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# A Factorial Study on the Design and Evaluation of Carbamazepine Floating Tablets Employing Starch-Urea-Borate

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The objective of the study is to design and evaluate carbamazepine floating tablets employing starch-urea-borate, a modified starch based polymer to enhance its oral bioavailability and to achieve controlled release of carbamazepine. The individual and combined effects of sodium bicarbonate (gas generating agent), bees wax (hydrophobic floating agent) and ethyl cellulose (floating enhancer) on floating time and drug release were also investigated in a 23-factorial study. 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. The individual and combined effects of sodium bicarbonate, bees wax and ethyl cellulose on the floating time and drug release were significant ($p < 0.05$). 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 and were found suitable for once-a-day administration.

**Key Words: Floating tablets, Carbamazepine, Starch-urea-borate, Melt granulation method.**

## INTRODUCTION

The oral route of administration is the most convenient and commonly used method of drug delivery. However, this route has certain problems such as unpredictable gastric emptying rate, short gastro-intestinal transit time (8-12 h) and existence of an absorption window in the gastric and upper small intestine for several drugs[1,2] leading to low and variable oral absorption over shorter period of time. The real issue in the development of oral drug delivery systems is to prolong the residence time of dosage form in the stomach or upper gastro-intestinal tract until the drug is completely released and absorbed.

Several approaches are currently used to retain the dosage form in the stomach. These include bioadhesive systems[3], swelling and expanding systems[4,5], floating systems[6,7] and other delayed gastric emptying devices[8,9]. The principle of floating

tablet 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.

The objective of the study is to develop a floating drug delivery system (FDDS) containing carbamazepine, a poorly soluble drug, in order to enhance its oral bioavailability and to achieve controlled release. Carbamazepine is a widely used anticonvulsant drug belonging to the chemical category of iminostilbenes. It is used in doses of 100, 200 and 400 mg, 2 or 3 times a day. Carbamazepine is poorly soluble in water with erratic oral absorption. This erratic absorption may lead to fluctuations in plasma concentrations, which are responsible for its side effects and neurotoxicity. Hence controlled release formulations are needed for carbamazepine to avoid erratic absorption, fluctuating plasma concentrations and associated toxicity. Design of carbamazepine floating tablets is aimed to enhance its oral bioavailability and to achieve controlled release. A $2^3$ factorial design was employed to study the effects of variables involved in the design of carbamazepine floating tablets employing starch-urea-borate as matrix agent, sodium bicarbonate as gas generating agent, bees wax as hydrophobic floating agent and ethyl cellulose as floating enhancer.

## EXPERIMENTAL

Carbamazepine was a gift from M/s. Ranbaxy Research Laboratories, Gurgaon, Haryana. Starch-urea-borate prepared in the laboratory was used. Ethyl cellulose (viscosity of 5 % w/w solution in 80:20 toluene: ethanol by weight at 25 ºC in 18 cps, containing not less than 46.5 % ethoxy groups), Bees wax. I.P., sodium bicarbonate (SD Fine Chemie), talc, I.P and magnesium stearate I.P were procured from commercial sources. All other materials used were of pharmacopoeial grade.

**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 g) and urea (15 g) were dissolved 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 min to gelatinize starch to form starch-urea-borate polymer. The mass formed was spread on to a stainless steel plate and dried at 80 ºC for 6-8 h. The dried polymer was powdered and passed through mesh No. 120.

**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 16 mesh 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., Ahmedabad) to a hardness of 6-8 kg/cm$^2$.

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 the three factors as per a $2^3$-factorial design. Formulae of carbamazepine floating tablets prepared as per $2^3$-factorial design are given in Table-1.

