

Formulation and Evaluation of Fast Dissolving Tablets of Metoprolol Tartrate Using Natural Superdisintegrant

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ABSTRACT

Metoprolol tartrate is effective β -blocker which is having antianginal properties and used in the treatment of myocardial infarction. Oral bioavailability of metoprolol tartrate is around 40 %. In present work an attempt has been made to prepare Fast dissolving tablets of metoprolol tartrate by direct compression method using different concentrations of *plantago ovata* mucilage as a natural superdisintegrant. Drug compatibility with excipients was checked by FTIR and DSC studies. The values of pre-compression and post-compression parameters evaluated were within prescribed limits and indicated good free flowing property. In all the formulations, friability is less than 1 %, indicated that tablets had a good mechanical resistance. Drug content was found to be in the range of 99 to 101 %, which is within acceptable limits. Hardness of the tablets was found to be in the range of 2.40-2.90 kg/cm², thickness was found to be in the range 4.30-4.85 mm. The formulations F4 and F5 shows less *in vitro* dispersion time 29, 16 sec respectively with rapid *in vitro* dissolution within 12 mins. *In vitro* dispersion time decreases with increase in concentration of natural superdisintegrant. No chemical interaction between drug and excipients was confirmed by DSC and FTIR studies. The stability study conducted as per the ICH guidelines for three months and the formulations were found to be stable. The results concluded that mouth dissolving tablets of metoprolol tartrate showing enhanced release rate may lead to improved bioavailability and effective therapy by using *plantago ovata* mucilage as natural superdisintegrant.

Keywords: Fast dispersible tablet, metoprolol tartrate, *plantago ovata* mucilage.

INTRODUCTION

Metoprolol tartrate (MT) is a selective beta1-adrenoreceptor blocking agent. Metoprolol tartrate is (\pm)-1-(isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol (2:1) dextro-tartrate salt used in Essential hypertension, prevention after a myocardial infarction, tachycardia, coronary heart disease (prevention of angina attacks), treatment of heart failure.^[1]

The most popular solid dosage forms are being tablets and capsules, one important drawback of these dosage form for some patients, is the difficulty to swallow. Drinking water plays an important role in swallowing of oral dosage forms. For these reasons tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Orodispersible tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people. Orodispersible tablets are those when put on tongue, disintegrates instantaneously releasing the drug, which dissolves or disperse in saliva.^[2-3]

Various natural substances gum karaya, modified starch and agar have been used in the formulations of mouth dissolving tablets. 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. In the present investigation, the preparation and evaluation of fast dissolving tablets by using different concentrations of natural superdisintegrant that is *plantago ovata* husk was studied. The reasons for selection of *plantago ovata* husk because it's high swelling index.^[4] Mucilage of *plantago ovata* has various characteristics like binding, disintegrating and sustaining properties (baveja 1968).^[5] Hence, in present study, mucilage of *plantago ovata* was used to develop fast dissolving tablets of metoprolol tartrate. The concept of formulating fast dissolving tablets (FDT) of MT (anti-anginal)^[1] using different concentrations of natural superdisintegrant which increase the water uptake with shortest wetting time and there by decrease the disintegration time of the tablets by simple and cost effective direct compression technique. The objective of present work was to develop fast dissolving Metoprolol Tartrate tablet by direct compression method and to study the effect of functionality differences of natural superdisintegrant *plantago ovata* mucilage on the tablet

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properties. A total six formulations were prepared, compositions of which are given in Table 1.

Table 1: The composition of fast dissolving tablets of MT

| Ingredient (mg) | Formulation code | | | | | |
|-----------------------------|------------------|-----|-----|-----|-----|-----|
| | F0 | F1 | F2 | F3 | F4 | F5 |
| Metoprolol Tartrate | 25 | 25 | 25 | 25 | 25 | 25 |
| Plantago ovata mucilage | - | 15 | 30 | 45 | 60 | 90 |
| Aspartame | 15 | 15 | 15 | 15 | 15 | 15 |
| Mg stearate | 2 | 2 | 2 | 2 | 2 | 2 |
| Talc | 5 | 5 | 5 | 5 | 5 | 5 |
| MCC (Avicel PH-102) | 50 | 50 | 50 | 50 | 50 | 50 |
| Mannitol (Pearlitol SD 200) | 103 | 88 | 73 | 58 | 43 | 13 |
| Total | 200 | 200 | 200 | 200 | 200 | 200 |

