Orodispersible Tablets of Carbamazepine Prepared by Direct Compression Method Using 3^2 Full Factorial Design

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ABSTRACT: Orodispersible tablets of carbamazepine were prepared with a view to enhance patient compliance by direct compression method using 3^2 full factorial design. Crospovidone (2-10% w/w) was used as superdisintegrant and microcrystallinecellulose (0-30% w/w) was used as diluent, along with directly compressible mannitol to enhance mouth feel. The tablets were evaluated for hardness, friability, thickness, drug content uniformity, *in vitro* dispersion time, wetting time and water absorption ratio. Based on *in vitro* dispersion time (approximately 10 s); the formulation containing 2% w/w crospovidone and 30%w/w microcrystallinecellulose was found to be promising and tested for *in vitro* drug release pattern (in pH 6.8 phosphate buffer), short-term stability (at 40°/75 % RH for 3 w) and drug-excipient interaction. This formulation showed four-fold faster drug release ($t_{25\%}$) compared to the conventional commercial tablet formulation. Short-term stability studies on the formulation indicated that there are no significant changes in drug content and *in vitro* dispersion time ($p < 0.05$).

Key words: Orodispersible tablets, carbamazepine, crospovidone, micro crystallinecellulose, 3^2 full factorial design

INTRODUCTION

Dysphagia is a common problem encountered in all age groups in concern to solid dosage forms, which results in high incidence of non-compliance and ineffective therapy.[1] Recent advances in novel drug delivery systems (NDDS) aim to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance i.e., one, which will rapidly disintegrate in the mouth without need of water (orodispersible tablet). Advantages of this drug delivery system include administration without water, accuracy of dosage, easy portability, alternative to liquid dosage forms, ideal for pediatric and geriatric patients and rapid onset of action.[2-4] Carbamazepineb (CBZ) is a dibenzazepine derivative with an anti-convulsant and psychotropic properties. It is used in the treatment of epilepsy, multiple sclerosis, manic depressive illness and painful diabetic neuropathy and trigeminal neuralgia.[5] It was selected as drug candidate, as it is not available in such dosage form. Aim of the present study was to develop such a NDDS for CBZ by simple and cost-effective direct compression method.

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MATERIALS AND METHODS

CBZ and crospovidone were gift samples from Nicholas Piramal, Mumbai and Wockhardt Research Centre, Aurangabad respectively. Directly compressi-

ble mannitol (Pearlitol SD200), sodium stearyl fumarate and microcrystallinecellulose (Avicel PH-102) were generous gifts from Strides Arco Labs, Bangalore, Glenmark Ltd., Nashik and Alkem Labs Pvt Ltd, Mumbai. All other chemicals were of analytical reagent grade.

Preparation of orodispersible tablets of CBZ. Orodispersible tablets (OT) of CBZ were prepared by direct compression method[6] according to the formulae given in Table 1. All the ingredients were passed through #60 mesh separately, weighed and mixed in geometrical order in a tumbling cylindrical blender for 10 min at 15 rpm (fabricated in our laboratory, Fig. 1) Then lubricant and glidant (# 200 mesh) were added and mixed for further 5 min. The blend thus obtained was directly compressed using 9.5 mm flat round punches in to tablets of 400 mg on a 10-station rotary tablet machine (Clit, Ahmedabad,India). A batch of 60 tablets was prepared for all the designed formulations.