TABLE-1
FORMULAE OF CARBAMAZEPINE FLOATING TABLETS PREPARED AS PER $2^3$ FACTORIAL DESIGN

| Ingredient (mg/tablet) | $F_1$ | $F_a$ | $F_b$ | $F_{ab}$ | $F_c$ | $F_{ac}$ | $F_{bc}$ | $F_{abc}$ |
|---|---|---|---|---|---|---|---|---|
| Carbamazepine | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| 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 |
| Bees wax | 33 | 33 | 33 | 33 | 44 | 44 | 44 | 44 |
| 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 |

**Evaluation of tablets:** Hardness of the tablets was tested using a Monsanto hardness tester. Friability of the tablets was determined in a Roche friabilator. Disintegration time of the tablets prepared was determined using a thermonic tablet disintegration test machine using water, 0.1 N HCl and phosphate buffer of pH 7.4 as test fluids.

**Estimation of carbamazepine:** An ultraviolet (UV) spectrophotometric method based on the measurement of absorbance at 288 nm in 0.1 N HCl was used for the estimation of carbamazepine. The method obeyed Beer-Lambert's law in the concentration range of 1-10 µg/mL. When a standard drug solution was assayed repeatedly (n = 6), the relative error (accuracy) and coefficient of variation (precision) were found to be 0.80 and 1.10 %, respectively. No interference, from the excipients used, was observed.

**Floating lag time and floating time:** *In vitro* buoyancy was determined by measuring floating lag time and duration of floating. The tablets were placed in a 250 mL glass beaker containing 0.1 N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time. The period during which the tablet remains floating was determined as floating time.

**Drug release study:** Drug release from the matrix tablets formulated was studied using 8-station dissolution rate test apparatus (Labindia, Disso 2000) employing a paddle stirrer at 50 rpm and at 37 ± 1 ºC. Hydrochloric acid, 0.1 N (900 mL) was used as dissolution fluid. A 5 mL aliquot of dissolution medium was withdrawn through a filter (0.45 µm) at different time intervals and assayed spectrophoto-

metrically by measuring absorbance at 288 nm. All drug release experiments were conducted in triplicate.

**Data analysis:** Drug release data were analyzed as per zero order, first order, Higuchi[10] and Peppas[11] equation models to assess drug release kinetics and mechanism from the tablets prepared.

## RESULTS AND DISCUSSION

Floating tablets each containing 50 mg of carbamazepine could be prepared employing starch-urea-borate as matrix former and release retardant, sodium bicarbonate as gas generating agent, bees wax as hydrophobic floating agent and ethyl cellulose as floating enhancer by melt granulation technique. Hardness of the tablets was in the range of 5-9 kg/cm$^2$. Weight loss in the friability test was less than 0.18 % in all the cases. All the matrix tablets prepared containing carbamazepine with in 100 ± 5 % of the labeled 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-2).

TABLE-2
PHYSICAL PROPERTIES AND RELEASE CHARACTERISTICS OF CARBAMAZEPINE FLOATING TABLETS PREPARED EMPLOYING STARCH-UREA-BORATE

| Formulation | Hardness (kg/cm$^2$) | Friability (%) | Drug content (mg/tab) ± SD | Floating lag time (min) | Floating time (h) | Release parameter (% release in 24 h) ± SD | $K_0$ (mg/h) | 'n' in Peppas equation |
|---|---|---|---|---|---|---|---|---|
| $F_1$ | 5.5 | 0.12 | 48.65 ± 0.42 | 135.00 | 07.50 | 74.47 ± 0.56 | 2.0229 | 0.634 |
| $F_a$ | 6.0 | 0.16 | 49.82 ± 0.24 | 44.00 | 03.00 | 76.37 ± 0.32 | 1.8096 | 0.524 |
| $F_b$ | 5.5 | 0.18 | 49.61 ± 0.36 | 34.33 | 42.00 | 59.55 ± 0.87 | 1.9639 | 0.979 |
| $F_{ab}$ | 5.0 | 0.16 | 47.32 ± 0.24 | 11.66 | 03.66 | 58.54 ± 0.65 | 2.1406 | 0.923 |
| $F_c$ | 5.5 | 0.18 | 49.92 ± 0.51 | 63.33 | 43.00 | 86.13 ± 0.95 | 1.6976 | 0.936 |
| $F_{ac}$ | 5.5 | 0.14 | 48.82 ± 0.47 | 31.66 | 04.33 | 80.19 ± 0.57 | 2.1094 | 0.926 |
| $F_{bc}$ | 5.5 | 0.16 | 47.72 ± 0.34 | 58.33 | 43.00 | 36.99 ± 0.65 | 0.7965 | 0.964 |
| $F_{abc}$ | 5.5 | 0.13 | 48.37 ± 0.65 | 29.33 | 33.85 | 46.39 ± 0.69 | 0.9954 | 0.991 |

