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Preparation And Evaluation of Fast Dissolving Tablets of Atenolol With Combination of Different Concentrations of Superdisintegrants By Direct Compression Technique

Lakshmi Radhika G, Chandan NJ, Aroodha V Maragur, Lalu Gowda V
Department of pharmaceutics, SJM college of pharmacy, chitradurga-577502, karnataka, India.

Corresponding author Email –chandanchandu1718@gmailcom, aroodhamaragur130@gmail.com

Abstract : The purpose of this research was to formulate fast dissolving tablets (FDT) In the present work efforts have been made to prepare and evaluate fast dissolving tablets of atenolol with combination of different concentrations of superdisintegrants crospovidone, sodium starch glycolate by direct compression technique. fast dissolving tablets are designed to disintegrate and dissolve in saliva and then easily swallowed without need of water which is a major benefit over conventional dosage form. Atenolol, a β1-blocker, is prescribed widely in diverse cardiovascular diseases, eg, hypertension, angina pectoris, arrhythmias, and myocardial infarction. preparation and evaluation preparation of atenolol fast dissolving tablet with combination of different concentrations of superdisintegrants crospovidone, sodium starch glycolate by direct compression technique. The results revealed that the increased proportion of various superdisintegrants were associated with increase in the overall cumulative drug release rate. The developed tablets were evaluated for hardness, friability, drug content, weight variation, uniformity of dispersion, wetting time, wetting volume, *in vitro* dispersion time, *in vitro* disintegration time and *in vitro* drug release. The dissolution profiles of prepared tablets were compared with pure drug and marketed product. Rapid disintegration of tablets formulated in this research possibly help in administration

Key words: Atenolol, fast dissolving Tablets (FDTs), Superdisintegrants

I. INTRODUCTION

The tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness and ease in manufacturing. However, geriatric and paediatric patients experience difficulty in swallowing conventional tablets, which leads to poor patient compliance. To overcome this weakness, scientists have developed innovative drug delivery systems known as orally disintegrating tablets (ODTs).These are novel types of tablets disintegrate/dissolve/disperse in saliva. Their characteristic advantages such as administration without water, anywhere, anytime lead to their suitability to geriatric and paediatric patients. They are also suitable for the mentally ill, the bedridden, and patients who do not have easy access to water. The benefits, in terms of patient compliance, rapid onset of action, increased bioavailability and good stability make these tablets popular as a dosage form of choice in the current market[1,2].The basic approach used in the development of the ODTs is the use of superdisintegrants. Another approach used in developing ODTs is maximizing pore structure of the tablets. Freeze-drying [3,4] and vacuum-drying [5,6]techniques have been tried by researchers to maximize the pore structure of tablet matrix. Freeze drying is cumbersome and it yields a fragile and hygroscopic product. Therefore, it was decided to adopt the vacuum drying technique in the present investigation. Vacuum drying was adopted after addition of a subliming agent to increase porosity of the tablets. It is likely that a porous hydrophilic matrix will easily pick up the disintegrating medium and break quickly.

Atenolol, a β1-blocker, is prescribed widely in diverse cardiovascular diseases, eg, hypertension, angina pectoris, arrhythmias and myocardial infarction. The drug is also frequently indicated in the prophylactic treatment of migraine [7]. Administration of conventional tablets of atenolol has been reported to exhibit fluctuations in the plasma drug levels, resulting either in manifestation of side effects or reduction in drug concentration at the receptor site [8,9]. An attempt was made in the present investigation to prepare ODTs of atenolol using superdisintegrants at different concentrations.

II. MATERIALS AND METHODS:

Materials

Atenolol obtaind from Kopran Ltd.(Mumbai, India). Microcrystaline cellulose, Sodium starch glycolate, crosspovidone were obtained as gift sample from Micro Labs (Banglore, India). Manitol from Lobachemicals(Mumbai,India). Magenisim stearate, talc and Aspartam from S.D. fine chemicals (Mumbai, India). All other materials used were of pharmaceutical grade.

