



Research Article

FORMULATION AND EVALUATION OF FAST DISSOLVING TABLETS OF CARBAMAZEPINE USING NATURAL SUPERDISINTEGRANT *PLANTAGO OVATA* SEED POWDER AND MUCILAGE

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ABSTRACT

An attempt has been made for the development of fast dissolving tablets of the carbamazepine by wet granulation method, using different concentrations of natural superdisintegrating agent like plantago ovata seed powder and mucilage. The major problem of this drug is very low solubility in biological fluids and poor bioavailability after oral administration. Prepared formulations were evaluated for precompressional parameters such as angle of repose, % compressibility and Hausner's ratio. Tablets were subjected to post compressional analysis for the parameters such as hardness, friability, *in vitro* disintegration time, wetting time and dissolution test. Drug compatibility with excipients was checked by FTIR studies. Stability studies were carried out as per ICH guidelines for three months. The formulations prepared with mucilage of plantago ovata were showed disintegration time between the ranges of 84.58 to 24.74 sec and drug release showed between the ranges of 14 – 16 min. However the formulations prepared with seed powder did not disintegrate in specified limit of time for fast dissolving tablet. Among all formulations SM5 showed 99.71 % drug release within 16 min. The prepared tablets were characterized by FTIR Studies. No chemical interaction between drug and excipient 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 fast dissolving tablets of poorly soluble drug, carbamazepine showing enhanced dissolution, will lead to improved bioavailability, improved effectiveness and hence better patient compliance by using natural superdisintegrant like *plantago ovata* mucilage.

**Key words:** Fast dissolving tablets, Carbamazepine, Plantago ovata, Mucilage.

INTRODUCTION

Carbamazepine, a dibenzazine 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 hrs that results into poor bioavailability after oral administration<sup>1,2</sup>. It shows erratic dissolution profile in gastric and intestinal fluid due to its poor water solubility. The peak plasma concentration (C<sub>max</sub>) and the time taken to reach C<sub>max</sub> (t<sub>max</sub>) 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)<sup>3</sup>. 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<sup>4</sup> and fast-disintegrating tablets<sup>5</sup> have been developed. Most commonly used methods to prepare these tablets are; freeze-drying/Lyophilization<sup>6</sup>, tablet molding<sup>7</sup> and direct-compression methods<sup>8</sup>. Lyophilized tablets show a very porous structure, which causes quick penetration of saliva into the pores when placed in oral cavity<sup>6,9</sup>.

Fast dissolving drug delivery is rapidly gaining acceptance as an important new drug delivery technology<sup>10</sup>. These dosage forms dissolve or disintegrate within few minutes. Usually, superdisintegrant are added to a drug formulation to facilitate the break up or disintegration of tablet content into smaller particles that can dissolve more rapidly than in the absence of disintegrants<sup>11,12</sup>. Many substances like microcrystalline cellulose<sup>13</sup>, croscovidone<sup>14</sup>, croscarmellose sodium<sup>15</sup>, sodium starch glycolate<sup>16</sup>, have been used in the

formulation of fast dissolving tablets (FDT's). Similarly, various natural substances like gum karaya, modified starch and agar have been used in the formulation of FDT's. Mucilage of natural origin is preferred over semi-synthetic and synthetic substances because they are comparatively cheaper, abundantly available, non-irritating and non-toxic in nature. Mucilage of *plantago ovata* has various characteristics like binding, disintegrating and sustaining properties<sup>17</sup>. Hence in the present work *plantago ovata* was used to develop FDT's. In the present research work fast dissolving tablets of carbamazepine were prepared by wet granulation technique using different concentrations natural superdisintegrant like *plantago ovata* seed powder and mucilage. A total ten formulations were prepared, compositions of which are given in Table 1.

MATERIALS AND METHODS

Materials

Carbamazepine was procured as a gift sample from Cadila Health Care, Ahmedabad. Seeds of *Plantago ovata* were purchased from the local market of Gulbarga, Karnataka, and sodium lauryl sulphate (SLS), dicalcium phosphate, poly vinyl pyrrolidone (PVP), aspartame, talc, and magnesium stearate purchased from S.D. Fine Chem., Mumbai. All other materials were of analytical reagent grade.