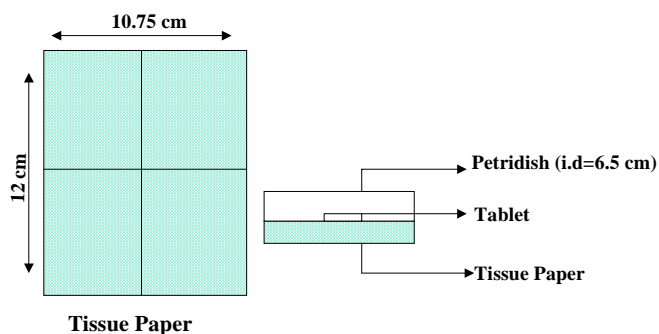


Fig. 1: Simple method for the measurement of wetting time of a tablet

MATERIALS AND METHODS

MT was obtained as a gift sample from Emcure Pharma Ltd, Pune. *Plantago ovata* seeds were purchased from local market Gulbarga. Microcrystalline cellulose (directly compressible), Aspartame and Mannitol (directly compressible) were obtained as a gift sample from Cipla Pharma Ltd, Vikroli, Mumbai. Other reagents were of analytical grade.

Isolation of Mucilage

The seeds of *plantago ovata* were soaked in distilled water for 48 h and then boiled for few minutes so that mucilage was completely released into water.^[6] The material collected was squeezed through muslin cloth for the 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 fast dissolving tablets of MT by direct compression method

The powder blend was subjected for pre-compression studies. The values of pre-compression parameters evaluated were within prescribed limits and indicated good free flowing property. Fast dissolving tablets of MT were prepared by direct compression. All the ingredients were passed through # 60 meshes separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 200 mg using 8mm round flat punches on ten station rotary tablet machine (Rimek). A batch of 30 tablets of each formulation was prepared for all the designed formulations.^[7-11]

Evaluation of MT fast dissolving tablets

The prepared tablets were evaluated for weight variation, hardness, friability, *in vitro* dispersion time, wetting time, drug content, *in vitro* release study, FTIR and DSC studies, and stability studies.

Weight variation^[12]: Twenty tablets were selected randomly from each formulation and weighed individually using a Shimadzu digital balance (BL-220H). The individual weights were compared with the average weight for the weight variation.

Thickness variation: Ten tablets from each formulation were taken randomly and their thickness was measured with a micrometer screw gauge.

Hardness and Friability^[13]: Hardness of the tablets was measured using the Pfizer hardness tester. The friability of a sample of twenty tablets was measured using a USP type Roche friabilator (Pharmalab, Ahmedabad, India). Pre-weighed tablets were placed in a plastic chambered friabilator attached to a motor revolving at a speed of 25 rpm for 4 min. The tablets were then dusted, reweighed and percentage weight loss (friability) was calculated.

Drug content uniformity^[14]: For the content uniformity test, ten tablets were weighed and pulverized to a fine powder, a quantity of powder equivalent to 10 mg of Metoprolol Tartrate was extracted into distilled water and liquid was filtered (0.22 μm membrane filter disc (Millipore Corporation)). The MT content was determined by measuring the absorbance at 223 nm (using UV-VIS Spectrophotometer, Shimadzu 1700) after appropriate dilution with distilled water. The drug content was determined using standard calibration curve. The mean percent drug content was calculated as an average of three determinations.

***In vitro* dispersion time**^[15]: 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.

Wetting time and water absorption ratio (R)^[16]: Twice folded tissue paper was placed in a Petri dish having an internal diameter of 5 cm containing 6 ml of water. A tablet was carefully placed on the surface of the tissue paper in the Petri dish. The time required for water to reach the upper surface of the tablet and to completely wet it was noted as the wetting time. Measurement of wetting time of a tablet was shown in Fig. 1.

Water absorption ratio (R) was then determined according to the following equation:

$$R = 100 \times (w_a - w_b) / w_b$$

Where; w_b and w_a are tablet weights before and after water absorption, respectively.

