.12 ± 0.012	48.65 ± 0.42	5.1 ± 1.11	07.50 ± 0.051
CFF2	6.0 ± 0.04	0.16 ± 0.013	49.82 ± 0.24	1.9 ± 0.61	03.00 ± 0.021
CFF3	5.5 ± 0.08	0.18 ± 0.018	49.61 ± 0.36	1.2 ± 0.35	42.00 ± 0.032
CFF4	5.0 ± 0.09	0.16 ± 0.015	47.32 ± 0.24	0.8 ± 0.21	03.66 ± 0.041
CFF5	5.5 ± 0.45	0.18 ± 0.017	49.92 ± 0.02	0.6 ± 0.09	43.00 ± 0.056
CFF6	5.5 ± 0.31	0.14 ± 0.016	48.82 ± 0.47	1.0 ± 0.29	04.33 ± 0.024
CFF7	5.5 ± 0.57	0.16 ± 0.014	47.72 ± 0.34	2.1 ± 0.85	43.00 ± 0.031
CFF8	5.5 ± 0.65	0.13 ± 0.010	48.37 ± 0.65	1.1 ± 0.22	33.85 ± 0.024

CFF1 Carbamazepine Floating Tablets

At zero time At T = 5.1 m At T = 7.5 h

CFF2 Carbamazepine Floating Tablets

At zero time At T = 1.9 m At T = 3.0 h

CFF3 Carbamazepine Floating Tablets

At zero time At T = 1.2 m At T = 42.0 h

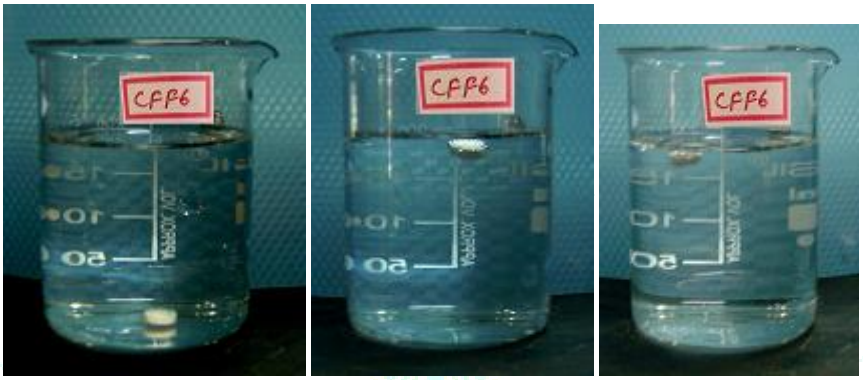
CFF4 Carbamazepine Floating Tablets

At zero time At T = 0.8 m At T = 3.66 h

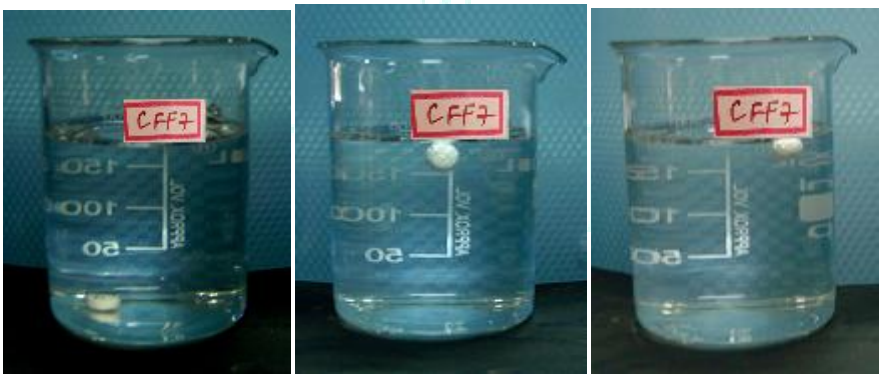
Figure 4: CARBAMAZEPINE FLOATING TABLETS

