RESEARCH ARTICLE

Development and evaluation of carbamazepine fast dissolving tablets prepared with a complex by direct compression technique

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The present study deals with the formulation of fast dissolving tablets of poorly soluble carbamazepine by the direct compression technique with β-cyclodextrin complexes using various super disintegrants like Indion-414, croscarmellose sodium, crospovidone and sodium starch glycolate. Carbamazepine is used to control different types of seizures in the treatment of epilepsy. Poor solubility in biological fluids is the major problem with this drug as also its poor bioavailability after oral administration. The rate of absorption and/or the extent of bioavailability for such a poor soluble drug is controlled by rate of dissolution in gastrointestinal fluids. Hence, to enhance the solubility of the drug, a complex of carbamazepine was prepared with β-cyclodextrin and this complex was compressed into tablets. The prepared tablets were evaluated for hardness, friability, drug content, weight variation, disintegrating time, wetting time, *in vitro* dissolution studies, etc. The prepared tablets were characterized by DSC, Fourier transform infrared spectroscopy (FTIR) and stability studies. The different formulations showed disintegration times between the ranges of 26.86 and 58.54 s. Drug release showed time between the ranges of 4 and 12 min. Among all the formulations, B8 showed 99.89% drug release within 4 min. Thus, B8 was considered as the best among the other formulations. No chemical interaction between the drug and the excipients was confirmed by DSC and FTIR studies. The stability study was conducted as per the ICH guidelines and the formulations were found to be stable, with insignificant changes in hardness, drug content and disintegration time. These results revealed that fast dissolving tablets of the poorly soluble drug, carbamazepine, showing enhanced dissolution and, hence, better patient compliance.

Key words: *Carbamazepine, croscarmellose sodium, crospovidone, fast dissolving tablets, Indion-414, sodium starch glycolate*

INTRODUCTION

Carbamazepine, a dibenzapine derivative with a structure resembling the tricyclic antidepressants, is used to control different types of seizures in the treatment of epilepsy. One of the major problems with this drug is its very low solubility in biological fluids. The plasma half-life ranges from 18 to 60 h following a single dose and from 10 to 35 h during chronic therapy, which results into poor bioavailability after oral administration.[1,2] It shows an erratic dissolution profile in gastric and intestinal fluid due to its poor water solubility. The peak plasma concentration (C max) and the time taken to reach C max (t max) depend on the extent and the rate of dissolution of the drug, respectively. The rate of dissolution can be increased by increasing the surface area of the available drug by various methods (micronization, complexation and solid dispersion).[3] The dissolution of a drug can also be influenced by the disintegration time of the tablets. Faster disintegration of tablets delivers a fine suspension of drug particles resulting in a higher surface area and faster dissolution.

Of all the orally administered dosage forms, tablet is most preferred because of easy administration, compactness and flexibility in manufacturing. Because of changes in various physiological functions associated with aging, including difficulty in swallowing, administration of the intact tablet may lead to poor patient compliance and ineffective therapy. The pediatric and geriatrics patients are of particular concern. To overcome this, dispersible tablets[4] and fast disintegrating tablets[5] have been developed. Most commonly used methods to prepare these tablets are freeze-drying/lyophilization[6] tablet molding[7] and direct compression. Lyophilized tablets show a very porous structure, which causes quick penetration of saliva into the pores when placed in the oral cavity.[8,9] The main

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disadvantages of tablets produced are, in addition to the cost-intensive production process, a lack of physical resistance in standard blister packs and their limited ability to incorporate higher concentrations of active drug. Molded tablets dissolve completely and rapidly. However, lack of strength and taste masking are of great concern.[7,10] The main advantages of direct compression are low manufacturing cost and high mechanical integrity of the tablets.[8,11] Therefore, direct-compression appears to be a better option for manufacturing the tablets. The fast disintegrating tablets prepared by the direct compression method, in general, are based on the action established by superdisintegrants such as croscarmellose sodium (CCS), crospovidone (CP), Indion-414 and sodium starch glycolate (SSG). The effect of functionality differences of the superdisintegrants on tablet disintegration has been studied.[12,13]

