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FORMULATION AND EVALUATION OF FAST DISSOLVING TABLETS OF CARBAMAZEPINE BY SOLID DISPERSION METHOD

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ABSTRACT:

An attempt has been made for the development of fast dissolving tablets of the carbamazepine by solid dispersion methods, using different concentrations of croscarmellose sodium as super disintegrating agent. The major problem of this drug is very low solubility in biological fluids and poor bioavailability after oral administration. The tablets prepared were evaluated for hardness, friability, drug content, disintegrating time, wetting time and *in-vitro* dissolution studies. The formulations prepared with mannitol solid dispersion were showed disintegration time between the ranges of 12.83 – 16.79 sec and Drug release showed between the ranges of 08 – 10 min. However the formulations prepared with PEG-6000 solid dispersion did not disintegrate in specified limit of time for fast dissolving tablet. Among all formulations SM4 showed 99.50 % drug release within 8 minutes. The prepared tablets were characterized by DSC and FTIR Studies. No chemical interaction between drug and excipient was confirmed by DSC and FTIR studies. The stability study conducted as per the ICH guidelines and the formulations were found to be stable. The results concluded that fast dissolving tablets of poorly soluble drug, carbamazepine showing enhanced dissolution, improved bioavailability, effective therapy and hence better patient compliance.

Key words: Fast dissolving tablets, carbamazepine, croscarmellose sodium, and solid dispersion.

INTRODUCTION:

Carbamazepine, a dibenzapine derivative with structure resembling the tricyclic antidepressants, is used to control some types of seizures in the treatment of epilepsy. One of the major problems with this drug is its very low solubility in biological fluids and its biological half-life between 18 to 65 h that results into poor bioavailability after oral administration[1-2]. It shows 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 upon extent and rate of dissolution of drug respectively. The rate of dissolution can be increased by increasing the surface area of available drug by various methods (micronization, complexation and solid dispersion) [3]. The dissolution of a drug can also be influenced by 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 ease of administration, compactness and flexibility in manufacturing. Because of changes in various physiological functions associated with aging including difficulty in swallowing, administration of intact tablet may lead to poor patient compliance and ineffective therapy. The paediatric 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 methods[8]. Lyophilized tablets show a very porous structure, which causes quick penetration of saliva into the pores when placed in oral cavity [6, 9]. The main 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 [4]. Moulded tablets dissolve completely and rapidly. However, lack of

strength and taste masking are of great concern [7, 10]. 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 of tablets. The fast disintegrating tablets prepared by direct compression method, in general, are based on the action established by superdisintegrants such as croscarmellose sodium, crospovidone and sodium starch glycolate. The effect of functionality differences of the superdisintegrants on tablet disintegration has been studied [12].

Hence in the present work Carbamazepine fast dissolving tablets were prepared by using solid dispersion technique using different concentrations of croscarmellose sodium as super disintegrants and micro crystalline cellulose and directly compressible mannitol was used as diluent. A total eight formulations were prepared by solid dispersion technique, compositions of which are given in **Table 1**.

Table 1: Composition of Carbamazepine fast dissolving Tablets.

Ingredients (mg)	SM1	SM2	SM3	SM4	SP1	SP2	SP3	SP4
Amount of Solid dispersion equivalent to 100 mg of drug (with Mannitol)	200	200	200	200	---	---	---	---
Amount of Solid dispersion equivalent to 100 mg of drug (with PEG-6000)	---	---	---	---	200	200	200	200
Croscarmellose sodium	7.5	15	22.5	30	7.5	15	22.5	30
Micro crystalline cellulose	50	50	50	50	50	50	50	50
DC-Mannitol	32.5	25	17.5	10	32.5	25	17.5	10
Aspartame	6	6	6	6	6	6	6	6
Talc	2	2	2	2	2	2	2	2
Magnesium Stearate	2	2	2	2	2	2	2	2

MATERIAL AND METHODS:

Materials:

Carbamazepine was procured as a gift sample from Cadila Health Care, Ahmedabad. Sperdisintegrating agent was procured as a gift sample from Maruti Chem. Ahmedabad, Sodium lauryl sulphate, D.C. Mannitol, Microcrystalline cellulose, Aspartame, Talc, and Mg.stearate purchased from S.D. fine chem., Mumbai. All other materials were of analytical reagent grade.