Method

**Preparation of seed powder of *Plantago ovata*:** The dried *Plantago ovata* seeds were comminuted and sieved through mesh no. 80 and stored in desiccator.

**Isolation of *Plantago ovata* Mucilage:** The seeds of *Plantago ovata* were soaked in distilled water for 48 hrs and then boiled for few minutes so that mucilage was completely released into water<sup>18</sup>. 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 filtrate so as to precipitate the mucilage. The separated mucilage was dried (in oven at temperature less than 60° C), powdered, sieved (80#) and stored in a desiccator until use.

### Formulation of carbamazepine fast dissolving tablets

Carbamazepine fast dissolving tablets were prepared by non-aqueous wet granulation method using absolute alcohol as the solvent, *Plantago ovata* seed powder and mucilage were used as a superdisintegrants, dicalcium phosphate as a diluent, PVP as binder, aspartame as sweetener, purified talc as lubricant and magnesium stearate as glidant. The drug and other ingredients with the half the quantity of superdisintegrants (intra granular disintegrants) were mixed together,

sufficient quantity of alcohol was added and mixed to form a coherent mass. The wet mass was granulated using sieve no 12 and granules formed were dried dryer at 40°C for 30 min and regranulated through sieve no 18. The granules were further blended with the remaining quantity of superdisintegrants (extra granular disintegrants), purified talc, and magnesium stearate and compressed into tablet using a 8 mm concave punches in rotary tablet machine<sup>19</sup>(Rimek mini press 1' a 10 station rotary compression machine Cadmach, Ahmedabad, India).

**Table 1: Composition of Carbamazepine fast dissolving tablets**

| Ingredients (mg)        | SP1 | SP2 | SP3 | SP4 | SP5 | SM1 | SM2 | SM3 | SM4 | SM5 |
|-------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Carbamazepine           | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 |
| Seed powder             | 5   | 10  | 15  | 20  | 25  | --  | --  | --  | --  | --  |
| plantago ovata mucilage | --  | --  | --  | --  | --  | 5   | 10  | 15  | 20  | 25  |
| Dicalcium phosphate     | 60  | 55  | 50  | 45  | 40  | 60  | 55  | 50  | 45  | 40  |
| PVP                     | 25  | 25  | 25  | 25  | 25  | 25  | 25  | 25  | 25  | 25  |
| Aspartame               | 6   | 6   | 6   | 6   | 6   | 6   | 6   | 6   | 6   | 6   |
| Talc                    | 2   | 2   | 2   | 2   | 2   | 2   | 2   | 2   | 2   | 2   |
| Magnesium Stearate      | 2   | 2   | 2   | 2   | 2   | 2   | 2   | 2   | 2   | 2   |

### 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 twenty 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<sup>20</sup> study tablets 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 digital tablet disintegration test apparatus and in wetting time<sup>21</sup> 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% SLS solution and filtered the solution through the whatman filter paper. The filtrate was collected and diluted to a sufficient amount with 1% SLS 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% SLS 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°C / 75 ± 5 %RH for 3 months by storing the samples in stability chamber (Lab-Care, Mumbai). *In vitro* release studies<sup>22</sup> 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% SLS solution) was taken in covered vessel and the temperature was maintained at 37 ± 0.5°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°C was replenished to the dissolution medium. The sample withdrawn and diluted with 1% SLS solution and analyzed in the UV spectrophotometer (UV-1700 Shimadzu corporation, Japan) at 287 nm. All the studies 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.

### RESULT AND DISCUSSION

The values of pre-compression parameters evaluated were within prescribed limits and indicated good free flowing property. The results are shown in **Table2**.

The data obtained from post-compression parameters such as weight variation, hardness, friability, wetting time, drug content and *in vitro* disintegration time. In all the formulations, hardness test indicated good mechanical strength, hardness of the tablets was in the range of 4.4 to 3.0 kg/cm<sup>2</sup>. 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 results of weight variation, hardness, friability, wetting time, and drug content were shown in Table 3.

