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Comparative study on effect of Natural and Synthetic super Disintegrants in the formulation of Carbamazepine Fast Dissolving Tablets

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ABSTRACT:

A direct compression method was used to prepare fast dissolving tablets containing Carbamazepine as a model drug using natural as well as synthetic superdisintegrants such as isolated mucilage of *Plantago ovata* and croscarmellose sodium and sodium starch glycolate respectively. Prepared formulations were evaluated for precompression parameters such as micromeritic properties like angle of repose, %compressibility and Hausner's ratio. Tablets were also subjected to postcompression analysis for the parameters such as weight variation, hardness, friability, *in vitro* disintegration time, wetting time, drug content, *in vitro* dissolution study, and stability studies. The prepared tablets were characterized by FTIR for drug-excipient compatibility study. No chemical interaction between drug and excipients was confirmed by FTIR studies. The stability study conducted as per the ICH guidelines and the formulations were found to be stable. The results concluded that amongst all formulations prepared with mucilage of *Plantago ovata* showed better superdisintegrating property than the most widely used synthetic superdisintegrant like croscarmellose sodium and sodium starch glycolate.

KEY WORDS: Fast dissolving tablets, Carbamazepine, Mucilage of *Plantego ovata*, Croscarmellose sodium, Sodium starch glycolate.

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Introduction:

Carbamazepine (CBZ), a dibenzapine derivative is a sodium channel blocker that routinely used as anticonvulsant drug in the treatment of epilepsy and trigeminal neuralgia. Its rate of absorption varied markedly with different pharmaceutical formulations.

Nevertheless oral dosing remains the preferred mode of administration for many types of medication due to its simplicity, versatility, convenience, and patient acceptability.

CBZ (class II drug) have very low water solubility and dissolution rate-limited absorption, so absorption of its immediate-release tablets is generally slow and irregular. It has been reported that time to peak concentration (T max) of CBZ immediate-release tablets vary from 4 h to 8 h [1-3].

The poor aqueous solubility of CBZ has been overcome by many techniques, such as solid dispersion with polyethylene glycols (PEG); coprecipitation with phospholipids and complexation with cyclodextrin. Amongst these techniques, cyclodextrin complexation has been proved to be especially useful to improve the oral bioavailability [4-10].

The peak plasma concentration and the time taken to reach that concentration depend on extent and rate of dissolution of drug respectively.

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 [11-12].

Many attempts having rapidly disintegrating behavior have been reported by lyophilizing or molding, and compressing wet powders to construct highly porous structure[13].

Although these methods required the particular machines and the time consuming techniques, moreover, the hardness of the products was not enough to stand up to process of packaging and transportation. Therefore, direct compression is a convenient and cheap way to produce tablets with sufficient structural integrity. So far there have been many patents for fast disintegrating tablets, but only a few publications dealing with this dosage form [14-16].

Use of directly compressible superdisintegrant(s) are preferred probably due to the reason that direct compression method is inexpensive, most convenient and produces tablets of sufficient mechanical integrity without the use of complicated unit operations. Ideally, superdisintegrants should not only produce stronger tablets but also, disintegrate the tablet in the oral cavity in less than 30s [17].

The disintegration of fast dissolving tablets (FDTs) prepared by direct compression method is often compromised while improving the tensile strength of tablets. Superdisintegrants like croscarmellose sodium, crospovidone and sodium starch glycolate can disintegrate the tablets faster. However, they are of limited use when tablets are prepared with crushing strength of more than 4 kg [18-19].

Similarly, various natural substances like gum karaya, modified starch and agar have been used as superdisintegrants in the formulation of FDTs. Mucilage of natural origin is preferred over semi-synthetic and synthetic substances because they are comparatively cheaper, abundantly available, non-irritating and nontoxic in nature. Mucilage of *plantego ovata* has various characteristics like binding, disintegrating and sustaining properties [20].

Hence in the present research work FDTs of CBZ were prepared by direct compression technique using different concentrations natural superdisintegrant like mucilage of *plantego ovata* and widely used synthetic superdisintegrants like croscarmellose sodium and sodium starch glycolate.