Preparation of solid dispersions of carbamazepine:

Solid dispersions of carbamazepine were prepared by solvent evaporation method. Drug was weighed and taken in a china dish, dissolved in methanol and then carrier was added (Mannitol and PEG-6000 in ratio of 1:1). The solvent was evaporated at room temperature and dried in hot air oven at 50^0 C for 4 hours. The resultant mass was passed through sieve no. 60 and stored in dessicator.

Preparation of tablets containing solid dispersions of Carbamazepine:

The solid dispersions equivalent to 100 mg of drug were taken then mixed with directly compressible diluent and superdisintegrants in a plastic container. Magnesium stearate and talc were passed through sieve no. 60, mixed and blended with initial mixture in the plastic container followed by compression of the blend.

Evaluation of Carbamazepine tablets:

The prepared tablets were evaluated for weight variation, hardness, friability, disintegration time, wetting time, drug content, and stability studies. In Weight variation test **t**wenty tablets were selected at a random and 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. Tablet was placed in contact between the plungers, and the handle was pressed, the

force of the fracture was recorded. The friability of tablets was determined using Roche friabilator (Cambel Electronics, Mumbai, India). Six tablets were tested from each formulation. In the Disintegration time[13] study **t**ablet was put into 100 ml distilled water at 37± 2°. Time required for complete dispersion of a tablet was measured with the help of digital tablet disintegration test apparatus and in wetting time[14] study a piece of tissue paper folded twice was placed in a small Petri dish (internal diameter = 6.5cm) containing 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 drug content total 10 tablets were weighed and powdered, powder equivalent to 100mg of Carbamazepine was weighed and dissolved in 1% sodium lurayl sulphate solution and filtered the solution through the whatman filter paper. The filtrate was collected and diluted to a sufficient amount with 1% sodium lurayl sulphate solution till the concentration of the drug lies with in the standard plot range. The diluted solution was analyzed for the Carbamazepine content by UV-spectrophotometer (UV-1700 Shimadzu Corporation, Japan) at 287 nm. Using 1% sodium lurayl sulphate solution as a blank. The stability study of the tablets was carried out according to International conference on Harmonization guidelines for zone III and IV. The formulations were stored at 40 ± 2^{o} / 75 ± 5 %RH for 4 weeks by storing the samples in stability chamber (Lab-Care, Mumbai).

In vitro Release Studies[15, 16] was carried out in the USP dissolution test apparatus (Electrolab TDT - 08 L Dissolution tester USP) type 2 (paddle). 900 ml of the dissolution medium (1% sodium lurayl sulphate solution) was taken in covered vessel and the temperature was maintained at 37 ± 0.5^{o} C. The speed of the paddle was set at 75 rpm. Sampling was done every one min interval. For each sample 5 ml of the dissolution medium was withdrawn and the same amount of dissolution medium at 37^{o} C was replenished to the dissolution medium. The sample withdrawn and diluted with 1% sodium lurayl

sulphate solution and analyzed in the UV spectrophotometer (UV-1700 Shimadzu corporation, Japan) at 287 nm. All the results were performed in triplicate.

Characterization of Carbamazepine tablets:

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 10mg, using an automatic thermal analyzer system performed accurately weighed Carbamazepine and formulation (Mettler Toledo, USA). Sealed and perforated aluminium pans were used in the experiments for all the samples. Temperature calibrations were performed using indium as 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 50-300°.

RESULT AND DISCUSTION:

The values of pre-compression parameters evaluated were within prescribed limits and indicated good free flowing property. 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 2.**

In all the formulations, hardness test indicated good mechanical strength, friability is less than 1%, indicated that tablets had a good mechanical resistance. Drug content was found to be high (≥99.1%) and uniform in all the tablet formulations.

The tablets were subjected for evaluation of in vitro disintegration time. The formulations prepared with mannitol solid dispersion were showed disintegration time between the ranges of 12.83 – 16.79 sec. In the formulation prepared with mannitol solid dispersion the disintegration time decrease with increasing the concentration of croscarmellose sodium. However the formulations prepared with PEG-6000 solid dispersion did not disintegrate in specified limit of time for

fast dissolving tablet. This may be due to more hardness of the tablets as these carriers act as strong binders at higher level with in the tablets. During compression, the carrier could plasticize, soften or melt, filling the pores within tablets and thus making them non-disintegrating. It is also possible that the soften and melted carriers coat the disintegrants and other ingredients used in tablets, and such a coating along with the reduction of porosity of tablets makes disintegration difficult.