**Table 2: Precompressional parameters:**

| Formulation | Angle of Repose (θ) (±SD), n=3 | Compressibility (%) (±SD), n=3 | Hausner's Ratio (±SD), n=3 |
|-------------|--------------------------------|--------------------------------|----------------------------|
| SP1         | 26.5 ± 0.44                    | 22.82 ± 0.41                   | 1.22 ± 0.005               |
| SP2         | 27.0 ± 0.41                    | 23.27 ± 0.64                   | 1.31 ± 0.01                |
| SP3         | 31.5 ± 0.21                    | 22.60 ± 1.81                   | 1.24 ± 0.02                |
| SP4         | 32.6 ± 0.14                    | 24.70 ± 1.12                   | 1.32 ± 0.02                |
| SP5         | 29.4 ± 0.12                    | 23.26 ± 0.61                   | 1.31 ± 0.01                |
| SM1         | 24.4 ± 0.42                    | 25.16 ± 1.12                   | 1.32 ± 0.01                |
| SM2         | 27.6 ± 0.06                    | 22.28 ± 0.62                   | 1.24 ± 0.01                |
| SM3         | 26.4 ± 0.82                    | 25.00 ± 0.42                   | 1.32 ± 0.005               |
| SM4         | 27.4 ± 0.46                    | 25.27 ± 0.52                   | 1.30 ± 0.01                |
| SM5         | 26.6 ± 0.64                    | 22.84 ± 0.42                   | 1.24 ± 0.005               |

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

The tablets were subjected for evaluation of *in vitro* disintegration time. The formulations prepared with mucilage of plantago ovata were showed disintegration time between the ranges of 84.58 to

24.74 sec. The *in vitro* disintegration time of the tablet was found to be decreased with increased concentration of both the seed powder and mucilage powder. However the isolated mucilage powder was

found to have better disintegrating property when compared to seed powder. 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 isolated mucilage of *plantago ovata*. The least average wetting time and disintegration time of formulation SM 5 proved the superior disintegrating property of the isolated mucilage. The results of wetting time and disintegration time were shown in Table 3.

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 isolated mucilage of *plantago ovata*. Among all formulations SM5 showed 99.71 % drug release within 16 min.

The stability study for tablets was carried out according to ICH guidelines at  $40 \pm 2^\circ\text{C}$  ( $75 \pm 5\%$  RH for 3 months) by storing the

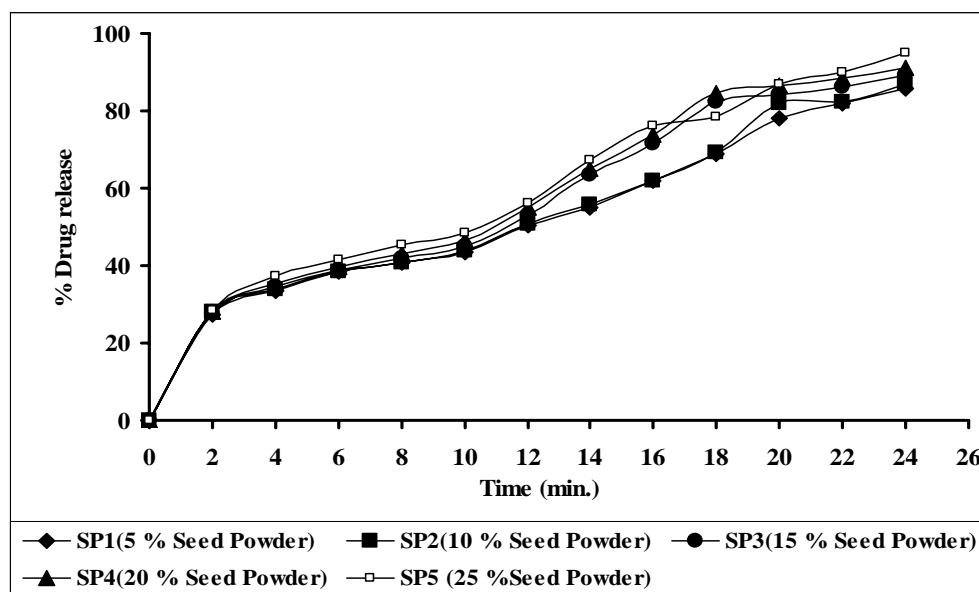
sample in stability chamber (lab-care, Mumbai). No appreciable change in physical characteristics hardness, disintegration time and drug content was observed even after the evaluation for 3 months. Stability study results are given in Table 4.