Hence, in the present work, carbamazepine fast dissolving tablets were prepared using carbamazepine with a β-cyclodextrin complex using different superdisintegrants like CCS, CP, Indion-414 and SSG. Microcrystalline cellulose (MCC) and directly compressible mannitol were used as diluents. A total number of 16 formulations were prepared with the complex by the direct compression technique, compositions of which are given in Table 1.

MATERIALS AND METHODS

Materials

Carbamazepine was a gift sample from Cadila Health Care, Ahmedabad, India. CCS and SSG were gift samples from Maruti Chem., Ahmedabad, India. Aspartame and CP were gift sample from Aurobindo Pharma, Hyderabad, India. Indion-414 was a gift sample from Ion Exchange India Limited, Mumbai, India. Sodium lauryl sulfate (SLS), D.C. mannitol, MCC, talc and magnesium stearate (Mg. stearate) were purchased from S.D. Fine Chem., Mumbai, India. All other materials were of analytical reagent grade.

Methods

Preparation of complex of carbamazepine with β-cyclodextrin

A mixture of carbamazepine and β-cyclodextrin was ground in a glass container and a minimum amount of solvent (methanol:water = 1:1 v/v) was added. The mixture was reacted for 90 s at 60°C in the microwave oven. After the reaction was completed, an adequate amount of solvent was added to remove residual carbamazepine and β-cyclodextrin and then the precipitate was filtered. After drying in a vacuum oven at 80°C, a white powder product was attained, which was the inclusion complex of carbamazepine and β-cyclodextrin.[14]

Preparation of tablets containing a complex of carbamazepine with β-cyclodextrin

The amounts of complex equivalent to 100 mg of drug were taken and then mixed with directly compressible diluent and superdisintegrants in a plastic container. Mg. stearate and talc were passed through sieve no. 60, mixed and blended with the initial mixture in the plastic container followed by compression of the blend. Compression was performed on a 10 station Rimek tablet compression machine (M/s Karnawati Engg. Ltd, Ahemadabad, India) using 8-mm punches.

Evaluation of carbamazepine tablets

The prepared tablets were evaluated for weight variation, hardness, friability, disintegration time, wetting time, drug content and stability studies. In the weight variation test, 20 tablets were selected at random and the average weight was calculated. Then, individual tablets were weighed and the weight was compared with an average weight. The Pfizer hardness tester was used for the determination of the hardness of tablets. The tablet was placed in contact between the plungers and the handle was pressed. The force of the fracture was recorded. The friability of the tablets was determined using a Roche friabilator (Cambel Electronics, Mumbai, India). Six tablets were tested from each formulation. In the disintegration time[15] study, the tablet was put into 100 ml distilled water at 37 ± 2°C. Time required for complete dispersion of a tablet was measured with the help of a digital tablet disintegration test apparatus and in the wetting time[16] study, a piece of tissue paper folded twice was placed in a small petridish (internal diameter = 6.5 cm) containing

Table 1: Composition of carbamazepine fast dissolving tablets

Ingredients (mg)	B1	B2	B3	B4	B5	B6	B7	B8	B9	B10	B11	B12	B13	B14	B15	B16
Amount of complex equivalent to 100 mg of carbamazepine (with β-cyclodextrin)	340.2	340.2	340.2	340.2	340.2	340.2	340.2	340.2	340.2	340.2	340.2	340.2	340.2	340.2	340.2	340.2
SSG	12.5	25	37.5	50	–	–	–	–	–	–	–	–	–	–	–	–
CCS	–	–	–	–	12.5	25	37.5	50	–	–	–	–	–	–	–	–
CP	–	–	–	–	–	–	–	–	12.5	25	37.5	50	–	–	–	–
Indion-414	–	–	–	–	–	–	–	–	–	–	–	–	12.5	25	37.5	50
MCC	80	80	80	80	80	80	80	80	80	80	80	80	80	80	80	80
DC-mannitol	53.3	40.8	28.3	15.8	53.3	40.8	28.3	15.8	53.3	40.8	28.3	15.8	53.3	40.8	28.3	15.8
Aspartame	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Talc	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Mg. stearate	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2