The stability study for tablets was carried out according to ICH guidelines at 40 ± 2^{o}C (75 ± 5% RH for 4 weeks) by storing the sample in stability chamber (lab-care, Mumbai). No appreciable change in physical characteristics hardness, disintegration time and drug content was observed even after the evaluation for 4 weeks. Results were showed in **Table-3**.

Since the dissolution process of a tablet depends upon the wetting followed by disintegration of the tablet, the measurement of wetting time may be used as another confirmative test for the evaluation of fast dissolving tablets. In wetting time study, the wetting time was decrease with increasing the concentration of croscarmellose sodium.

The dissolution of carbamazepine from the tablets is shown in, [**Fig- 1 and 2**]. The $t_{50\%}$ and $t_{90\%}$ (time for 50% and 90% of release) values decreased with increase in the level of croscarmellose sodium. The rapid increase in dissolution of carbamazepine with the increase in croscarmellose sodium may be attributed to rapid swelling and disintegration [17] of tablet into apparently primary particles[12]. Among all formulations SM4 showed 99.50 % drug release within 8 minutes.

IR spectra of carbamazepine and formulation SM4 are shown in (**Fig -3**). Pure drug showed characteristic absorption bands at 3467 (NH Stretching of NH_2), 3080 (Aromatic CH stretching), 1678 (C=O stretching of CO NH_2), 1605, 1489 (C = C ring stretching) and the formulation SM4 showed characteristic absorption band at 3464 (NH Stretching of NH_2), 3080 (Aromatic CH stretching), 1678 (C=O stretching of CO NH_2), 1605, 1488 (C = C ring stretching). The IR spectra of pure carbamazepine

and formulation reveled that there is no appreciable changes in the position of absorption band. This reveled that there was no chemical interaction between drug and the polymer.

Thermograms of pure drug carbamazepine and the formulation SM4 (**Fig- 4**) revealed that the pure drug has a sharp endotherm at 193.91^{o}C. How ever the drug and its formulation showed characteristic changes in the appearance of the thermogram. It is observed that in SM4 the nature of thermogram is totally changed and the sharp peaks are shifted to lower range around 167.93^{o}C and the peaks of pure drug have change to broad peaks with reduction of the height of each peak. These changes ndicate that the dehydration of pure drug and change in the partical size giving more amorphous type of the product this may help in increasing the fast release of tablets.

Table 2: Results of Post Compression Parameters.

Formulation	Hardness Kg/cm^2 (±S.D), n=3	Friability (%) (±SD),n=6	Drug content (mg %) (±SD), n=10	Disintegration Time (sec) (±S.D), n=6	Wetting Time (sec) (±S.D), n=3	Weight variation (mg) (±SD), n=20
SM1	3.4 ± 0.16	0.54 ± 0.24	99.14 ± 0.7	16.79 ± 1.1	33.28 ± 0.1	300.58 ± 1.8
SM2	3.3 ± 0.15	0.59 ± 0.28	99.62 ± 0.1	14.75 ± 0.8	29.22 ± 1.8	301.54 ± 1.4
SM3	3.2 ± 0.19	0.66 ± 0.15	99.51 ± 1.5	13.14 ± 1.5	22.41 ± 1.4	300.65 ± 2.2
SM4	3.1 ± 0.14	0.67 ± 0.16	99.81 ± 0.8	12.83 ± 0.4	18.54 ± 1.8	301.48 ± 1.8
SP1	4.4 ± 0.11	0.62 ± 0.20	99.22 ± 1.8	240.33 ± 1.5	300.45 ± 1.1	302.41 ± 1.5
SP2	4.3 ± 0.18	0.64 ± 0.09	99.71 ± 1.6	240.11 ± 1.8	300.98 ± 1.8	300.60 ± 1.4
SP3	4.2 ± 0.14	0.65 ± 0.15	99.66 ± 0.9	180.96 ± 0.9	240.11 ± 1.4	301.41 ± 1.1
SP4	4.3 ± 0.22	0.55 ± 0.16	99.46 ± 0.5	180.82 ± 0.8	240.87 ± 1.4	300.48 ± 0.9

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

Table 3: Results of stability study.