Table 1. Factorial design formulations of CBZ prepared by direct compression method

Ingredients (mg/ tablet)	Formulation code											
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_0	C_1	C_2
Carbamazepine	100	100	100	100	100	100	100	100	100	100	100	100
Crospovidone	8	8	8	24	24	24	40	40	40	-	16	32
Micro crystalline cellulose	0	60	120	0	60	120	0	60	120	40	30	90
Flavour	4	4	4	4	4	4	4	4	4	4	4	4
Sodium saccharin	4	4	4	4	4	4	4	4	4	4	4	4
Sodium stearyl fumarate	4	4	4	4	4	4	4	4	4	4	4	4
Purified talc	4	4	4	4	4	4	4	4	4	4	4	4
Pearlitol SD-200	276	216	156	260	200	140	244	184	124	244	238	162
Total weight	400	400	400	400	400	400	400	400	400	400	400	400

Formulation F_3 was selected as the best and used in further studies
F_0 is control formulation, C_1 and C_2 are extra check-point formulations

Figure 1: Cylindrical tumbling mixer

Evaluation of tablets. Twenty tablets were selected at random and weighed individually. The individual weights were compared with the average weight for determination of weight variation.[7] Hardness and friability of the tablets were determined by using Monsanto Hardness Tester and Roche friabilator respectively. For content uniformity test, ten tablets were weighed and powdered, a quantity of powder equivalent to 100 mg of CBZ was extracted into methanol and liquid was filtered. The CBZ content was determined by measuring the absorbance at 285 nm after appropriate dilution with methanol. The drug content was determined using the standard calibration curve. The mean percent drug content was calculated as an average of three determinations.[8] For determination of *in vitro* dispersion time, one tablet was placed in a beaker containing 10 ml of pH 6.8 phosphate buffer at 37 ± 0.5° C and the time required for complete dispersion was determined.[9]

For determination of wetting time and water absorption ratio,[10] a piece of tissue paper folded twice was placed in a small petri dish(internal duiameter of 5 cm) containing 6 ml of water. A tablet was placed on the paper and the time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio 'R' was determined using the equation, $R=100(W_b-W_a)/W_a$; where W_a is weight of tablet before water absorption and W_b is weight of tablet after water absorption. The results are shown in Table 2. IR spectra of the pure drug and its formulations were obtained by KBr pellet method using Perkin-Elmer FTIR series (model 1615) spectrophotometer in order to rule out drug-carrier interactions.

Dissolution study.[11] *In vitro* dissolution of CBZ mouth dissolving tablets was studied in USP XXIII type-II dissolution apparatus (Electrolab, Model-TDT 06N) employing a paddle stirrer at 50 rpm using 900 ml of pH 6.8 phosphate buffer at 37 ± 0.5º C as dissolution medium. One tablet was used in each test. Aliquots of dissolution medium (5 ml) were withdrawn at specified intervals of time and analyzed for drug content by measuring the absorbance at 285 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Cumulative percent of CBZ released was calculated and plotted against time.

Stability testing. Short-term stability studies on the promising formulation (F_3) were carried out by storing the tablets (in amber coloured rubber stoppered vials) at 40º/ 75% RH for 3 w. At intervals of one week, the tablets were visually examined for any physical changes, changes in drug content and *in vitro* dispersion time.

RESULTS AND DISCUSSION

Mouth dissolving tablets of CBZ were prepared by direct compression method using CP used as superdisintigrant and MCC as diluent along with directly compressible mannitol (Pearlitol SD 200), which serves as a sweetening agent and helps in masking slight bitter taste of the drug. A total of nine formulations and a control formulation (F_0, without super-disintegrant) were designed.

As the material was free flowing (angle of repose value <30º and Carr's index <15) tablets obtained were of uniform weight (due to uniform die fill), with acceptable variation as per IP specifications (±5%). Drug content was found to be in the range of 95-105%, which is within acceptable limits. Hardness of the tablets was found to be 2.0 to 2.5 kg/cm². Friability below 1% was an indication of good mechanical resistance of the tablets (Table 2). Formulation F_3 was found to be promising and displayed an *in vitro* dispersion time of 15 s, which facilitates faster dispersion in the mouth.