5 ml of distilled water. A tablet was placed on the paper and the time for complete wetting of the tablet was measured in seconds. For the determination of the drug content, a total 10 tablets were weighed and powdered and powder equivalent to 100 mg of carbamazepine was weighed and dissolved in 1% SLS solution then filtered a Whatman filter paper. The 1% SLS solution was used in the present study because carbamazepine is practically insoluble in water and ether and freely soluble in acetone, chloroform, alcohol, dioxane and propylene glycol. The solubility studies of carbamazepine in different solvents/buffer solutions were carried out to know the solubility and decide the appropriate dissolution medium. Table 2 shows the solubility data of carbamazepine in solvent/buffer solutions. In this study, 1% SLS was used as dissolution media because it can maintain perfect sink conditions. The filtrate was collected and diluted to a sufficient amount with 1% SLS solution till the concentration of the drug lay within the standard plot range. The diluted solution was analyzed for the carbamazepine content by a UV-spectrophotometer (UV-1700 Shimadzu Corporation, Japan) at 287 nm using 1% SLS solution as a blank. The stability study of the tablets was carried out according to International conference on Harmonization guidelines for zones III and IV. The formulations were stored at 40 ± 2°C/75 ± 5% RH for 4 weeks by storing the samples in a stability chamber (Lab-Care, Mumbai, India).

In vitro release studies

The *in vitro* dissolution study[17] was carried out in the USP dissolution test apparatus (Electrolab TDT - 08 L Dissolution tester USP) type 2 (paddle). Nine hundred milliliters of the dissolution medium (1% SLS solution) was taken in a covered vessel and the temperature was maintained at 37 ± 0.5°C. The speed of the paddle was set at 75 rpm. Sampling was performed at every 1-min interval. For each sample, 5 ml of the dissolution medium was withdrawn and the same amount of dissolution medium at 37 ± 0.5°C was replenished to the dissolution medium. The sample was withdrawn and diluted with 1% SLS solution and analyzed in the UV spectrophotometer (UV-1700 Shimadzu Corporation) at 287 nm. All the results were performed in triplicate.

Characterization of carbamazepine tablets

Fourier transform infrared spectroscopy (FTIR) studies

IR spectra for drug and powdered tablets were recorded in a Fourier transform infrared spectrophotometer (FTIR 1615; Perkin Elmer, USA) with KBr pellets.

DSC studies

DSC scans of about 10 mg, using an automatic thermal analyzer system, were performed accurately that weighed carbamazepine and the formulation (Mettler Toledo, USA). Sealed and perforated aluminum pans were used in the experiments for all the samples. Temperature calibrations were performed using indium as a standard. An empty pan sealed in the same way as the sample was used as a reference. The entire samples were run at a scanning rate of 10°/min from 50 to 300°C.

Table 2: Solubility study data of carbamazepine in various solvents and buffers

Name of the solvent	Concentration (mg/ml) (± SD) (*n* = 3)
Phosphate buffer pH 6.8	2.18 ± 0.002
Phosphate buffer pH 7.2	0.928 ± 0.058
Phosphate buffer pH 7.4	0.833 ± 0.024
1% sodium lauryl sulfate	6.58 ± 0.008
2% sodium lauryl sulfate	5.42 ± 0.050
0.1N hydrochloric acid	0.528 ± 0.004

RESULT AND DISCUSSION

The values of pre-compression parameters evaluated were within prescribed limits and indicated a good free flowing property. The results are shown in Table 3. The data obtained from post-compression parameters such as weight variation, hardness, friability, wetting time, drug content and *in vitro* disintegration are shown in Table 4.