CFF5 Carbamazepine Floating Tablets
At zero time At T = 0.6 m At T = 43.0 h

C FF6 Carbamazepine Floating Tablets
At zero time At T = 1.0 m At T = 4.33 h



CFF7 Carbamazepine Floating Tablets
At zero time At T = 2.1 m At T = 43.0 h



CFF8 Carbamazepine Floating Tablets
At zero time At T = 1.1 m At T = 33 h

Figure 4(a): CARBAMAZEPINE FLOATING TABLETS

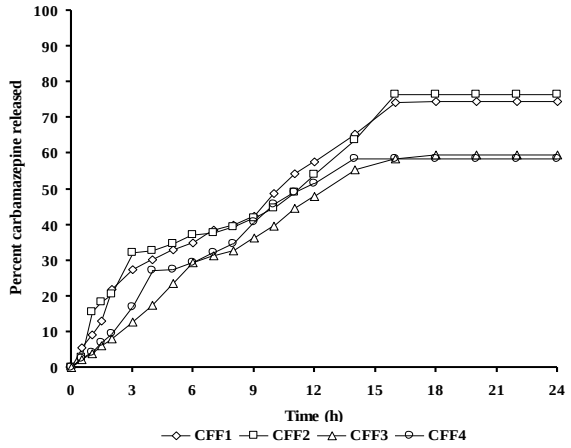


Figure 5: Release Profiles of Carbamazepine Floating Tablets (CFF1-CFF4)

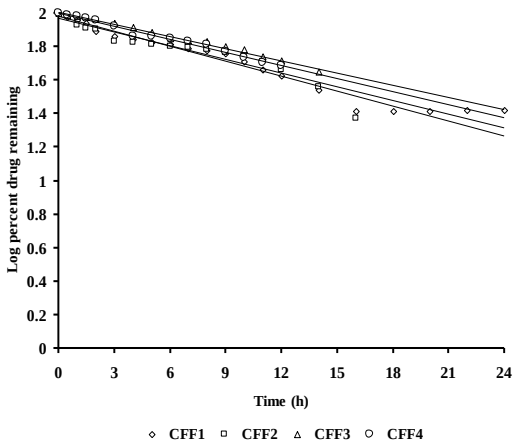


Figure 6: Time Vs Log Percent Drug Remaining Plots for Carbamazepine Floating Tablets (CFF1-CFF4)

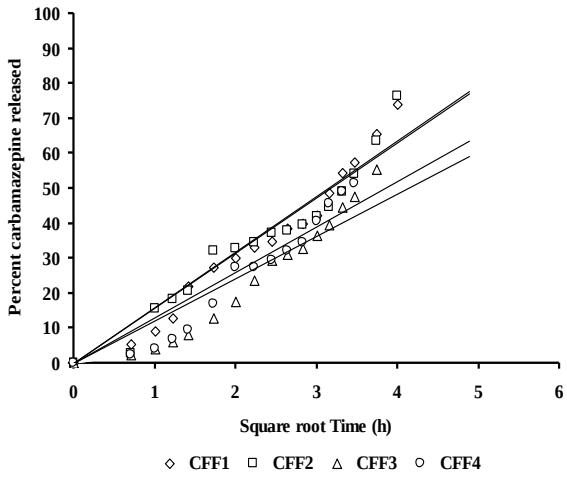


Figure 7: Square Root Time Vs Percent Released Plots of Carbamazepine Floating Tablets (CFF1-CFF4)

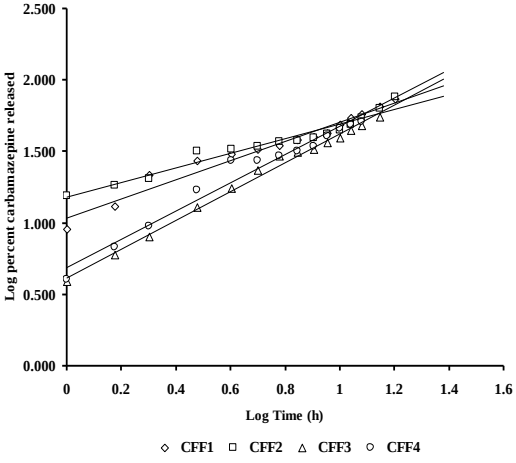


Figure 8: Log time Vs Log Percent Released Plots of Carbamazepine Floating Tablets (CFF1-CFF4)