Materials and Methods

CBZ was procured as a gift sample from Cadila Health Care, Ahmedabad, India. Seeds of *Plantego ovata* were purchased from the local market of Ahmedabad, Gujarat, India. croscarmellose sodium and sodium starch glycolate were gift samples from Maruti Chem. Ahmedabad, India. Other materials used in the study were of pharmaceutical grade.

Isolation of mucilage of *plantego ovate*

The seeds of *Plantego ovata* were soaked in distilled water for 48 hrs and then boiled for few minutes so that mucilage was completely released into water [21]. The material collected was squeezed through muslin cloth for filtering and separating out the marc. Then, an equal volume of acetone was added to the filterate so as to precipitate the mucilage. The separated mucilage was dried in oven (Labline equipment pvt. Ltd., Vadodara, Gujarat, India) at temperature less than 60^{o} C, powdered, sieved (80#) and stored in a desiccators (Sabar Scientific, Ahmedabad, India) until use.

Preparation of FDTs

FDTs containing 100 mg of CBZ were prepared by direct compression method and the various formulae used in the study of formulations F1 to F12 are shown in the table 1. The drug, diluents, superdisintegrant and sweetener were passed through sieve no 40#. All the above ingredients were properly mixed together (in an air tight plastic container). Talc and magnesium stearate were passed through mesh number 80#, mixed, and blended with initial mixture in a plastic container followed by direct compression of the blend. The tablets were prepared by direct compression method using 7 mm bi

Table 1: Composition of FDTs of CBZ.

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
CBZ	100	100	100	100	100	100	100	100	100	100	100	100
Sodium starch glycolate	5	10	15	20	--	--	--	--	--	--	--	--
Croscarmellose sodium	--	--	--	--	5	10	15	20	--	--	--	--
mucilage of *plantego ovata*	--	--	--	--	--	--	--	--	5	10	15	20
Micro crystalline cellulose	40	40	40	40	40	40	40	40	40	40	40	40
DC-Mannitol	40	35	30	25	40	35	30	25	40	35	30	25
Aspartame	10	10	10	10	10	10	10	10	10	10	10	10
Talc	3	3	3	3	3	3	3	3	3	3	3	3
Magnesium Stearate	2	2	2	2	2	2	2	2	2	2	2	2

Table 2: Precompressional parameters

Formulation	Angle of Repose (θ) (±SD), n=3	Hausner's ratio (±SD), n=3	Compressibility (%) (±SD), n=3
F1	19.17 ± 0.14	1.13 ± 0.04	12.22 ± 0.11
F2	26.15 ± 0.12	1.14 ± 0.08	12.82 ± 0.20
F3	27.10 ± 0.16	1.17 ± 0.06	14.69 ± 0.25
F4	21.70 ± 0.15	1.15 ± 0.08	13.38 ± 0.14
F5	27.25 ± 0.14	1.19 ± 0.06	16.60 ± 0.16
F6	24.39 ± 0.16	1.16 ± 0.09	14.52 ± 0.18
F7	22.17 ± 0.21	1.17 ± 0.10	15.41 ± 0.14
F8	20.25 ± 0.24	1.15 ± 0.11	13.61 ± 0.16
F9	26.49 ± 0.14	1.17 ± 0.08	14.97 ± 0.15
F10	27.75 ± 0.16	1.17 ± 0.04	14.75 ± 0.19
F11	18.45 ± 0.18	1.14 ± 0.10	12.76 ± 0.15
F12	23.05 ± 0.11	1.13 ± 0.10	14.58 ± 0.16

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

concave punches on Mini Rotary Press, compression machine (Cadmach, Ahmedabad, India).

Evaluation of FDTs

The prepared formulations were evaluated for pre-compression parameters like angle of repose (The funnel method described by Carstesen and Chan [22]), Hausner's ratio and compressibility index by carr method [23].