In all the formulations, the hardness test indicated good mechanical strength, whereas friability is less than 1%, which indicated that the tablets had a good mechanical resistance. Drug content was found to be high (≥99.11%) and uniform in all the tablet formulations.

The tablets were subjected for evaluation of the *in vitro* disintegration time [Figure 1]. The tablets were evaluated for the *in vitro* disintegration time and it was observed that the time for all the formulations varied from 26.86 ± 0.9 to 58.54 ± 2.2 s. It was observed that when CP and Indion-414

Table 3: Pre-compressional parameters of powder blend used in the direct compression technique with the β-cyclodextrin complex

Formulation	Angle of repose (θ) (± SD) (*n* = 3)	Compressibility (%)(± SD) (*n* = 3)	Hausner's ratio (± SD) (*n* = 3)
B1	18.21 ± 0.08	12.25 ± 0.12	1.12 ± 0.09
B2	22.41 ± 0.11	14.28 ± 0.16	1.14 ± 0.11
B3	19.52 ± 0.09	16.68 ± 0.11	1.13 ± 0.12
B4	24.25 ± 0.12	17.71 ± 0.20	1.18 ± 0.08
B5	16.51 ± 0.16	12.48± 0.12	1.16 ± 0.12
B6	15.32 ± 0.18	16.59 ± 0.16	1.13 ± 0.11
B7	14.31 ± 0.12	15.98 ± 0.15	1.14 ± 0.11
B8	16.25 ± 0.14	14.32 ± 0.12	1.22 ± 0.09
B9	14.28 ± 0.11	13.57 ± 0.16	1.20 ± 0.05
B10	18.26 ± 0.12	16.36 ± 0.14	1.18 ± 0.11
B11	19.47 ± 0.15	14.29 ± 0.18	1.14 ± 0.08
B12	22.26 ± 0.16	13.72 ± 0.12	1.15 ± 0.10
B13	24.36 ± 0.18	12.82 ± 0.16	1.13 ± 0.12
B14	21.31 ± 0.12	14.52 ± 0.15	1.18 ± 0.06
B15	23.33 ± 0.15	15.65 ± 0.11	1.16 ± 0.05
B16	24.44 ± 0.16	11.41 ± 0.12	1.14 ± 0.04

Note: Values in parenthesis are standard deviation (± SD)

Figure 1: Photographs showing disintegration of tablets in water after 30, 60 and 90 s