Formulation	Disintegration Time (Sec) (±S.D), n=6	Hardness Kg/cm^2 (±S.D), n=3	Drug content (Mg %) (±SD), n=5
SM1	17.70 ± 1.8	3.9 ± 0.12	99.16 ± 0.7
SM2	15.75 ± 0.8	3.8 ± 0.14	99.62 ± 0.5
SM3	14.44 ± 1.5	3.8 ± 0.19	99.58 ± 1.5
SM4	13.23 ± 0.4	3.5 ± 0.15	99.81 ± 0.5
SP1	240.13 ± 1.5	4.4 ± 0.21	99.12 ± 1.8
SP2	240.51 ± 1.8	4.4 ± 0.18	99.65 ± 1.6
SP3	180.66 ± 0.9	4.2 ± 0.18	99.45 ± 0.9
SP4	180.62 ± 0.8	4.3 ± 0.32	99.32 ± 0.5

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

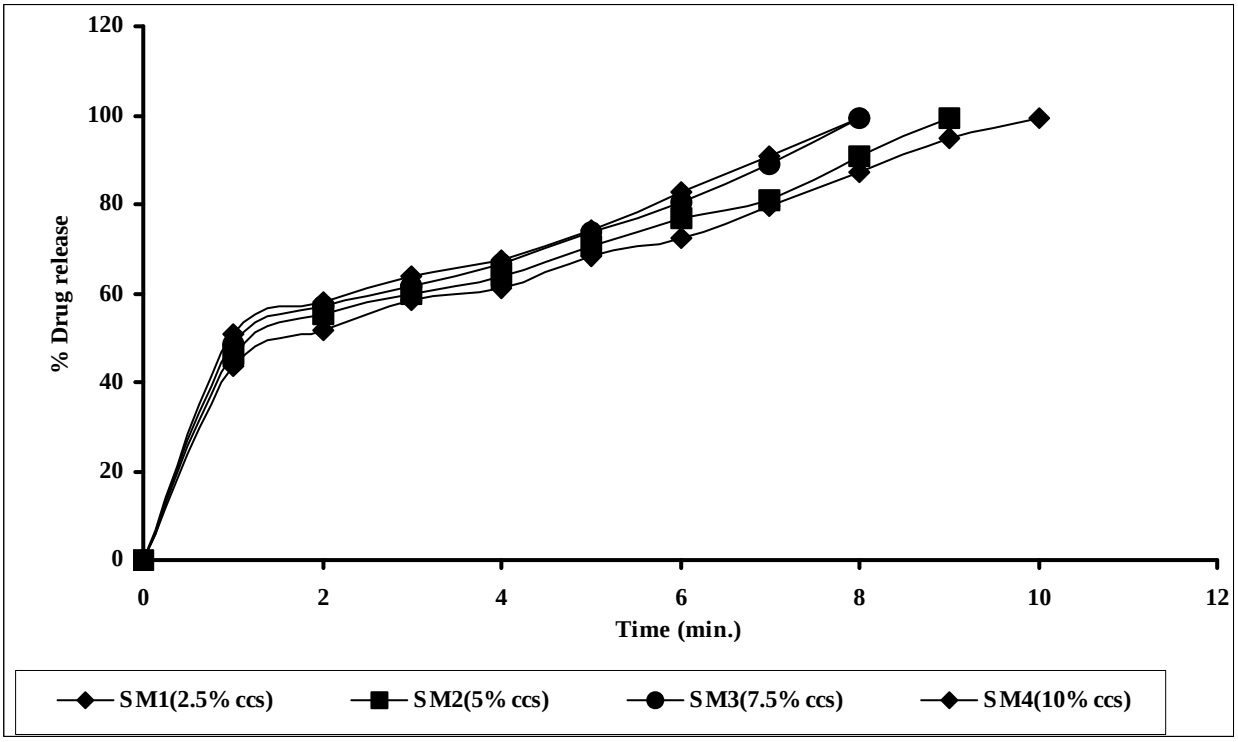

Figure 1: Dissolution profiles of formulations prepared with mannitol solid dispersion.