***In vitro* drug release study**^[17-18]: *In-vitro* dissolution studies of the fast dissolving tablets of MT formulation were performed according to 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 ± 0.5°C as dissolution medium. One tablet was used in each test. Aliquots of the dissolution medium (5 ml) were withdrawn at specific time intervals and replaced immediately with equal volume of fresh medium. The samples were filtered through 0.22 μm membrane filter disc and analyzed for drug content by measuring the absorbance at 223 nm. Drug concentration was calculated from the standard calibration curve and expressed as cumulative percent drug dissolved. The release studies were performed in replicates of three.

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.

Table 2: Pre-compression parameters of powder blend

| Formulation code | Bulk density (gm/cc) \pm SD, n=3 | Tapped density (gm/cc) \pm SD, n=3 | Angle of repose \pm SD, n=3 | Carr's index (%) \pm SD, n=3 | Hausner's Ratio \pm SD, n=3 |
|------------------|------------------------------------|--------------------------------------|-------------------------------|--------------------------------|-------------------------------|
| F0 | 0.51 \pm 0.007 | 0.62 \pm 0.02 | 31.56 \pm 1.37 | 16 \pm 1.41 | 1.21 \pm 0.02 |
| F1 | 0.52 \pm 0.007 | 0.63 \pm 0.01 | 32.5 \pm 1.56 | 17 \pm 1.00 | 1.21 \pm 0.03 |
| F2 | 0.53 \pm 0.007 | 0.63 \pm 0.01 | 31.02 \pm 1.20 | 15 \pm 1.51 | 1.18 \pm 0.04 |
| F3 | 0.53 \pm 0.007 | 0.64 \pm 0.02 | 32.1 \pm 1.70 | 17 \pm 1.20 | 1.20 \pm 0.03 |
| F4 | 0.55 \pm 0.007 | 0.65 \pm 0.01 | 33.20 \pm 0.88 | 15 \pm 2.51 | 1.18 \pm 0.03 |
| F5 | 0.50 \pm 0.007 | 0.63 \pm 0.01 | 31.43 \pm 1.48 | 20 \pm 1.58 | 1.26 \pm 0.03 |

Table 3: Post-compression parameters of fast dissolving tablets of MT

| Formulation code | Hardness (kg/cm ²) \pm SD, n=3 | Friability (%) \pm SD, n=3 | Drug Content* (%) \pm SD, n=3 | Thickness (mm) \pm SD, n=3 |
|------------------|--|------------------------------|---------------------------------|------------------------------|
| F0 | 2.9 \pm 0.14 | 0.54 \pm 0.31 | 98.44 \pm 0.50 | 4.15 \pm 0.20 |
| F1 | 2.8 \pm 0.11 | 0.66 \pm 0.12 | 99.18 \pm 0.72 | 4.30 \pm 0.12 |
| F2 | 2.7 \pm 0.11 | 0.56 \pm 0.11 | 99.81 \pm 1.07 | 4.85 \pm 0.15 |
| F3 | 2.6 \pm 0.10 | 0.52 \pm 0.13 | 99.54 \pm 0.50 | 4.21 \pm 0.10 |
| F4 | 2.5 \pm 0.12 | 0.68 \pm 0.11 | 98.12 \pm 0.73 | 4.70 \pm 0.10 |
| F5 | 2.4 \pm 0.18 | 0.67 \pm 0.12 | 99.30 \pm 0.87 | 4.45 \pm 0.17 |

Table 4: Post-compression parameters of fast dissolving tablets of MT

| Formulation Code | Wetting time (sec) \pm SD, n=3 | <i>In vitro</i> dispersion time (sec) \pm SD, n=3 | Water absorption ratio (%) \pm SD, n=3 |
|------------------|----------------------------------|---|--|
| F0 | 92 \pm 1.56 | 235 \pm 1.68 | 83 \pm 0.315 |
| F1 | 68 \pm 2.51 | 80 \pm 2.78 | 54 \pm 1.32 |
| F2 | 42 \pm 2.0 | 65 \pm 1.0 | 65 \pm 1.52 |
| F3 | 31 \pm 2.40 | 44 \pm 1.0 | 72 \pm 1.35 |
| F4 | 25 \pm 1.89 | 29 \pm 2.0 | 80 \pm 1.58 |
| F5 | 15 \pm 2.20 | 16 \pm 1.5 | 84 \pm 1.21 |