Table 4: Results of the post-compression parameters

Formulation	Hardness (kg/cm^2) (± SD) (*n* = 3)	Friability (%) (± SD) (*n* = 6)	Drug content (mg%) (± SD) (*n* = 10)	Disintegration time (s) (± SD) (*n* = 6)	Wetting time (s) (± SD) (*n* = 3)	Weight variation (mg) (± SD) (*n* = 20)
B1	3.1 ± 0.16	0.62 ± 0.12	99.22 ± 1.4	34.26 ± 1.5	52.24 ± 1.8	500.47 ± 2.7
B2	3.4 ± 0.11	0.68 ± 0.18	99.41 ± 1.1	38.48 ± 0.7	73.08 ± 2.1	500.64 ± 2.1
B3	3.2 ± 0.15	0.59 ± 0.10	99.37 ± 0.9	44.56 ± 0.2	84.34 ± 1.3	500.55 ± 0.8
B4	3.1 ± 0.12	0.60 ± 0.08	99.69 ± 1.5	58.54 ± 2.3	99.19 ± 1.6	499.60 ± 1.4
B5	3.1 ± 0.13	0.54 ± 0.22	99.11 ± 1.2	39.28 ± 0.4	74.18 ± 1.9	500.58 ± 1.1
B6	3.6 ± 0.15	0.58 ± 0.24	99.46 ± 1.4	37.51 ± 0.1	62.58 ± 1.2	501.54 ± 1.9
B7	3.1 ± 0.10	0.64 ± 0.18	99.82 ± 1.2	31.35 ± 0.5	58.51 ± 0.6	500.65 ± 2.1
B8	3.3 ± 0.14	0.57 ± 0.14	99.74 ± 1.1	28.08 ± 0.4	54.55 ± 1.1	501.48 ± 1.1
B9	3.4 ± 0.12	0.62 ± 0.20	99.24 ± 0.5	32.34 ± 0.2	52.11 ± 1.1	502.41 ± 1.8
B10	3.3 ± 0.14	0.64 ± 0.09	99.08 ± 0.8	28.19 ± 0.4	48.10 ± 1.8	500.60 ± 1.2
B11	3.2 ± 0.18	0.68 ± 0.12	99.87 ± 1.4	27.12 ± 0.4	34.10 ± 1.3	501.41 ± 1.8
B12	3.3 ± 0.20	0.57 ± 0.15	99.67 ± 0.1	26.86 ± 0.5	32.18 ± 1.4	500.48 ± 0.5
B13	3.1 ± 0.18	0.59 ± 0.16	99.34 ± 1.1	42.04 ± 1.5	55.18 ± 1.8	502.78 ± 1.4
B14	3.1 ± 0.15	0.65 ± 0.18	99.48 ± 0.3	38.58 ± 1.1	49.12 ± 1.5	500.56 ± 1.8
B15	3.4 ± 0.13	0.68 ± 0.24	99.29 ± 0.8	30.14 ± 0.7	36.15 ± 1.1	501.70 ± 2.8
B16	3.5 ± 0.18	0.54 ± 0.21	99.82 ± 1.6	27.22 ± 0.2	34.11 ± 1.2	500.61 ± 2.1

Note: Values in parenthesis are standard deviation (± SD)

were used as disintegrants, the tablet disintegrated rapidly within a short time due to the easy swelling ability of CP and Indion-414 when compared with other tablets prepared using CCS and SSG. It is observed that the disintegration time of the tablets decreased with an increase in the level of CCS, CP and Indion-414. However, the disintegration time increased with an increase in the level of SSG in the tablets. It indicates that the increase in the level of SSG had a negative effect on the disintegration of the tablets. At higher levels, formation of a viscous gel layer by SSG[18] might have formed

a thick barrier to the further penetration of the disintegration medium and hindered the disintegration or leakage of the tablet contents. Thus, tablet disintegration is retarded to some extent with tablets containing SSG when compared with the disintegration time of the tablets containing CP.[19] These results suggest that using wicking type of disintegrants like CP and Indion-414 can decrease the disintegration time. The dissolution of carbamazepine from the tablets is shown in Figures 2-4. The results were compiled in Table 4.

Because the dissolution process of a tablet depends on the wetting followed by disintegration of the tablet, the measurement of wetting time may be used as another confirmative test for evaluation of the fast dissolving tablets. In the wetting time study, the wetting time was rapid in CP and Indion-414 followed by CCS and SSG. It was observed that as the concentrations of CCS, CP and Indion-414 increased, the time taken for wetting was reduced. However, in case of SSG, as the concentration increased, time taken for wetting also increased. Results were shown in Table 4.

The stability study for tablets was carried out according to the ICH guidelines at 40 ± 2°C (75 ± 5% RH for 4 weeks) by storing the sample in a stability chamber (Lab-Care). No appreciable change in physical characteristics, hardness, disintegration time and drug content was observed even after the evaluation for 4 weeks. Results are shown in Table 5.