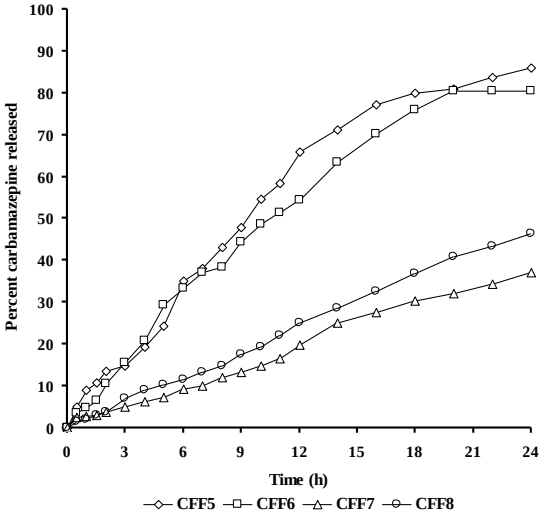


Figure 9: Release Profiles of Carbamazepine Floating Tablets (CFF5-CFF8)

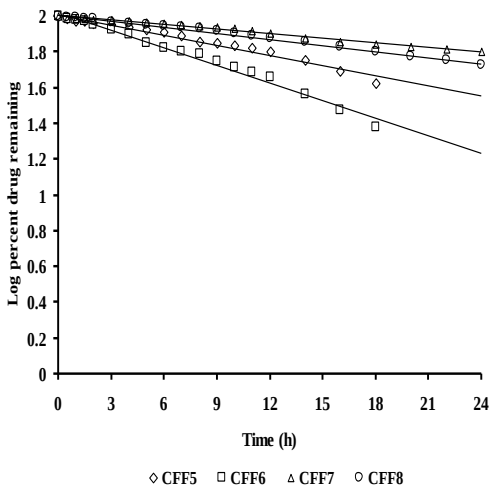


Figure 10: Time Vs Log Percent Drug Remaining Plots for Carbamazepine Floating Tablets (CFF5-CFF8)

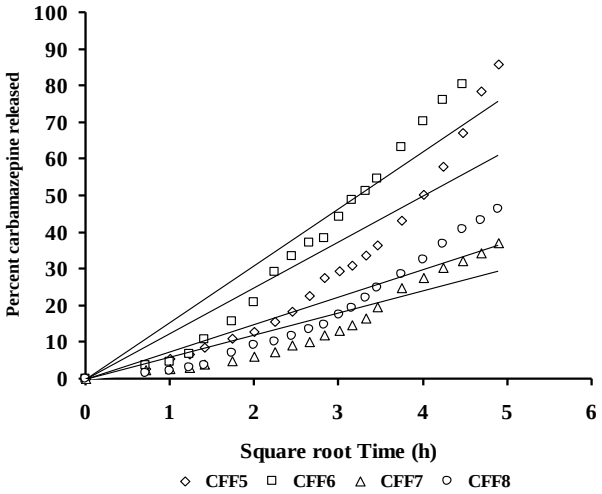


Figure 11: Square Root Time Vs Percent Released Plots of Carbamazepine Floating Tablets (CFF5-CFF8)

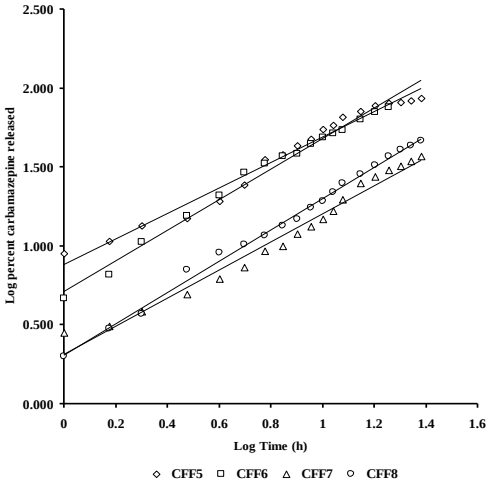


Figure 12: Log time Vs Log Percent Released Plots of Carbamazepine Floating Tablets (CFF5-CFF8)

Table 6: Correlation Coefficient (R^2) Values in the Analysis of Release Data as per Zero order, First order, Higuchi, and Peppas Equation Models.