Table 5: Release profile of MT fast dissolving tablets

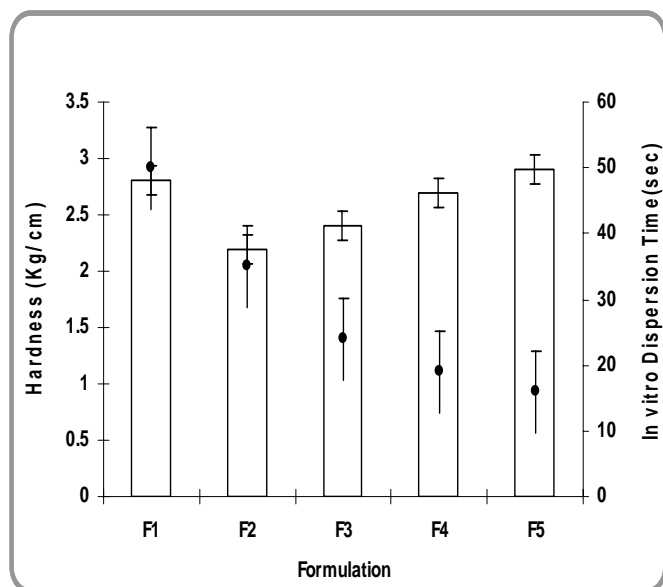
| Formulation Code | T ₅₀ (min) | T ₉₀ (min) |
|------------------|-----------------------|-----------------------|
| F0 | 11.65 | 43.65 |
| F1 | 6.05 | 15.98 |
| F2 | 5.02 | 14.21 |
| F3 | 4.07 | 11.88 |
| F4 | 3.92 | 9.79 |
| F5 | 2.94 | 6.81 |

Stability studies: The tablets of the promising formulation were subjected to accelerated stability studies, by storing in amber colored rubber stopper glass vials at 40°C/75% RH over a period of 3 months. At intervals of 1 month, 2 month and 3 month, the tablets were visually examined for any physical changes and evaluated for changes in drug content and *in-vitro* dispersion time.

RESULTS AND DISCUSSION

The values of pre-compression parameters evaluated were within prescribed limits and indicated good free flowing property is given in Table 2. The data obtained from post-compression parameters in all the formulations, friability is less than 1 %, indicated that tablets had a good mechanical resistance. Drug content was found to be in the range of 99 to 101 %, which is within acceptable limits. Hardness of the tablets was found to be in the range of 2.40-2.90 kg/cm². Thickness is in the range 4.30-4.85mm. The results of hardness, friability, drug content, and thickness were given in Table 3. Water absorption ratio and wetting time, which are important criteria for understanding the capacity of disintegrants to swell in presence of little amount of water were found to be in the range of 54-84 %, 15-92 sec and respectively. It is observed that *in-vitro* dispersion time of tablets decreased from (80-16 sec) with increase in concentration of *plantago ovata* mucilage. *In-vitro* dispersion time of tablets prepared without superdisintegrants shows 235 sec. The results of water absorption ratio, wetting time, and *in-vitro* dispersion time are given in Table 4.

It is observed that *in-vitro* dispersion time of tablets decreased from (80-16 sec) with increase in concentration of *plantago ovata* mucilage. *In-vitro* dispersion time of tablets prepared without superdisintegrants shows 235 sec. The disintegration time values decreased with increase in the concentration of volatile component. The graphical representation of comparison of hardness and *in-vitro* dispersion time were shown in Fig 2. The dissolution profiles of MT from the tablets are shown in Fig 3. The t_{50%} and t_{90%} (time for 50 % and 90 % of release) values (Table 5) decreased with increase in the concentrations level of *plantago ovata* mucilage. The dissolution study shows drug release for controlled formulation F0 without natural superdisintegrant shows 45.04 % drug release in 10 min but 90 % of drug released in 43.65 min. The formulations F1, F2 and F3 shows 50 % of drug released in 6.05, 5.02, and 4.07 min and 90 % drug released within 12-16 min. Whereas F4,

**Fig. 2: Graphical representation of Hardness and In vitro Dispersion time of tablets containing Metoprolol Tartrate**

DSC Studies: 5 mg of MT and tablet formulations were sealed in perforated aluminium pans for DSC scanning using an automatic thermal analyzer system (Mettler Toledo, USA). 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.