IR spectra of carbamazepine and formulation SM5 are shown in (Fig 3, 4). Pure drug showed characteristic absorption bands at 3467 (NH Stretching of  $\text{NH}_2$ ), 3080 (Aromatic CH stretching), 1678 (C=O stretching of CO  $\text{NH}_2$ ), 1605, 1489 (C = C ring stretching) and the formulation SM4 showed characteristic absorption band at 3465 (NH Stretching of  $\text{NH}_2$ ), 3080 (Aromatic CH stretching), 1676 (C=O stretching of CO  $\text{NH}_2$ ), 1605, 1488 (C = C ring stretching). The IR spectra of pure carbamazepine and formulation revealed that there is no appreciable changes in the position of absorption band. This revealed that there was no chemical interaction between drug and the polymer.

**Table 3: results of post compression parameters**

| Formulation | Hardness Kg/cm <sup>2</sup> ( $\pm$ S.D), n=3 | Friability (%) ( $\pm$ SD),n=6 | Drug content (mg %) ( $\pm$ SD), n=10 | Disintegration Time (sec) ( $\pm$ S.D), n=6 | Wetting Time (sec) ( $\pm$ S.D), n=3 | Weight variation (mg) ( $\pm$ SD), n=20 |
|-------------|---|--------------------------------|---------------------------------------|---|--------------------------------------|---|
| SP1         | 4.4 $\pm$ 0.11                                | 0.62 $\pm$ 0.20                | 99.33 $\pm$ 1.4                       | 240.33 $\pm$ 1.5                            | 200.57 $\pm$ 1.3                     | 300.42 $\pm$ 1.3                        |
| SP2         | 4.3 $\pm$ 0.18                                | 0.64 $\pm$ 0.09                | 99.79 $\pm$ 1.2                       | 222.21 $\pm$ 1.6                            | 197.61 $\pm$ 1.6                     | 300.24 $\pm$ 1.1                        |
| SP3         | 4.2 $\pm$ 0.14                                | 0.65 $\pm$ 0.15                | 99.44 $\pm$ 0.3                       | 180.24 $\pm$ 1.1                            | 185.27 $\pm$ 1.2                     | 301.33 $\pm$ 1.3                        |
| SP4         | 4.3 $\pm$ 0.22                                | 0.55 $\pm$ 0.16                | 99.63 $\pm$ 0.4                       | 166.44 $\pm$ 0.9                            | 172.45 $\pm$ 1.6                     | 301.28 $\pm$ 1.2                        |
| SP5         | 4.2 $\pm$ 0.12                                | 0.58 $\pm$ 0.26                | 99.96 $\pm$ 0.4                       | 142.21 $\pm$ 0.6                            | 147.35 $\pm$ 1.2                     | 300.12 $\pm$ 1.4                        |
| SM1         | 3.4 $\pm$ 0.16                                | 0.58 $\pm$ 0.22                | 99.24 $\pm$ 0.6                       | 84.58 $\pm$ 1.2                             | 95.38 $\pm$ 0.4                      | 300.58 $\pm$ 1.8                        |
| SM2         | 3.3 $\pm$ 0.15                                | 0.48 $\pm$ 0.26                | 99.72 $\pm$ 0.4                       | 68.65 $\pm$ 0.9                             | 77.41 $\pm$ 1.4                      | 301.54 $\pm$ 1.4                        |
| SM3         | 3.2 $\pm$ 0.19                                | 0.42 $\pm$ 0.14                | 99.61 $\pm$ 1.2                       | 54.42 $\pm$ 1.2                             | 56.22 $\pm$ 1.2                      | 300.25 $\pm$ 1.2                        |
| SM4         | 3.1 $\pm$ 0.28                                | 0.38 $\pm$ 0.14                | 99.91 $\pm$ 0.6                       | 35.66 $\pm$ 0.6                             | 43.66 $\pm$ 1.2                      | 300.22 $\pm$ 1.4                        |
| SM5         | 3.0 $\pm$ 0.14                                | 0.36 $\pm$ 0.12                | 99.96 $\pm$ 0.8                       | 24.74 $\pm$ 0.6                             | 29.86 $\pm$ 1.4                      | 301.48 $\pm$ 1.8                        |