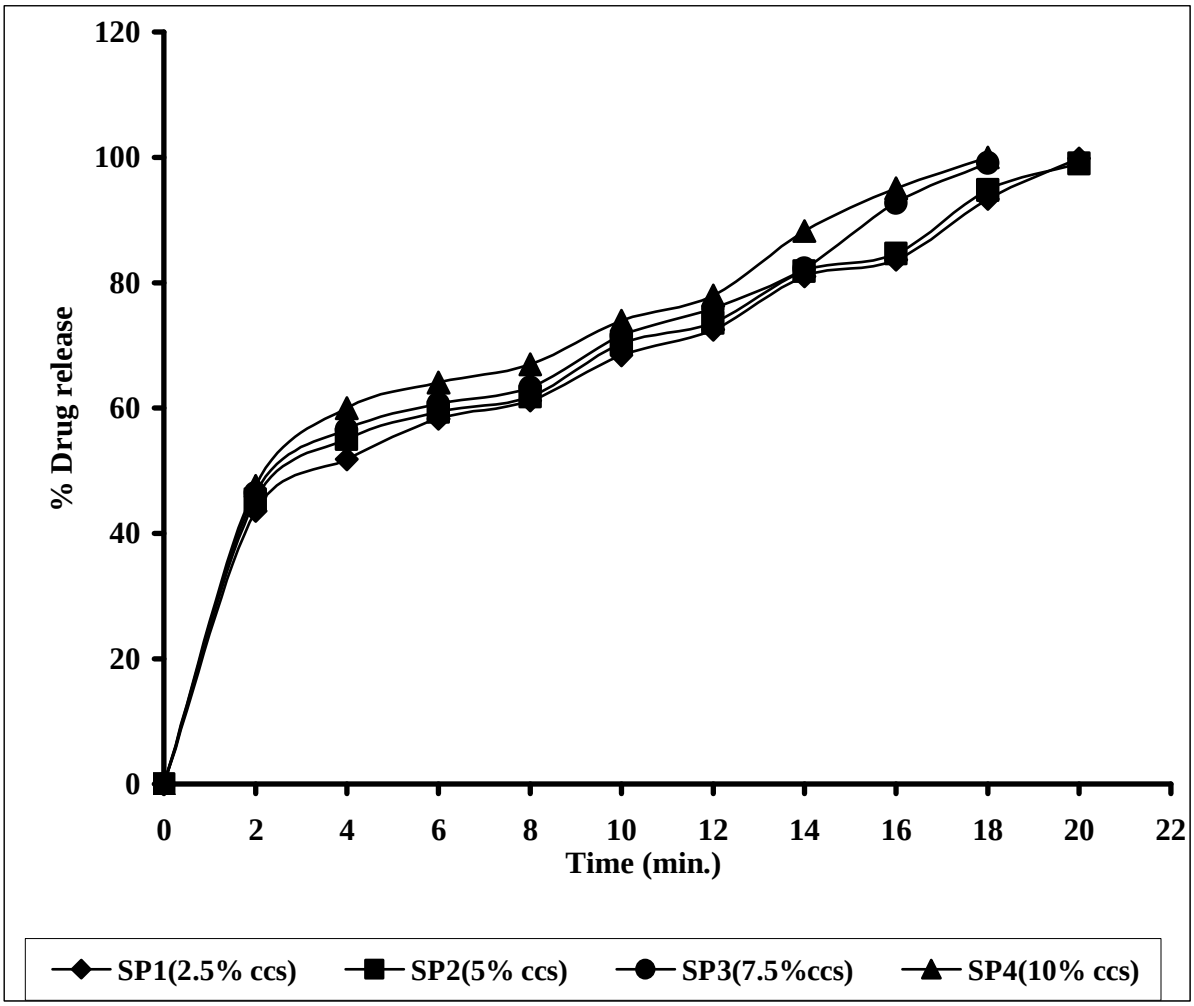

Figure 2: Dissolution profiles of formulations prepared with PEG-6000 solid dispersion.