The influence of superdisintegrants on the dissolution of carbamazepine from the tablets is shown in Figure 5. The $t_{50\%}$ and $t_{90\%}$ (time for 50% and 90% of release) values decreased with an increase in the level of CCS, CP and Indion-414. However, $t_{50\%}$ and $t_{90\%}$ values increased with an increase in the level of SSG. These results indicated that dissolution parameter values of CCS and SSG containing tablets are inconsistent with the disintegration time values observed. However, disintegration time values observed with CP and Indion-414 tablets are not predictable of dissolution of the drug. The rapid increase in dissolution of carbamazepine with the increase in CCS may be attributed to rapid swelling and disintegration[19] of the tablet into apparently primary

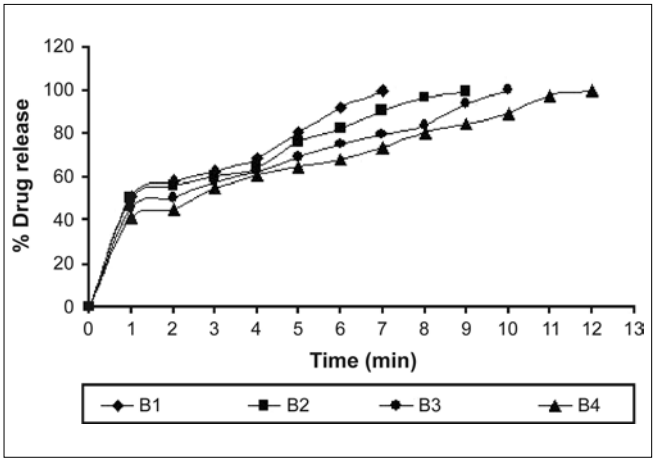

Figure 2: Dissolution profiles of different sodium starch glycolate formulations

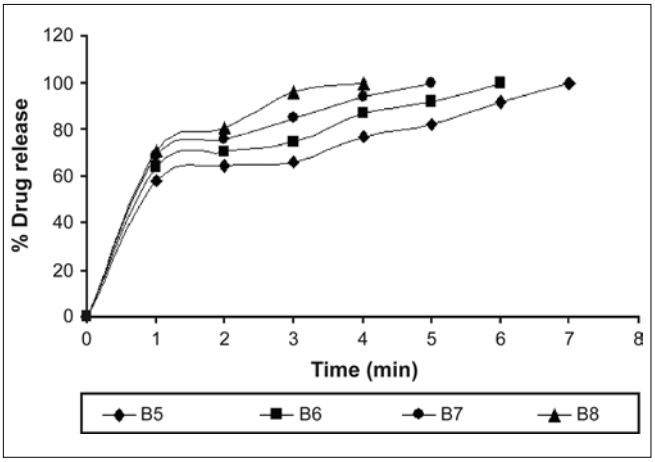

Figure 3: Dissolution profiles of different croscarmellose sodium formulations

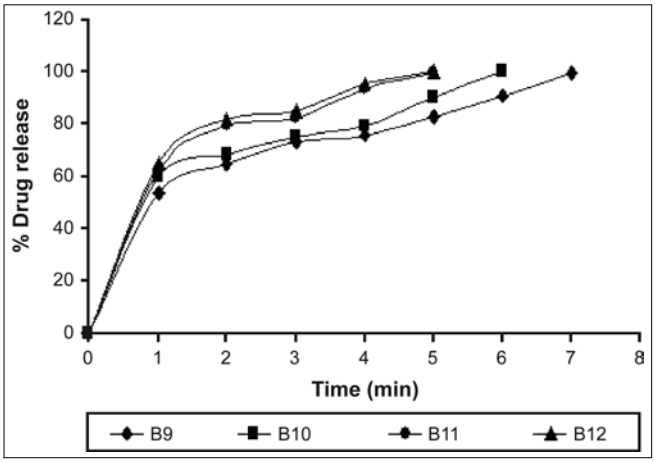

Figure 4: Dissolution profiles of different crospovidone formulations

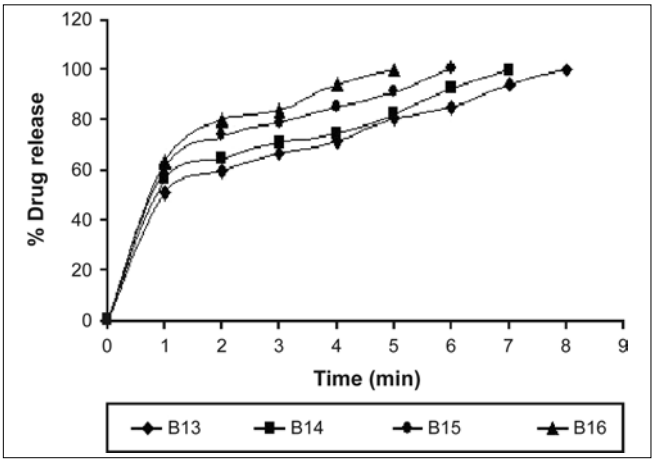

Figure 5: Dissolution profiles of different Indion-414 formulations

particles.[12] However, tablets prepared with SSG disintegrate by rapid uptake of water followed by rapid and enormous swelling[19] into primary particle, but more slowly[12] due to the formation of a viscous gel layer by SSG.[18] CP and Indion-414 exhibit high capillary activity and pronounced hydration, with little tendency to gel formation,[19] and disintegrate the tablets rapidly but into larger masses of aggregated particles.