Formulation	Zero order model	First order model	Higuchi model	Peppas equation
CFF1	0.9777	0.9370	0.9727	0.9624
CFF2	0.9419	0.9056	0.9414	0.9407
CFF3	0.9936	0.9901	0.9800	0.9915
CFF4	0.9795	0.9794	0.9774	0.9652
CFF5	0.9839	0.9837	0.9829	0.9715
CFF6	0.9898	0.9816	0.9878	0.9875
CFF7	0.9878	0.9875	0.9476	0.9867
CFF8	0.9975	0.9934	0.9624	0.9953

Table 7: Release Characteristics of Carbamazepine Floating Tablets

Formulation	% Release in 24 h ± S.D	K_0 (mg/hr)	K_1 (/h)	'n' in peppas equation
CFF1	74.47 ± 1.62	2.0229	0.07439	0.634
CFF2	76.37 ± 1.73	1.8096	0.06653	0.524
CFF3	59.55 ± 1.29	1.9639	0.05855	0.979
CFF4	58.54 ± 1.31	2.1406	0.06302	0.923
CFF5	86.02 ± 1.54	1.8513	0.08802	0.824
CFF6	80.52 ± 1.35	2.1094	0.08503	0.926
CFF7	36.99 ± 1.38	0.7965	0.01992	0.964
CFF8	46.39 ± 1.24	0.9954	0.02664	0.991

Floating tablets each containing 50 mg of carbamazepine (CBZ) could be prepared employing starch-urea-borate as floating matrix former and release retardant, sodium bicarbonate as gas generating agent, bees wax and ethyl cellulose as floating enhancers by melt granulation technique. Hardness of the tablets was in the range of 5-6 kg/sq.cm. Weight loss in the friability test was less than 0.18 % in all the cases. All the matrix tablets prepared contained carbamazepine with in 100 ± 5 % of the labelled claim. All the tablets were found to be non-disintegrating in water and aqueous acidic (pH 1.2) and alkaline (pH 7.4) fluids. As such the prepared tablets were of good quality with regard to drug content, hardness and friability. In the *in vitro* buoyancy study variations were observed in the floating lag time as well as the floating time (Table 5 & Fig. 4).

Carbamazepine release profiles of the floating tablets are shown Fig.5-12. Carbamazepine release from the floating tablets was slow and spread over more than 24 h and depended on the composition of the matrix i.e., concentration of sodium bicarbonate, bees wax and ethyl cellulose.

The dissolution data of batches CFF1 to CFF8 was fitted to zero-order, first order, Korsmeyer and Peppas, and Higuchi models. The results of Correlation coefficient (R^2) were used to select the most appropriate model. The release profile of formulations CFF1-CFF8 fitted best to zero-order model (Table 6). Thus, it may be concluded that drug release from the floating carbamazepine tablets is best explained by zero order model.

Percent drug released versus square root of time were found to be linear indicating that the drug release from the floating tablets prepared was diffusion controlled. The release data was also analyzed by the Korsmeyer and Peppas equation shown below in order to assess the release mechanism.

$M_t / M_\infty = Kt^n$. ---- Eq(1)

$\text{Log}\ (M_t / M_\infty) = \text{Log}\ K + n\ \text{Log}\ t$ ---- Eq(2)

In the above equation, Mt / M_∞ is the fractional release of the drug, t is the release time, K is the constant for incorporating structural and geometric characteristics of the release device and n is the release exponent that could be used to characterize the different release mechanism as, n = 0.5 (Fickian diffusion), 0.5 < n < 1 non-fickian (anomalous transport), n = 1 (case II transport; i.e., zero order release), and n > 1 (super case II transport). Release exponent 'n' was in the range 0.524-0.991 with all the floating tablets prepared indicating drug release from all these formulations was by non-fickian (anomalous) diffusion.

All the release parameters (Table 7) indicated much variation in the drug release from the floating tablets formulated. To evaluate the individual and combined effects of the three factors involved, floating tablets were formulated employing selected combinations of the factors as per 2^3-factorial design. The floating times and release parameters (percent drug released in 24 h) of the floating tablets formulated were analyzed as per ANOVA of 2^3-factorial design. ANOVA of floating times (Table 8) indicated that the individual effects of sodium bicarbonate (A), ethyl cellulose (B) and bees wax (C) as well as the combined effects of all the three (ABC) factors on the floating time of tablets were significant ($P<0.05$). The combined effects of any two factors (AB, AC, BC) on the floating time were not significant ($P>0.05$).

ANOVA of release parameter (Table 9) indicated, percent release at the end of 24 h is significantly influenced by ethyl cellulose (B) and interaction between ethyl cellulose and bees wax (BC) ($P<0.05$) only. Effects of other factors were not significant ($P>0.05$). The ANOVA results, thus indicated that the three factors, sodium bicarbonate (A), ethyl cellulose (B), bees wax (C) and interaction between sodium bicarbonate, ethyl cellulose and bees wax (ABC) significantly influence the floating time of the carbamazepine floating tablets where as ethyl cellulose (B), and interaction between ethyl cellulose & bees wax (BC) significantly influence the drug release characteristics of the floating tablets formulated.