The post-compression parameters such as weight variation, hardness, friability, *in vitro* disintegration time, wetting time, *in vitro* dissolution test, drug content, stability studies, FTIR, DSC studies also have been studied. All the results were taken in triplicates (±3SD).

The weight of the FDT being made was measured to ensure that a FDT contains the proper amount of drug. The USP weight variation test [24] was run by weighing 20 FDTs individually using electronic digital balance, calculating the average weight and comparing the individual FDT weights to the average. The FDTs meet the USP test if no more than 2 FDTs are outside the percentage limit and if no FDT differs by more than 2 times the percentage limit. The weight variation tolerances for FDTs differ depending on average FDT weight.

The Monsanto hardness tester (Teknik, India) was used for the determination of the hardness of FDT. FDT was placed in contact between the plungers, and the handle was pressed, the force needed to fracture the FDT was recorded.

The friability of FDTs was determined using Roche friabilator (Cambel Electronics, Mumbai, India). It included the determination of loss in weight of FDTs by placing pre-weighed FDTs in the apparatus and it was allowed to run for 100 revolutions with the speed of 25 rpm and weighed once again. The difference in the two weights represents friability. The weight loss should not be more than one percent. Six FDTs were tested from each formulation.

In the disintegration time study [24], FDT was placed into 900 ml distilled water at 37 ± 2°C in the disintegration test apparatus. The disintegration time was defined as the time required for the FDT to completely disintegrate until no solid residue remains or only a trace amount of soft residue remains on the screen. A stopwatch was used to measure the disintegration time to the nearest second. Only one FDT was analyzed at a time in order to ensure maximum accuracy.

In wetting time study [25], the FDT was placed in a petridish of 5.5 cm in diameter, containing 10 ml of water at room temperature, and the time for complete wetting was recorded. To check for reproducibility, the measurements were carried out six times and the mean value calculated.

For the determination of drug content total 10 FDTs were weighed and powdered, powder equivalent to 100 mg of CBZ was weighed and dissolved in 1% SLS solution (in water) and filtered the solution through the whatman filter paper. The filtrate was collected and diluted with sufficient amount with 1%w/v SLS solution till the concentration of the drug lies within the standard plot range. The diluted solution was analyzed for the CBZ content by UV spectrophotometer (UV-1700 Shimadzu Corporation, Japan) at 284.4 nm using 1%w/v SLS solution as a blank.

In vitro dissolution study (2) was carried out in the USP paddle method (Electrolab TDT - 08 L Dissolution tester USP). 900 ml of the dissolution medium (1%w/v SLS solution in water) was taken in covered vessel and the temperature was maintained at 37 ± 0.5°C. The speed of the paddle was set at 100±2 rpm. Sampling was done every one min interval. For each aliquots of 5 ml from the dissolution medium was withdrawn and the same amount of dissolution medium at 37°C was replenished to the dissolution medium. The samples were diluted with 1%w/v SLS solution and analyzed in the UV spectrophotometer at 284.4 nm.

The stability study [26] of the FDTs was carried out according to International conference on Harmonization (ICH) guidelines for zone III and IV. The formulations were stored at 40 ± 2°C / 75 ± 5 % relative humidity (RH) for 3 months by storing the samples under closed vial conditions in stability chamber (Lab-Care, Mumbai). After each month FDTs were analyzed for hardness, drug content and in vitro disintegration time.

An optimized formulation (on the basis of all the above evaluation parameters) was observed for FTIR and DSC studies.

Table 3: Results of Post Compression Parameters.