[12] Thus, the differences in the size distribution generated and the differences in the surface area exposed to the dissolution medium with different superdisintegrants rather than speed of disintegration of tablets may be attributed to the differences in the $t_{50\%}$ and $t_{90\%}$ values with the same amount of superdisintegrants in the tablets. Thus, although the disintegration times were lower in CP- and Indion-414-containing tablets than that of the CCS-containing tablet, comparatively higher $t_{50\%}$ and $t_{90\%}$ values were observed due to the larger masses of the aggregates.

Table 5: Results of the stability study

Formulation	Disintegration time (s) mean ± SD (*n* = 6)	Hardness kg/cm² mean ± SD (*n* = 3)	Drug content (mg%) (± SD) (*n* = 3)
B1	33.36 ± 1.8	3.3 ± 0.26	99.12 ± 1.1
B2	39.38 ± 1.7	3.2 ± 0.18	98.61 ± 1.8
B3	45.46 ± 0.8	3.1 ± 0.11	99.17 ± 1.9
B4	59.44 ± 1.3	3.2 ± 0.18	99.29 ± 1.9
B5	38.32 ± 1.4	3.3 ± 0.16	98.11 ± 1.9
B6	37.31 ± 1.1	3.5 ± 0.10	98.46 ± 1.5
B7	32.39 ± 1.5	3.2 ± 0.16	99.12 ± 1.8
B8	29.18 ± 1.4	3.2 ± 0.18	99.14 ± 1.7
B9	33.36 ± 1.2	3.3 ± 0.11	98.14 ± 0.5
B10	29.12 ± 1.4	3.2 ± 0.13	98.28 ± 0.6
B11	28.11 ± 1.5	3.3 ± 0.16	99.27 ± 1.8
B12	26.36 ± 1.5	3.2 ± 0.24	98.17 ± 1.1
B13	43.14 ± 0.5	3.2 ± 0.21	99.24 ± 2.1
B14	39.57 ± 1.8	3.2 ± 0.11	99.18 ± 1.3
B15	31.25 ± 0.5	3.3 ± 0.15	98.39 ± 2.8
B16	28.32 ± 1.2	3.4 ± 0.14	98.42 ± 1.1

Note: Values in parenthesis are standard deviation (± SD)

Among all formulations studied, formulation B8 showed 99.89% drug release in 4 min.