Table 8: ANOVA of Floating Times of Carbamazepine Floating Tablets Formulated Employing Starch-urea-borate.

Source of Variation	d.f	S.S	M.S.S	Variance Ratio (F)	Result
Replicates	2	231.02	115.51	0.8467	P>0.05
Treatments	7	917.46	1131.06	8.29	P< 0.05
Sodium bicarbonate (A)	1	3082.66	3082.66	22.59	P <0.05
Ethyl cellulose (B)	1	1568.16	1568.16	11.49	P <0.05
Sodium bicarbonate x Ethyl cellulose (AB)	1	66.66	66.66	0.4886	P> 0.05
Bees wax (C)	1	1734	1734	12.71	P< 0.05
Sodium bicarbonate x Bees wax (AC)	1	9.375	9.375	0.0687	P >0.05
Ethyl cellulose x Bees wax (BC)	1	12.04	12.04	0.0882	P> 0.05
Sodium bicarbonate x Ethyl cellulose x Bees wax (ABC)	1	1962.04	1962.04	14.38	P <0.05
Error	14	1909.98	136.42		
Total	23	10058.46			

P<0.05 indicate significance; P>0.05 indicate non-significance
Where, d.f = degress of freedom, S.S = sum of squares, M.S.S = mean sum of squares

Table 9: ANOVA of Release Parameter of Carbamazepine Floating Tablets Formulated Employing Starch-urea-borate.

Source of Variation	d.f	S.S	M.S.S	Variance Ratio (F)	Result
Replicates	2	313.454	156.727	5.021	P>0.05
Treatments	7	6322.717	903.24	28.94	P< 0.05
Sodium bicarbonate (A)	1	7.65	7.65	0.2451	P >0.05
Ethyl cellulose (B)	1	5033.53	5033.53	161.27	P <0.05
Sodium bicarbonate x Ethyl cellulose (AB)	1	59.50	59.50	1.9064	P >0.05
Bees wax (C)	1	141.08	141.08	4.520	P >0.05
Sodium bicarbonate x Bees wax (AC)	1	2.80	208.	0.0897	P >0.05
Ethyl cellulose x Bees wax (BC)	1	259.01	259.01	8.298	P<0.05
Sodium bicarbonate x Ethyl cellulose x Bees wax (ABC)	1	127.19	127.19	4.075	P >0.05
Error	14	437.05	31.21		
Total	23	7073.217			

P<0.05 indicate significance; P>0.05 indicate non-significance

Where, d.f = degress of freedom, S.S = sum of squares, M.S.S = mean sum of squares

CONCLUSION

Starch-urea-borate is an efficient matrix former for floating tablets based on gas generation principle. Drug release from the prepared tablets was slow and spread over more than 24 h and depended on the composition of the matrix i.e., concentration of sodium bicarbonate, bees wax and ethyl cellulose. Carbamazepine release was diffusion controlled and followed zero order kinetics. Non-fickian diffusion was the drug release mechanism from the prepared floating tablets. Floating tablets formulated employing sodium bicarbonate (10%), ethyl cellulose (10%) and bees wax (20%) and starch-urea-borate as matrix former exhibited *in vitro* buoyancy over 43 h and good controlled release over more than 24 h fulfilling USP specification and were found suitable for once – a-day administration.

Optimization of carbamazepine floating tablets is a complex process when a new starch based polymer, starch-urea-borate is used as a matrix former, which requires to consider a large number of variables and their interactions with each other. The present study conclusively demonstrates the use of 2^3 – factorial design in optimization of carbamazepine floating tablets.. The effervescent-based floating drug delivery is a promising approach to achieve *in vitro* buoyancy by using Starch-urea-borate, a new modified starch as a matrix former, sodium bicarbonate as gas-generating agent, ethyl cellulose and bees wax as floating enhancers.

The optimized formulation (CFF5) gives the best result in terms of the required lag time, floating duration, and drug release which was in accordance with the USP dissolution criteria for extended release tablets of carbamazepine. It is thus concluded that by adopting systematic approach, an optimum point can be reached in shortest time with minimum efforts when starch-urea-borate, a new modified starch is used as a floating matrix former for achieving floating formulations.

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