Formulation	Hardness Kg/cm^2 (±S.D),n=3	Friability (%) (±SD),n=6	Drug content (mg %) (±SD), n=10	*In vitro* Disintegration Time (sec) (±S.D), n=6	Wetting Time (sec) (±S.D), n=3	Weight variation (mg) (±SD), n=20
F1	3.2 ± 0.13	0.66 ± 0.8	99.86 ± 0.4	21.18 ± 1.2	32.14 ± 1.6	201.58 ± 1.7
F2	3.2 ± 0.12	0.58 ± 1.2	99.28 ± 0.2	28.21 ± 0.9	62.07 ± 1.4	200.64 ± 1.1
F3	3.2 ± 0.12	0.64 ± 0.4	99.49 ± 0.9	42.39 ± 0.5	74.04 ± 1.1	200.45 ± 0.8
F4	3.3 ± 0.13	0.57 ± 0.5	99.51 ± 0.7	53.20 ± 2.2	88.11 ± 1.8	199.68 ± 0.4
F5	3.3 ± 0.14	0.61 ± 0.2	99.22 ± 10	14.22 ± 0.8	51.16 ± 1.4	200.48 ± 1.5
F6	3.5 ± 0.11	0.65 ± 1.4	99.92 ± 0.8	13.21 ± 0.6	48.21 ± 1.2	201.64 ± 1.9
F7	3.2 ± 0.14	0.62 ± 0.9	99.52 ± 0.4	12.80 ± 0.9	41.23 ± 1.6	200.55 ± 2.1
F8	3.1 ± 0.15	0.59 ± 0.6	99.34 ± 1.1	12.50 ± 0.8	38.31 ± 1.2	201.48 ± 1.1
F9	3.4 ± 0.14	0.55 ± 1.1	99.64 ± 0.9	14.18 ± 0.9	22.11 ± 1.1	202.51 ± 1.8
F10	3.2 ± 0.11	0.61 ± 1.6	99.41 ± 0.6	10.30 ± 0.7	18.10 ± 1.8	200.66 ± 1.2
F11	3.2 ± 0.14	0.63 ± 0.4	99.28 ± 0.4	9.32 ± 0.5	14.10 ± 1.3	201.45 ± 1.8
F12	3.1 ± 0.11	0.59 ± 0.3	99.44 ± 1.1	9.13 ± 0.6	12.18 ± 1.4	200.68 ± 0.9

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

IR spectra for CBZ and powdered FDTs were recorded in a Fourier transform infrared spectrophotometer (FTIR 1615, Perkin Elmer, USA) with KBr pellets. DSC scans of about 10 mg, using an automatic thermal analyzer system performed for accurately weighed CBZ alone and FDTs (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°C/min from 50-300°C [2].

Result and Discussion

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

The data obtained from post-compression parameters such as weight variation, hardness, friability, wetting time, drugcontent and *in vitro* disintegration time for FDTs were shown in table 3**.**

In all the formulations, hardness test indicated good mechanical strength, as the hardness of the FDTs was found in the range of 3.14 to 3.5 kg/cm^2. Friability was observed less than 1%, indicated that FDTs had a good mechanical resistance. Drug content was found to be high (≥99.22%) and uniform in all the FDTs. The FDTs were subjected for evaluation of *in vitro* disintegration time. The *in vitro* disintegration time for all the formulations varies from 09.13 ± 0.6 to 53.20 ± 2.2 seconds. It was observed that when mucilage of *plantego ovata* used as superdisintegrant (F9 to F12), the FDTs disintegrates rapidly within short time. Due to easy swelling ability of mucilage of *plantego ovata* containing FDTs disintegrates rapidly as compared to other FDTs prepared using croscarmellose sodium and sodium starch glycolate. It was observed that the *in vitro* disintegration time of the FDTs decreased with increase in the level of croscarmellose sodium and mucilage of *plantego ovata*. However, *in vitro* disintegration time increased with increase in the level of sodium starch glycolate in the FDTs. It indicates that increase in the level of sodium starch glycolate had a negative effect on the *in vitro* disintegration of the FDTs. At higher levels, formation of a viscous gel layer by sodium starch glycolate [27] might have formed a thick barrier to the further penetration of the disintegration medium and hindered the disintegration or leakage of tablet contents. Thus, FDT disintegration was retarded to some extent with tablets containing sodium starch glycolate. Results were showed in table-3. Since the in vitro dissolution process of a FDT depends upon the wetting time followed by *in vitro* disintegration of the tablet. The measurement of wetting time may be used as another confirmative test for the evaluation of FDTs. In wetting time study, the wetting time was rapid in FDTs of MPO followed by croscarmellose sodium and sodium starch glycolate. It was observed that as concentration of croscarmellose sodium and mucilage of *plantego ovata* increased in the formulations, the time taken for wetting was reduced. However as in case of FDTs of sodium starch glycolate, as concentration was increased the time taken for wetting was also increased. Results were showed in table 3.