Table 2. Evaluation of factorial formulations

Formulation	Hardness* (Kg/cm²) ± SD	Friability (%)	Thickness* (mm) ± SD	Percent drug content*±SD	*In vitro* dispersion time* (s)±SD	Water absorption ratio
F_1	2.50 ± 0.1	0.40	6.07 ± 0.136	98.66 ± 1.86	58.11 ± 0.617	52.28
F_2	2.46 ± 0.057	0.45	6.05 ± 0.16	97.65 ± 0.99	31.21 ± 1.95	56.56
F_3	2.10 ± 0.1	0.46	6.21 ± 0.215	102.15 ± 1.16	15.54 ± 1.23	64.32
F_4	2.16 ± 0.115	0.50	6.07 ± 0.133	100.11 ± 0.80	26.6 ± 1.32	65.85
F_5	2.33 ± 0.057	0.42	6.22 ± 0.205	103.14 ± 1.16	22.1 ± 0.85	76.76
F_6	1.93 ± 0.115	0.60	6.15 ± 0.121	98.67 ± 0.78	12.2 ± 0.88	87.19
F_7	2.03 ± 0.057	0.48	5.95 ± 0.057	102.15 ± 1.16	18.3 ± 0.103	85.92
F_8	2.23 ± 0.057	0.50	5.93 ± 0.110	104.21 ± 1.16	11.1 ± 0.83	96.07
F_9	2.10 ± 0.10	0.52	6.11 ± 0.085	103.11 ± 1.01	10.0 ± 1.06	95.00

* Average of three determinations

Formulation optimization has been done by using 3^2 full factorial design, preparing nine batches of formulations (F_1 to F_9). Polynomial equation was derived for *in vitro* dispersion time, by backward stepwise linear regression analysis, using PCP Disso 2000 V3 software. Formulation F_3 containing 2% w/w CP, 30% w/w MCC was found to be promising with an *in vitro* dispersion time of 15 s against the 80

s displayed by control formulation (F_0), which does not contain CP.

In vitro dissolution studies on the promising formulation (F_3), the control (F_0) and commercial conventional tablet formulation (CF) were carried out in pH 6.8 phosphate buffer and the various dissolution parameter values, viz., percent drug dissolved in 5 min (D_5), 10 min (D_{10}), dissolution efficiency[12] at 10 min (DE_{10min}), $t_{25\%}$ and $t_{50\%}$ are shown in Table 3 and the dissolution profile depicted in Figure 2. This data reveals that overall, the formulation F_3 has shown 4-fold faster drug release ($t_{25\%}$=8.25 min) when compared to CF ($t_{25\%}$>30 min) and displayed 9-times greater dissolution efficiency at 10 min.

Table 3. *In vitro* dissolution parameters in pH 6.8 phosphate buffer

Formulation	D_5 (%)	D_{10} (%)	DE_{10min} (%)	$t_{25\%}$ (min)
F_0	15.0	22.0	13.40	17.0
F_3	21.5	27.43	18.62	8.25
CF	2.2	3.07	2.12	>30

F_0 is control formulation, F_3 is promising orodispersible tablet formulation, CF is conventional commercial tablet formulation, D_5 is percent drug released in 5 min, D_{10} is percent drug release in 10 min, DE_{10min} is dissolution efficiency at 10 min, $t_{25\%}$ is time for 25% drug dissolution

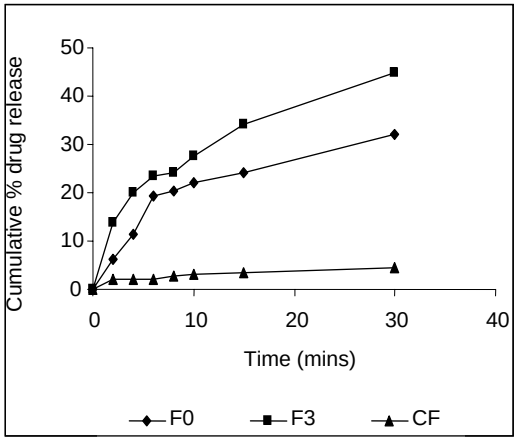

Figure 2. CBZ release profiles in pH 6.8 phosphate buffer

IR spectroscopic studies indicated that the drug is compatible with all the excipients. The IR spectrum of F_3 showed all the characteristic peaks of CBZ, thus confirming that no interaction of drug occurred with the components of the formulation. Short-term stability studies of the above formulation indicated that there are no significant changes in drug content and *in vitro* dispersion time at the end of 3 w period ($p<0.05$).