Carbamazepine release parameters of the tablets formulated are summarized in Table-2. 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. All the release parameters indicated much variation in the drug release from different tablets formulated. Carbamazepine release from the matrix tablet prepared followed zero order kinetics and the corresponding rate constants ($K_0$) are given in Table-2. When the release data are analyzed as per Peppas equation, the release exponent 'n' was found to be in the range 0.524-

0.991 indicating non-fickian diffusion as the release mechanism from all the floating tablets prepared.

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 (per cent 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-3) 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 ($p > 0.05$).

TABLE-3
ANOVA OF FLOATING TIMES OF 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 | $p < 0.05$ |
| Sod.bicarbonate X Ethyl cellulose (AB) | 1 | 66.66 | 66.66 | 0.4886 | $p > 0.05$ |
| Bees wax (C) | 1 | 1734 | 1734 | 12.71 | $p < 0.05$ |
| Sod.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.

ANOVA of release parameter (Table-4) indicated that the individual effects as well as combined effects of the three factors (*i.e.*, sodium bicarbonate, ethyl cellulose and bees wax) were all significant ($p < 0.05$). The ANOVA results, thus indicated that the three factors have significantly influence the floating as well as drug release characteristics.

Floating tablets ($F_C$) 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. USP 29 prescribed a release of NLT 75 % in 24 h for carbamazepine extended release tablets. Formulation ($F_C$) gave release of 86 % in 24 h fulfilling the official specification, based on *in vitro* buoyancy and drug release. Formulation ($F_C$) is considered as a good floating tablet formulation of carbamazepine providing slow and controlled release over 24 h and suitable for once-a-day administration.

TABLE 4
ANOVA OF RELEASE PARAMETER OF FLOATING TABLETS FORMULATED EMPLOYING STARCH-UREA-BORATE

| Source of variation | d.f | S.S | M.S.S | Variance ratio (F) | Result |
|---|---|---|---|---|---|
| Replicates | 2 | 0.81 | 0.405 | 1.31 | $p > 0.05$ |
| Treatments | 7 | 6357.42 | 908.20 | 2948.70 | $p < 0.05$ |
| Sodium bicarbonate (A) | 1 | 8.23 | 8.23 | 26.72 | $p < 0.05$ |
| Ethyl cellulose (B) | 1 | 5048.90 | 5048.90 | 16392.53 | $p < 0.05$ |
| Sod.bicarbonate X Ethyl cellulose (AB) | 1 | 58.90 | 58.90 | 191.23 | $p < 0.05$ |
| Bees wax (C) | 1 | 127.78 | 127.78 | 414.87 | $p < 0.05$ |
| Sod.bicarbonate X Bees wax (AC) | 1 | 6.74 | 6.74 | 21.88 | $p < 0.05$ |
| Ethyl cellulose X Bees wax (BC) | 1 | 1009.32 | 1009.32 | 3277.01 | $p < 0.05$ |
| Sod.bicarbonate X Ethyl cellulose X Bees wax (ABC) | 1 | 97.52 | 97.52 | 316.62 | $p < 0.05$ |
| Error | 14 | 4.32 | 0.308 | – | – |
| Total | 23 | 6362.55 | – | – | – |

$p < 0.05$ indicate significance; $p > 0.05$ indicate non-significance.

## 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. The individual and combined effects of sodium bicarbonate (gas generating agent), bees wax (hydrophobic floating agent) and ethyl cellulose (floating enhancer) on the floating time and drug release were significant ($p < 0.05$). 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 and were found suitable for once-a-day administration.

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