Table 4: Results of stability study.

Formulation	*In vitro* Disintegration Time (sec) (±S.D), n=6	Hardness Kg/cm^2 (±S.D), n=3	Drug content (mg %) (±SD), n=5
F1	21.14 ± 1.3	3.2 ± 0.5	99.41 ± 0.2
F2	28.25 ± 1.0	3.2 ± 0.9	99.18 ± 0.6
F3	42.29 ± 1.5	3.1 ± 0.22	99.24 ± 1.1
F4	53.31 ± 2.1	3.2 ± 0.11	99.21 ± 0.8
F5	15.23 ± 0.6	3.2 ± 0.24	99.16 ± 1.2
F6	13.11 ± 1.6	3.4 ± 0.16	99.81 ± 0.5
F7	12.91 ± 1.8	3.1 ± 0.11	99.41 ± 0.8
F8	12.70 ± 0.9	3.1 ± 0.8	99.28 ± 1.3
F9	14.20 ± 0.4	3.3 ± 0.11	99.44 ± 1.1
F10	10.32 ± 0.3	3.1 ± 0.13	99.26 ± 0.9
F11	9.33 ± 0.2	3.2 ± 0.4	99.29 ± 0.6
F12	9.18 ± 1.5	3.1 ± 0.10	99.11 ± 1.2

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

The influence of superdisintegrants on the *in vitro* dissolution of CBZ from the FDTs is shown in [Figure 1], [Figure 2], [Figure 3]. The $t_{50\%}$ and $t_{90\%}$ (time for 50% and 90% of release) values decreased with increase in the level of croscarmellose sodium and mucilage of *plantego ovata* in FDTs. However, $t_{50\%}$ and $t_{90\%}$ values increased with increase in the level of sodium starch glycolate in FDTs. Among all formulation F12 prepared with mucilage of *plantego ovata* showed 99.47% drug release in 3 min.

The stability study for FDTs was carried out according to ICH guidelines at 40 ± 2^{o}C (75 ± 5% RH for 3 months) by storing the sample in stability chamber (Lab-care, Mumbai). No appreciable change in physical characteristics hardness, *in vitro* disintegration time and drug content was observed even after the evaluation for 3 months. Stability study results are given in table 4.

IR spectra of CBZ and formulation F12 are shown in figure 4. 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 F12 showed characteristic absorption band at 3465 (NH Stretching of NH_2), 3080 (Aromatic CH stretching), 1681 (C=O stretching of CO NH_2), 1605, 1489 (C = C ring stretching). The IR spectra of pure CBZ and F12 revealed that there was no appreciable change in the position of absorption band. This revealed that there was no chemical interaction between CBZ and the excipients.

Thermograms of pure drug CBZ and the F12 (figure 5) revealed that CBZ has a sharp endotherm at 193.91^{o}C. However the drug and its formulation showed characteristic changes in the appearance of the thermogram. It is observed that in F12 the nature of thermogram is totally changed and the sharp peaks are shifted to lower range around 167.61^{o}C and the peaks of pure drug have change to broad peaks with reduction of the height of each peak. These changes indicate 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.

Conclusion

From the present study it can be concluded that natural super disintegrant like mucilage of *Plantego ovata* showed batter disintegration property and better in vitro dissolution profile than the most widely used synthetic super disintegrant like Croscarmellose sodium and Sodium starch glycolate in the formulations of FDTs.