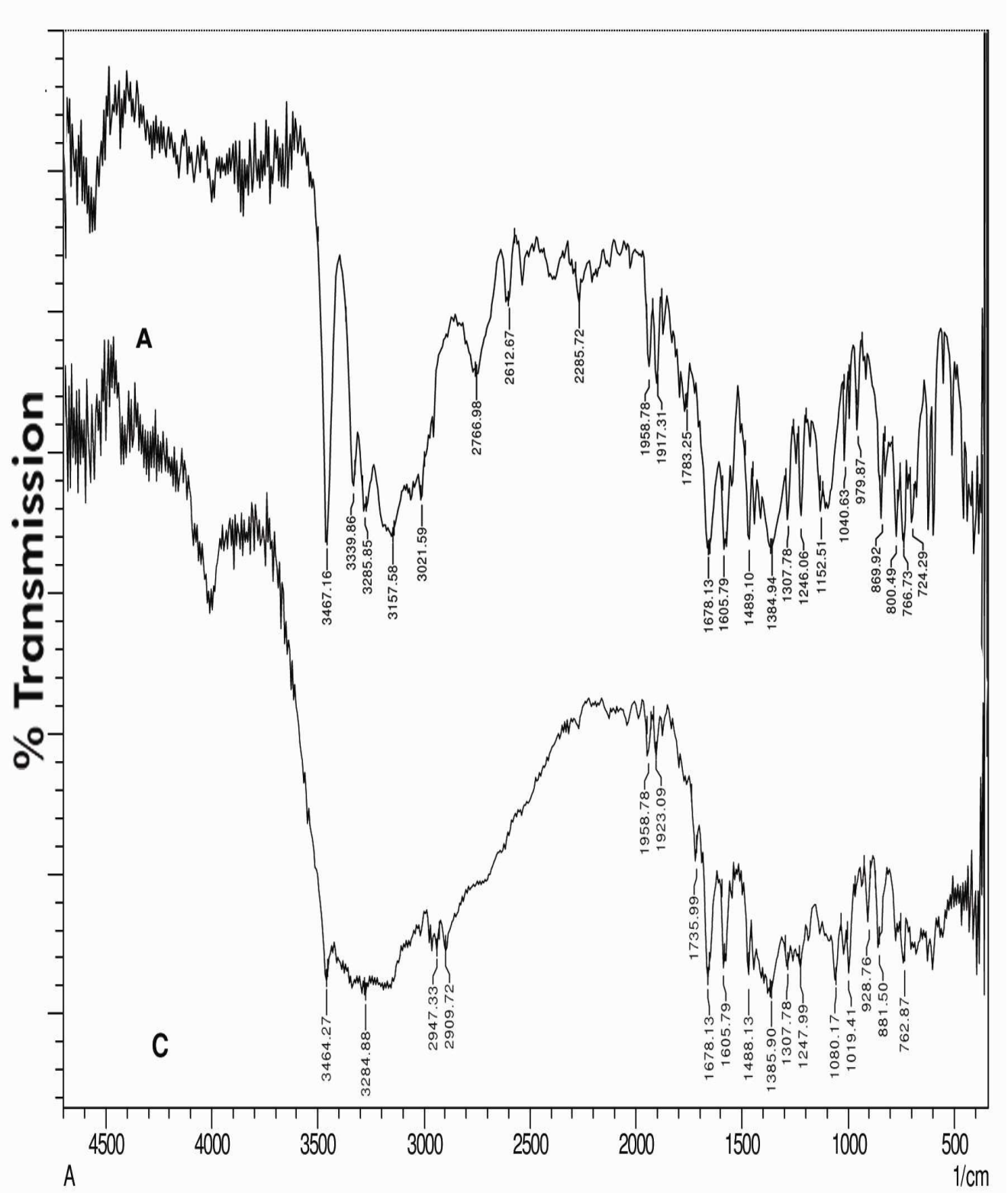

Figure 3: A) IR spectrum of Carbamazepine, C) IR spectrum of Formulation SM4.