Development of polynomial equation. From the data of *in vitro* dispersion time of the factorial formulations F_1 to F_9, polynomial equation for *in vitro* dispersion time has been derived using 'PCP Disso 2000 V3 software'. Polynomial equation for 3^2 full factorial design is[13]:

$$Y = b_0+b_1X_1 +b_2X_2+b_{12}X_1X_2+b_{11}X_1^2 +b_{22}X_2^2 \text{ ..... } 1$$

Where Y is dependent variable, b_0 arithmetic mean response of nine batches, and b_1 estimated coefficient for factor X_1. The main effects (X_1 and X_2) represent the average results 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 two factors are simultaneously changed. The polynomial terms X_1^2 and X_2^2 are included to investigate non-linearity.

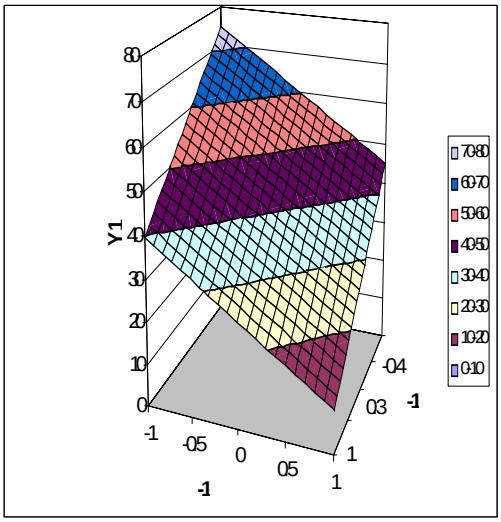

Figure 3. Response surface plot showing effect of factorial variables on *in vitro* dispersion time

The equation derived for *in vitro* dispersion time of the factorial formulations is:

$$Y_1 = 22.84 – 10.97X_1 – 10.94X_2 \quad \ldots \quad 2$$

The negative sign for coefficients of X_1 and X_2 indicate that as the concentration of disintegrants increases, *in vitro* dispersion time decreases.

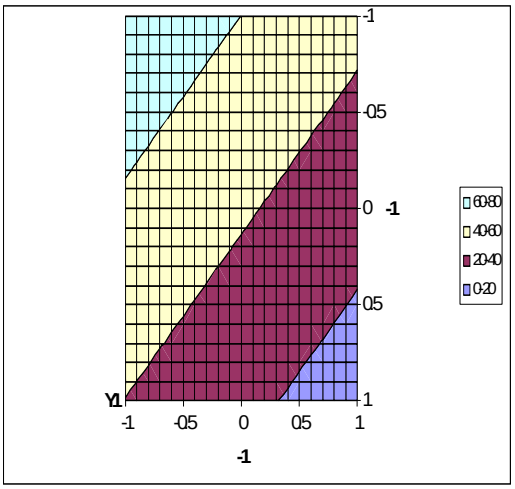

Figure 4. Contour plot showing effect of factorial variables on *in vitro* dispersion time

Validity of the above equation was verified by designing two check point formulations (C_1 and C_2) and determining the *in vitro* dispersion time. The *in vitro* dispersion time values predicted from the equation derived and those observed from experimental results are summarized in the table below.

Formulation Code	Predicted value (s)	Observed value (s)
C_1	32.25	33.79
C_2	12.81	11.89

The closeness of the predicted and observed values for C_1 and C_2 in the method indicates validity of derived equations for the dependent variable (*in vitro* dispersion time).

The computer generated response surface and contour plots for the dependent variable are shown in Figures 3 and 4, respectively.

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