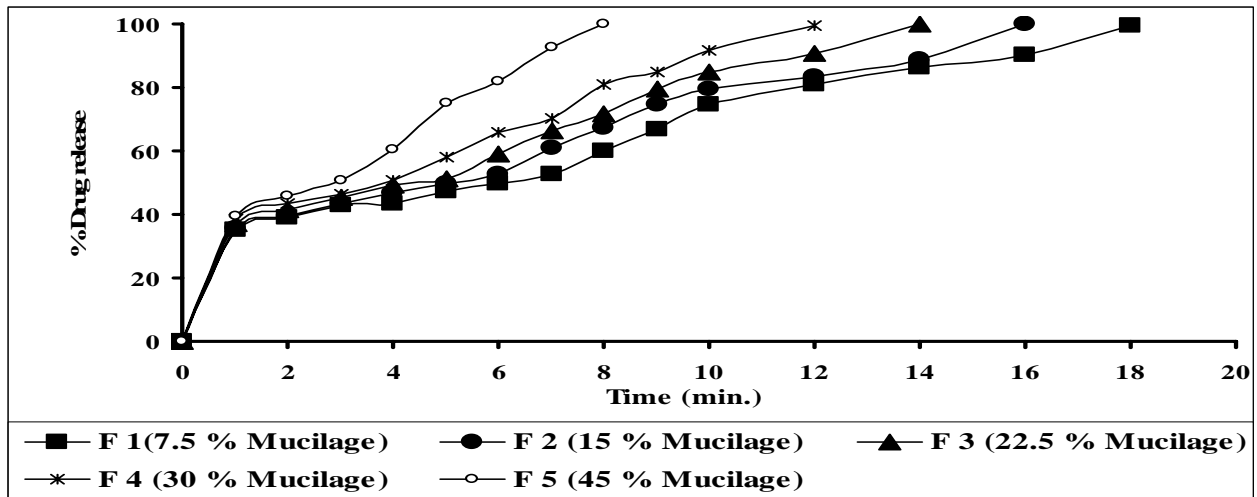


Fig. 3: Dissolution profiles of formulations F1 – F5

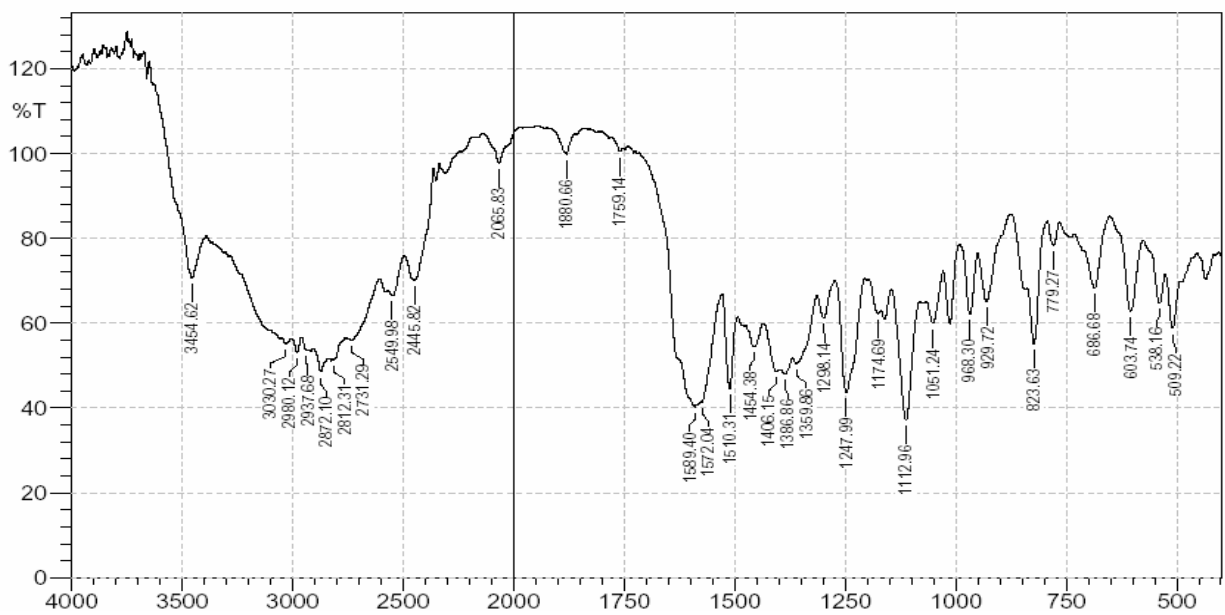


Fig. 4: FTIR spectrum of pure drug

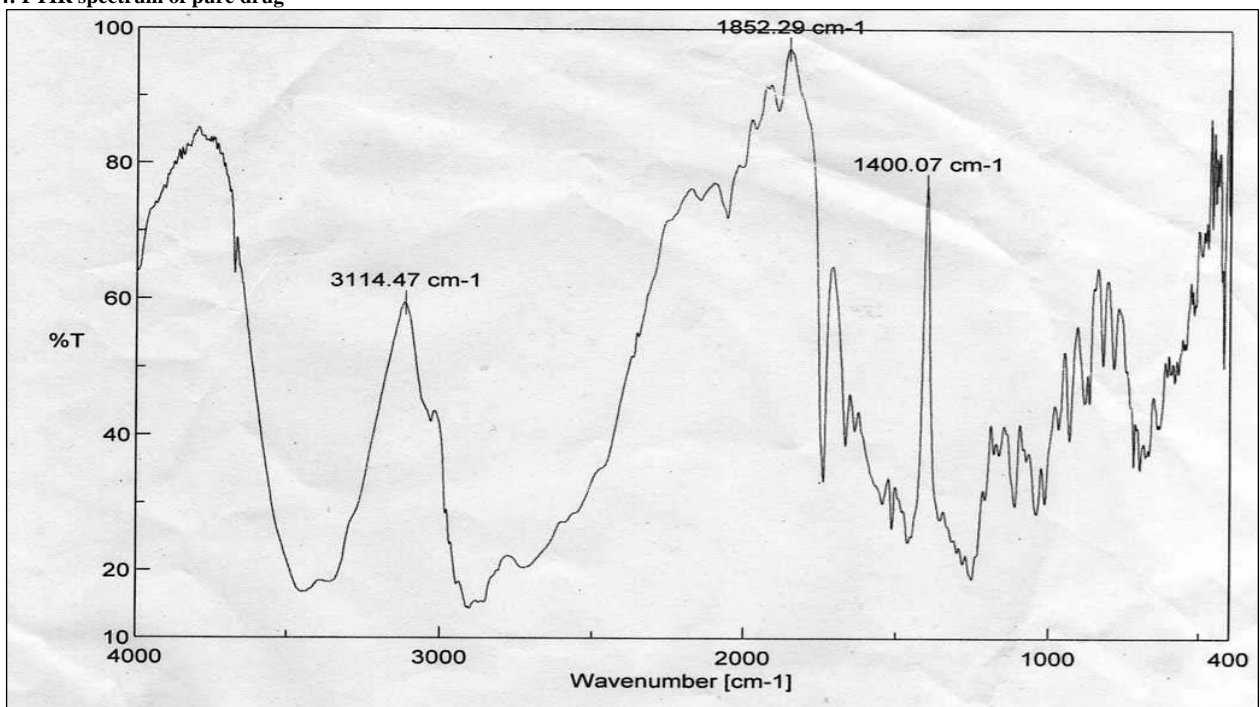


Fig. 5: FTIR spectra of formulation F5

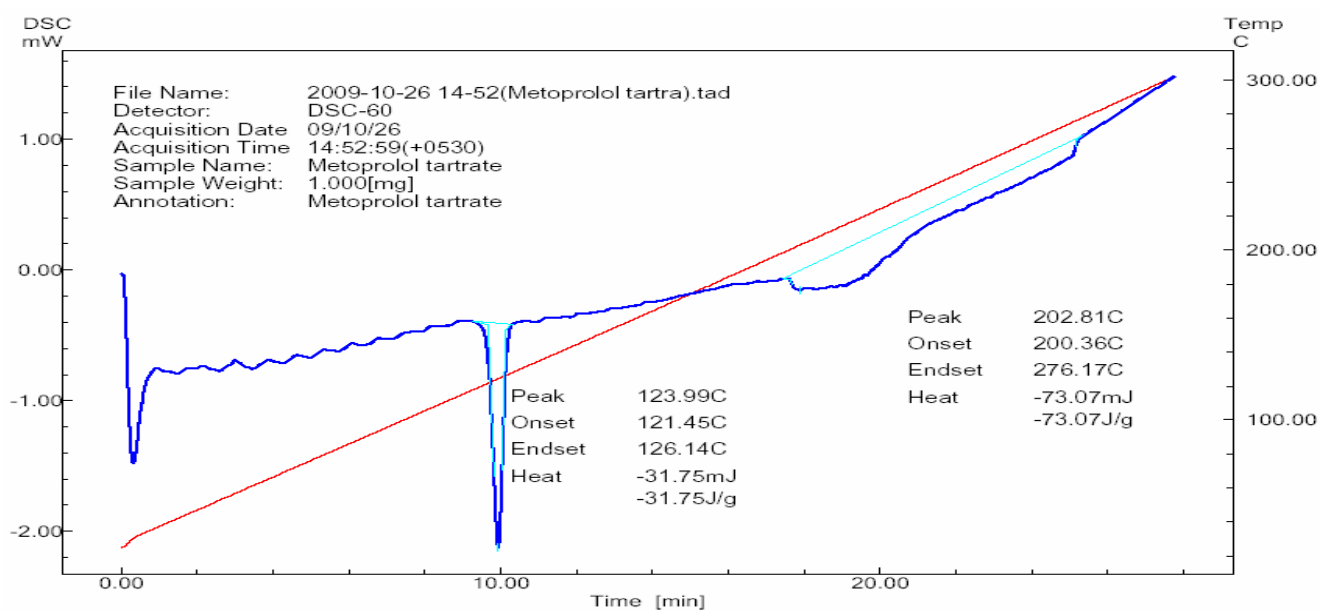


Fig. 6: DSC of formulation pure drug

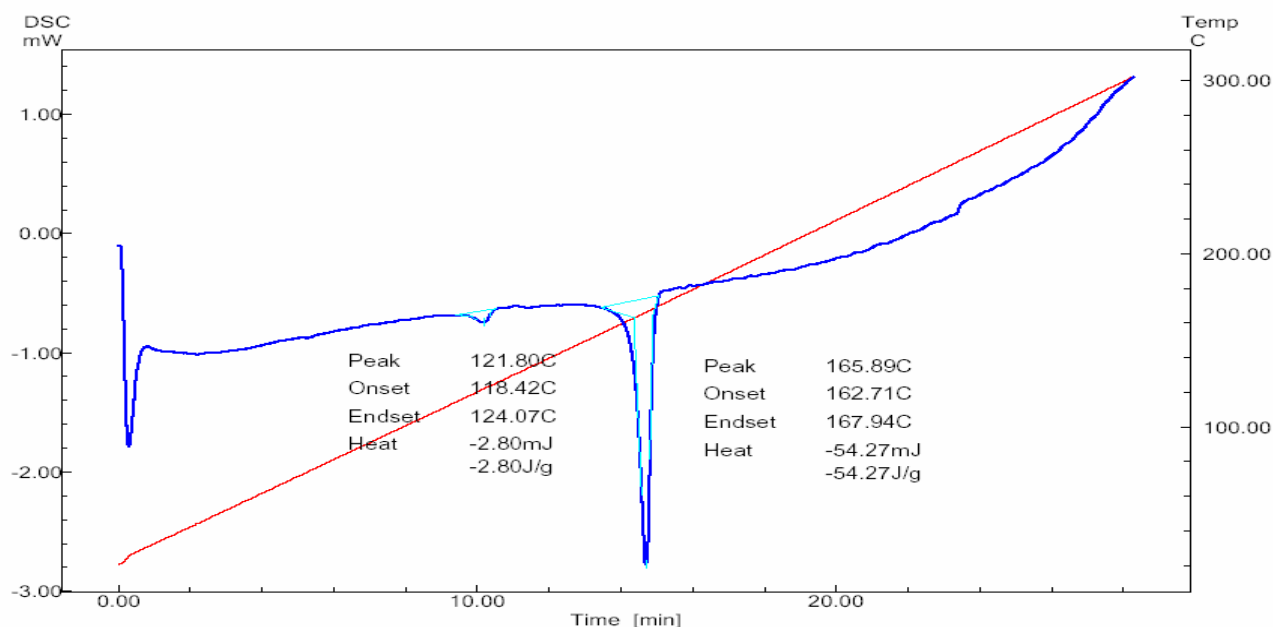


Fig. 7: DSC of formulation F5

Table 6: Result for stability study for best formulation

| Formulation code | Period | Hardness (Kg/cm ²) | Friability (%) | Dispersion time (sec) | Drug content |
|--------------------|---------|--------------------------------|----------------|-----------------------|--------------|
| 25°C/60% RH | | | | | |
| F 3 | 30 Days | 2.6 | 0.71 | 44 | 99.41 |
| | 60 Days | 2.4 | 0.73 | 41 | 99.32 |
| | 90 Days | 2.4 | 0.82 | 38 | 98.81 |
| F 4 | 30 Days | 2.5 | 0.69 | 29 | 98.53 |
| | 60 Days | 2.4 | 0.75 | 25 | 98.33 |
| | 90 Days | 2.4 | 0.76 | 24 | 98.21 |