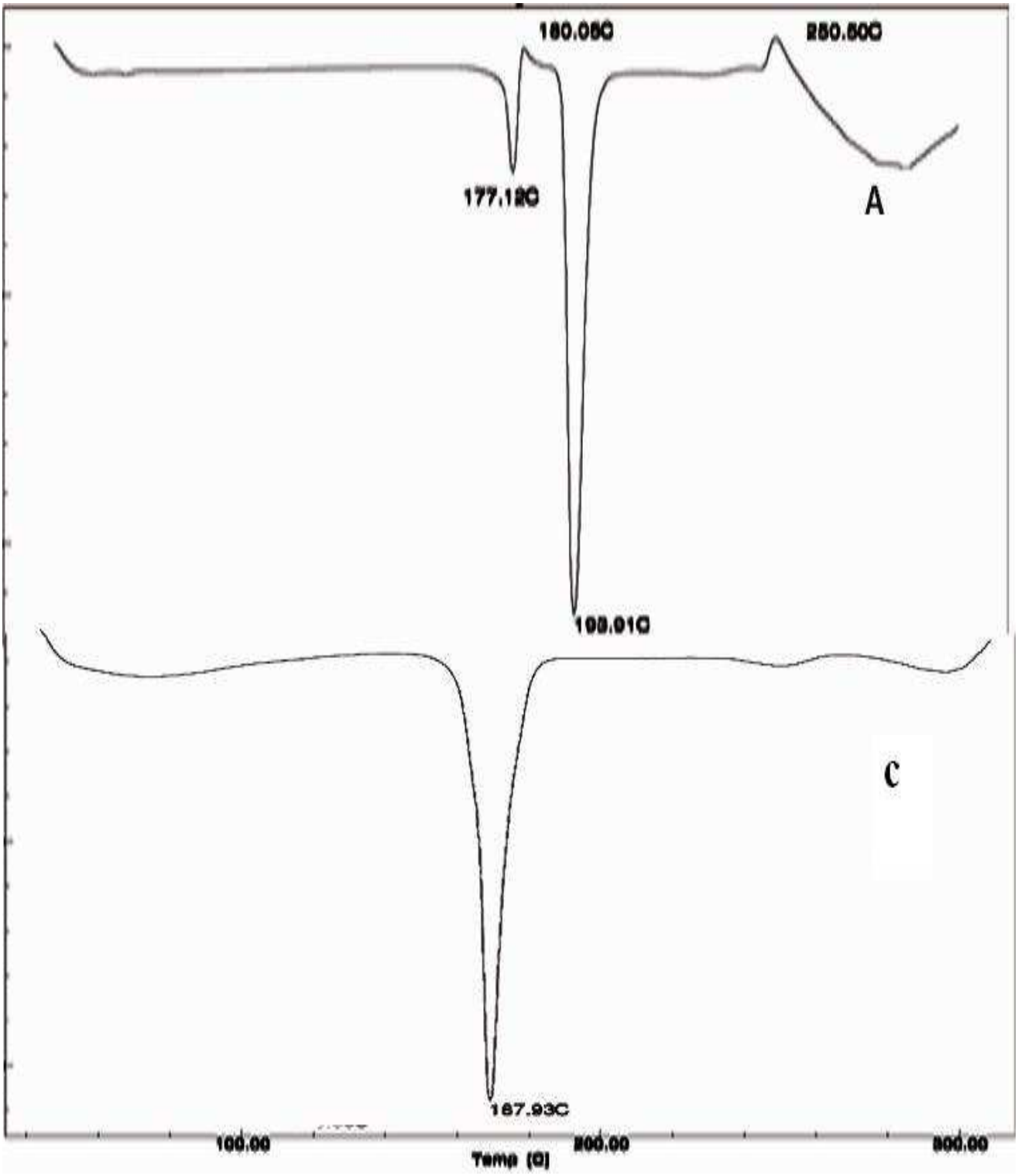

Figure 5: DSC Thermograms of Carbamazepine (A), Formulation SM4 (C).

CONCLUSION:

The major problem of carbamazepine that it is erratically absorbed from GIT, its limited aqueous solubility which may hinder dissolution and decrease bioavailability. Results revealed that it is possible to enhance dissolution rate and bioavailability by using solid dispersion technique using different concentrations of croscarmellose sodium as super disintegrants. Over all results indicates that formulation SM4 that contain 10% Croscarmellose sodium was better one and satisfies all the criteria as fast dissolving tablet.

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