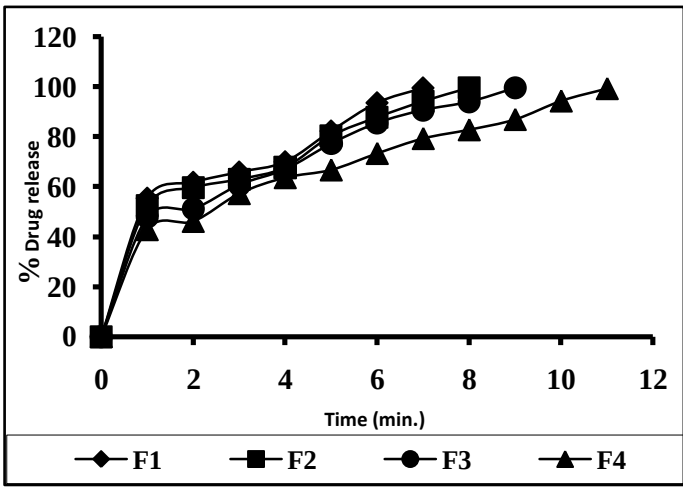

Figure 1: *In vitro* Dissolution profiles of different sodium starch glycolate formulations F1 to F4.

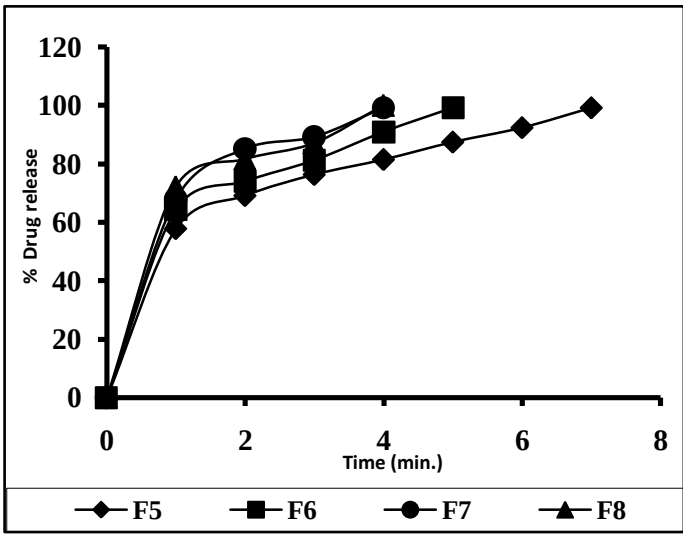

Figure 2: *In vitro* Dissolution profiles of different croscarmellose sodium formulations F5 to F8.

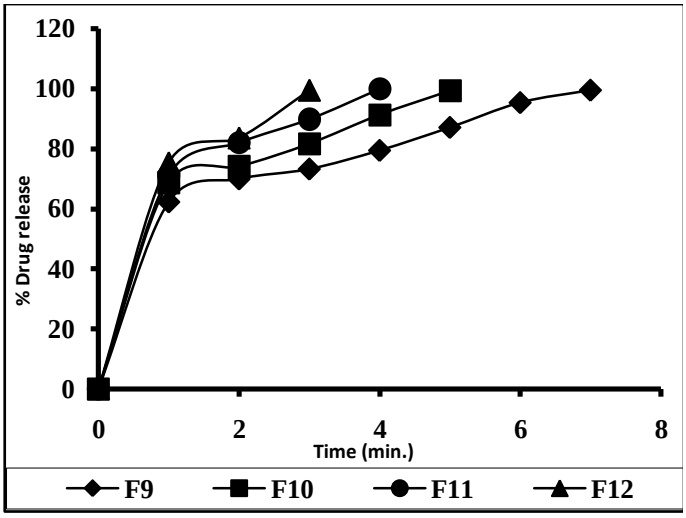

Figure 3: *In vitro* Dissolution profiles of different mucilage of *plantego ovata* formulations F9 to F12.