**Note:** values in parenthesis are standard deviation ( $\pm$ SD)



**Fig 1: dissolution profiles of formulations prepared with seed powder.**

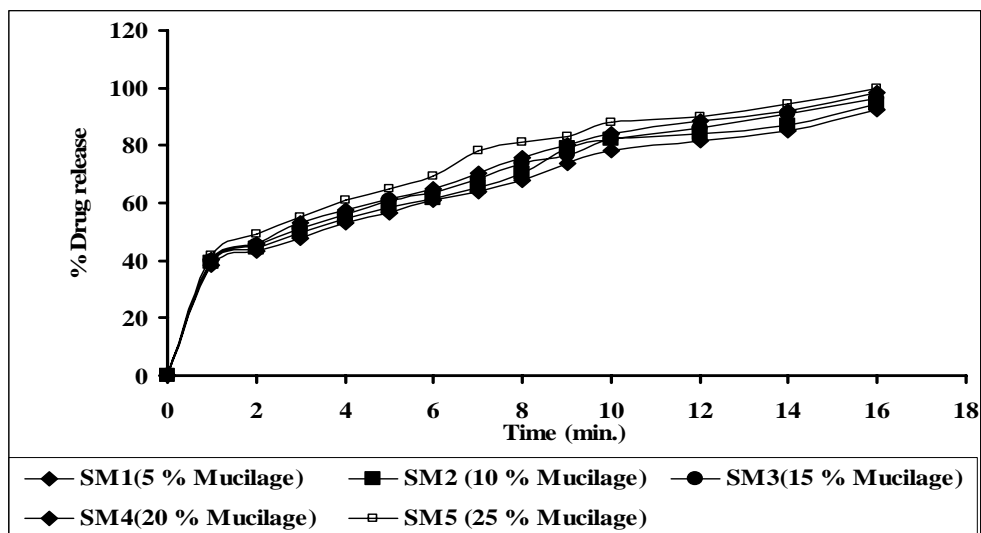


Fig 2: Dissolution profiles of formulations prepared with mucilage

Table 4: Results of stability study

| Formulation | Disintegration Time (Sec) ( $\pm$ S.D), n=6 | Hardness Kg/cm <sup>2</sup> ( $\pm$ S.D), n=3 | Drug content (Mg %) ( $\pm$ S.D), n=5 |
|-------------|---|---|---------------------------------------|
| SP1         | 241.34 $\pm$ 1.2                            | 4.4 $\pm$ 0.14                                | 99.45 $\pm$ 1.2                       |
| SP2         | 221.14 $\pm$ 1.4                            | 4.3 $\pm$ 0.12                                | 99.66 $\pm$ 1.1                       |
| SP3         | 181.22 $\pm$ 1.2                            | 4.2 $\pm$ 0.12                                | 99.54 $\pm$ 0.6                       |
| SP4         | 165.24 $\pm$ 0.8                            | 4.3 $\pm$ 0.14                                | 99.77 $\pm$ 0.6                       |
| SP5         | 141.22 $\pm$ 0.4                            | 4.2 $\pm$ 0.16                                | 99.66 $\pm$ 0.2                       |
| SM1         | 83.54 $\pm$ 1.4                             | 3.4 $\pm$ 0.12                                | 99.74 $\pm$ 0.6                       |
| SM2         | 67.75 $\pm$ 0.8                             | 3.3 $\pm$ 0.12                                | 99.78 $\pm$ 0.4                       |
| SM3         | 55.44 $\pm$ 1.1                             | 3.2 $\pm$ 0.16                                | 99.68 $\pm$ 0.8                       |
| SM4         | 35.22 $\pm$ 0.4                             | 3.1 $\pm$ 0.14                                | 99.97 $\pm$ 0.4                       |
| SM5         | 23.76 $\pm$ 0.2                             | 3.0 $\pm$ 0.12                                | 99.98 $\pm$ 0.68                      |