| F 5 | 30 Days | 2.4 | 0.62 | 16 | 98.42 |
| | 60 Days | 2.4 | 0.76 | 16 | 98.31 |
| | 90 Days | 2.3 | 0.85 | 15 | 98.18 |
| 40°C/75% RH | | | | | |
| F 3 | 30 Days | 2.6 | 0.60 | 44 | 98.01 |
| | 60 Days | 2.5 | 0.78 | 41 | 97.89 |
| | 90 Days | 2.3 | 0.81 | 38 | 97.75 |
| F 4 | 30 Days | 2.5 | 0.64 | 29 | 98.18 |
| | 60 Days | 2.5 | 0.73 | 27 | 97.85 |
| | 90 Days | 2.2 | 0.80 | 26 | 97.80 |
| F 5 | 30 Days | 2.4 | 0.52 | 16 | 98.09 |
| | 60 Days | 2.3 | 0.66 | 16 | 97.92 |
| | 90 Days | 2.1 | 0.81 | 15 | 97.75 |

and F5 shows about 99 % drug release within 12 and 8 min respectively. Among all the formulation F5 shows 99.97 % drug release within 8 min.

The pure drug MT (Racemic mixture) exhibited characteristic OH absorption at 3454^{-1} cm. which is the normal range of absorption for aliphatic hydroxyl group. Secondary amine (NH) has given a weak absorption in the form of a hump. Merged with aromatic C-H at 3030^{-1} cm and aliphatic C-H of CH_3 and OCH_3 at 