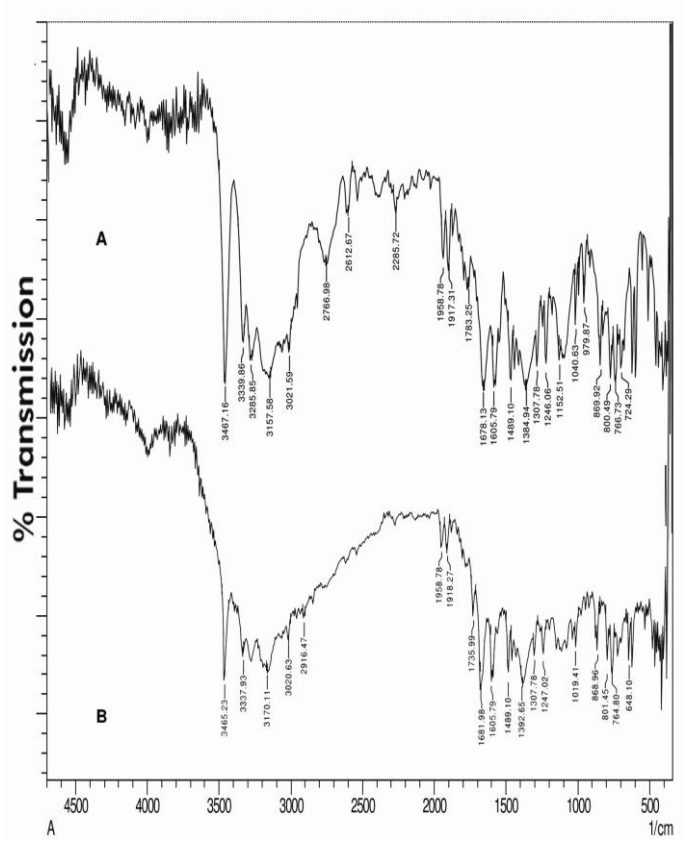

Figure 4: A) IR spectrum of CBZ, **B)** IR spectrum of Formulation F12.

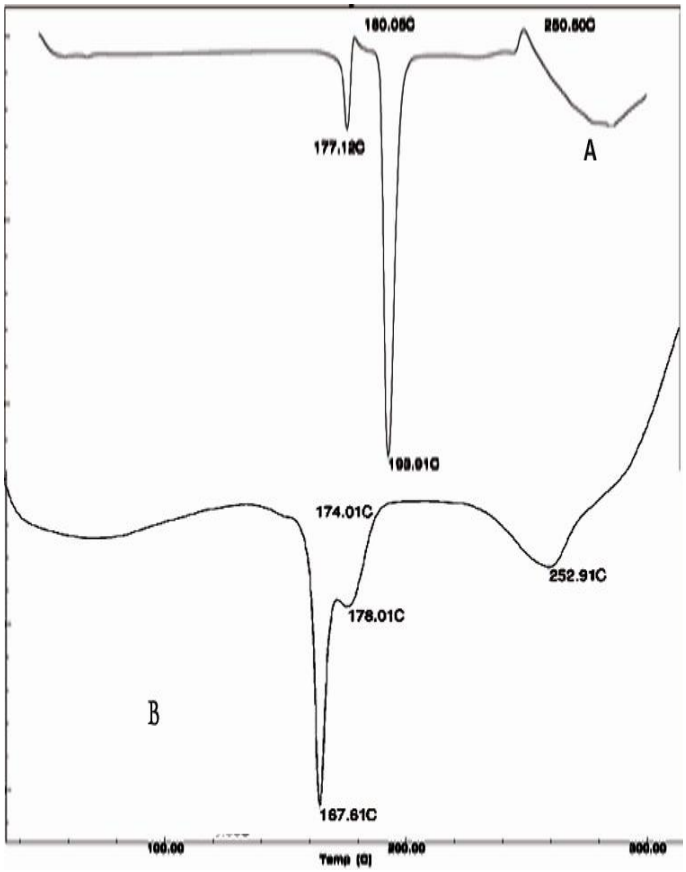

Figure 5: A) DSC Thermograms of CBZ**, B)** Formulation F12.

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