Note: values in parenthesis are standard deviation ( $\pm$ SD)

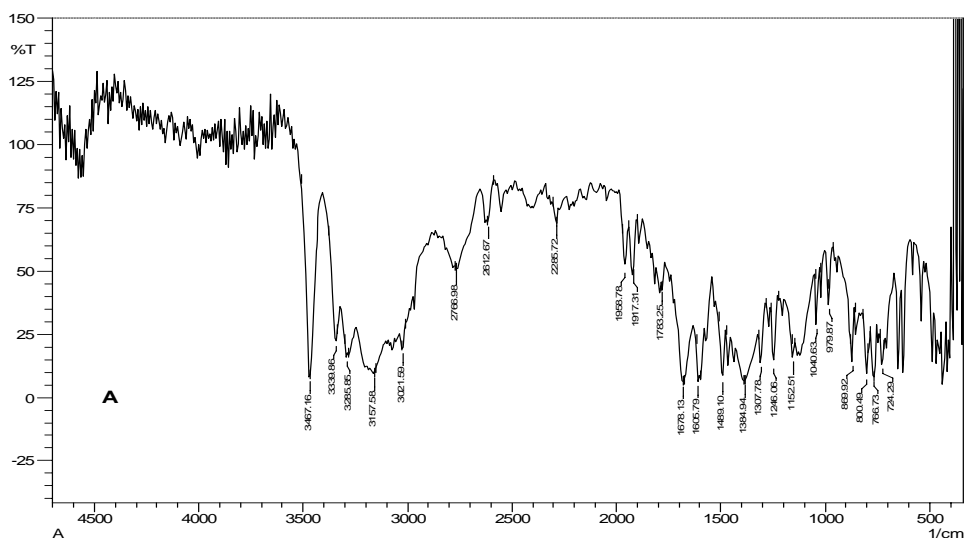


Fig 3: FTIR spectrum of Carbamazepine

## 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 will lead to improve bioavailability by using wet granulation technique using different

concentrations of both seed powder and mucilage of plantago ovata as superdisintegrants. Over all results indicates that formulation SM5 that contain 25 % natural superdisintegrant like mucilage *plantago ovata* exhibited faster drug dissolution will lead to improve bioavailability, effective therapy, improve patient compliance, and satisfies all the criteria as fast dissolving tablet.

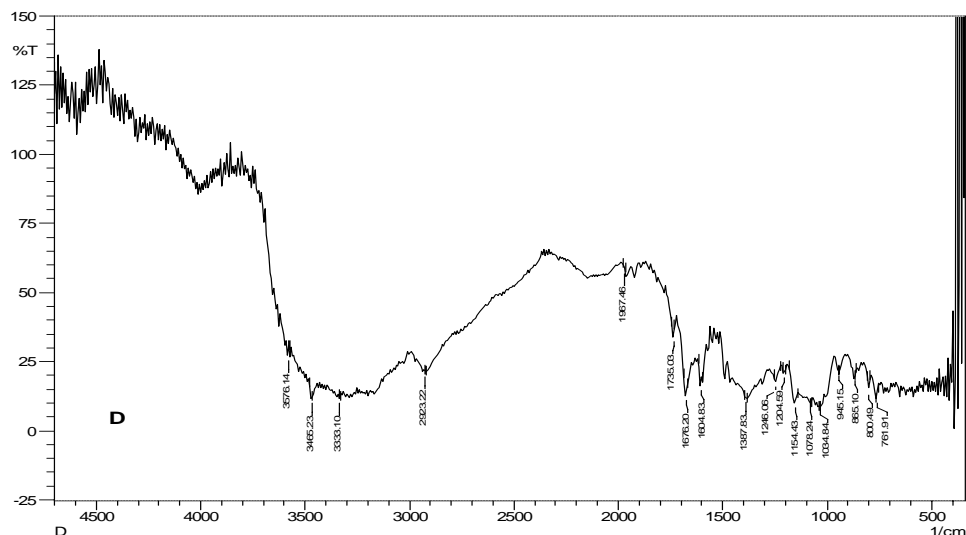


Fig 4: FTIR spectrum of formulation SM5.

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