IR spectra of carbamazepine and formulation B8 are shown in Figure 6. The pure drug showed characteristic absorption bands cm^{-1} at 3467 (NH stretching of NH_2), 3080 (aromatic CH stretching), 1678 (C=O stretching of CO NH_2) and 1605, 1489 (C=C ring stretching) and the formulation B8 showed a characteristic absorption band at 3465 (NH Stretching of NH_2), 3080 (aromatic CH stretching), 1676 (C=O stretching of CO NH_2) and 1605, 1488 (C=C ring stretching). The IR spectra of pure carbamazepine and the formulation reveled that there is no appreciable change in the position of the absorption band. This reveled that there was no chemical interaction between the drug and the polymer.

Thermograms of pure drug carbamazepine and the formulation B8 [Figure 7] revealed that the pure drug has a sharp endotherm at 193.91°C. However, the drug and its formulation showed characteristic changes in the appearance of the thermogram. It is observed that in B8 the nature of the thermogram is totally changed and the sharp peaks are shifted to a lower range, around 167.31°C, and the peaks of the pure drug have changed to broad peaks with a reduction of the height of each peak. These changes indicate that the dehydration of the pure drug and the change in the particle size give a more amorphous type of the product, which may help in increasing the fast release of the tablets.

CONCLUSION

The major problem of carbamazepine is that it is erratically absorbed from the gastrointestinal tract and its limited aqueous solubility, which may hinder dissolution. Results reveled that it is possible to enhance the dissolution rate and the bioavailability by a direct compression technique using different superdisintegrants. The overall results

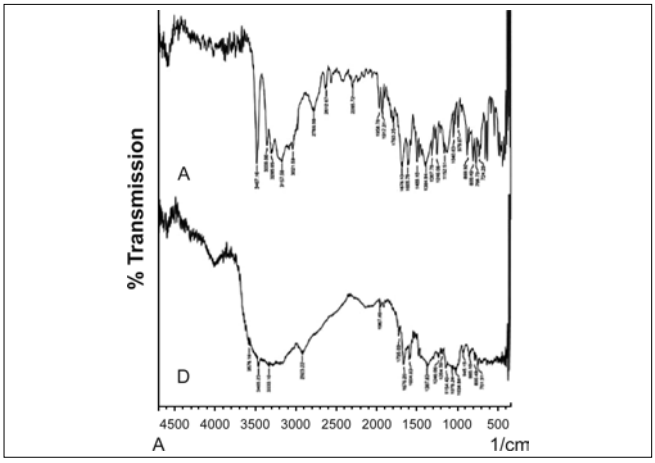

Figure 6: (A) Infrared (IR) spectrum of carbamazepine and (D) IR spectrum of formulation B8

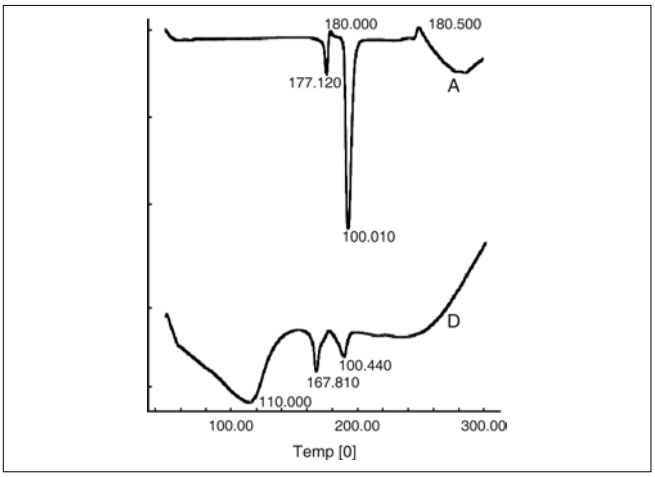

Figure 7: DSC thermograms of carbamazepine (A) and formulation B8 (D)

indicate that formulation B8, which contains 10% CCS, was better and that it satisfies all the criteria as a fast dissolving tablet.

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