2980^{-1} cm. The C-O absorption is found at 1589^{-1} cm merged with C=C of aromatic. These data are in support of the structure of the drug taken for study. In formulation F5 the pure drug is with the natural superdisintegrant like *plantago ovata*. *Plantago ovata* is an inert substance there is no interaction. The pure drug characteristic absorption bands and formulations major characteristic absorption bands have shown all most same range. As there is no variation and shift in the position of characteristic absorption bands it can be justified there is no interaction between drug and polymer is shown in Fig 4-5.

In DSC thermal analysis when the drug MT is taken to study its properties at higher temperature it has exhibited melting peak at 123.99°C . In formulation F5 exhibited melting peak at 121.80°C . DSC studies revealed that there is no change in the melting point suggesting that there is no interaction between drug and other excipients shown in Fig 6-7.

The stability studies were carried out at $25^\circ\text{C}/60\% \text{RH}$, $40^\circ\text{C}/75\% \text{RH}$, for a specific time period up to 90 days for the promising formulations. No appreciable change in physical characteristics like hardness, friability, *in vitro* dispersion time and drug content. The results of stability study were given in Table 6.

CONCLUSION

Oral bioavailability of MT is around 40 %. From this study, results revealed that it is possible to enhance dissolution rate by using direct compression technique using different concentrations of mucilage of *plantago ovata* as superdisintegrants. Overall results indicates that formulation F5 that contain 45 % natural superdisintegrant like mucilage *plantago ovata* exhibited faster drug dissolution rate will lead to improve bioavailability, effective therapy, improve patient compliance, and satisfies all the criteria as fast dissolving tablet.

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