METHOD

Spectrophotometric determination of atenolol

In this experiment, 100 mg of atenolol was dissolved in ethanol to create stock I. From stock I, 10 ml was pipetted into another flask to form stock II. Working solutions of atenolol (2-10 µg/ml) were prepared from stock II. Absorbance of these concentrations was measured using a Shimadzu UV-visible double beam spectrophotometer. A calibration curve was obtained by plotting concentration versus absorbance. The method was validated for linearity, accuracy, and precision and followed Beer-Lambert's law in the 2-10 µg/ml concentration range.

Preparation of mixed blend of drug and excipients

All the materials were passed through sieve no. 60. Required quantity of each ingredient was taken for each specified formulation (Mentioned in Table no.1) and all the ingredients were subjected to grinding to a required degree of fineness (except sodium stearyl fumarate and talc). The powdered blend was evaluated for flow properties as follows.

Table- 1: Composition of Orodispersible Tablet of Atenolol.

	F1	F2	F3	F4	F5	F6
Atenolol	25	25	25	25	25	25
SSG	10	10	10	10	10	10
Crosspovidone	2	4	6	2	4	6
Aerosil	2	2	2	2	2	2
Lactose	30	30	30	30	30	30
Aspartame	3	3	3	3	3	3
Mg.stearate	1	1	1	1	1	1
MCC	127	125	123	122	120	118
Total weight	200	200	200	200	200	200

Angle of repose [10]

Angle of repose was determined using fixed funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose (ɵ) was calculated using the formula.

$$\theta = \tan^{-1}(h / r)$$

Bulk density [10, 11]

Bulk density was determined by pouring the blend into a graduated cylinder. The bulk volume (Vb) and weight of the blend (M) was determined. The bulk density was calculated by using the below mentioned formula,

$$\text{Bulk density} = \frac{\text{Weight of the blend}}{\text{Volume of blend(Vb)}}$$

Tapped density [10, 12]

The measuring cylinder containing a known mass of blend was tapped for a fixed number of times. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density was calculated using the following formula,

$$\text{Tapped density} = \frac{\text{Weight of the blend}}{\text{Volume occupied in the cylinder (Vt)}}$$

Total Porosity [12]

It was determined by measuring the volume occupied by a selected weight of blend and the true volume of blend. (The space occupied by the granules exclusive of spaces greater than the intermolecular spaces).

$$\text{Porosity (\%)} = \frac{Vb - V}{Vb} \times 100$$

V bulk = initial volume of the blend,

V = final volume of the blend.

Compressibility index [13]

The simplest way for measurement of free flow of powder is compressibility , a indication of the ease with which a material can be induced to flow is given by compressibility index (I) which is calculated as follows,

$$I = \frac{Vb - Vt}{Vb}$$

Here, Vb is bulk volume and
Vt is tapped volume.
The value between 13-19% indicates a powder with usually good flow characteristics, whereas above 21% indicate poor flowability.

Hausner's Ratio [13]

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula,

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Lower Hausner's ratio (<1.25) indicates better flow properties and higher Hausner's ratio (>1.25) indicates poor flow properties.

Compression of tablets by using direct compression technique

Finally sodium stearyl fumarate and talc were added to the prepared blend. The mixed blend of drug and excipients was compressed into tablets weighing 150 mg using a flat faced punches of 8 mm diameter in a rotary tablet press(Rimek mini press- 1, Model RSB-4,Karnavati Engineering, Ahmedabad) weighing 150 mg each with a diameter of 8 mm. A minimum of 50 tablets were prepared for each batch.

III. COMPATIBILITY STUDIES

FTIR Study

From the FTIR spectra of the pure drug and the combination spectra of drug with the polymers it was observed that all the characteristic peaks of atenolol was present in the combined spectra as well thus indicating the compatibility of the drug with the polymers. The individual FTIR spectra of the pure drug atenolol, polymers as well as the combination spectra of the drug and polymers physical mixture are shown in the Figure. It was found that the drug was compatible with polymer in physical mixture.

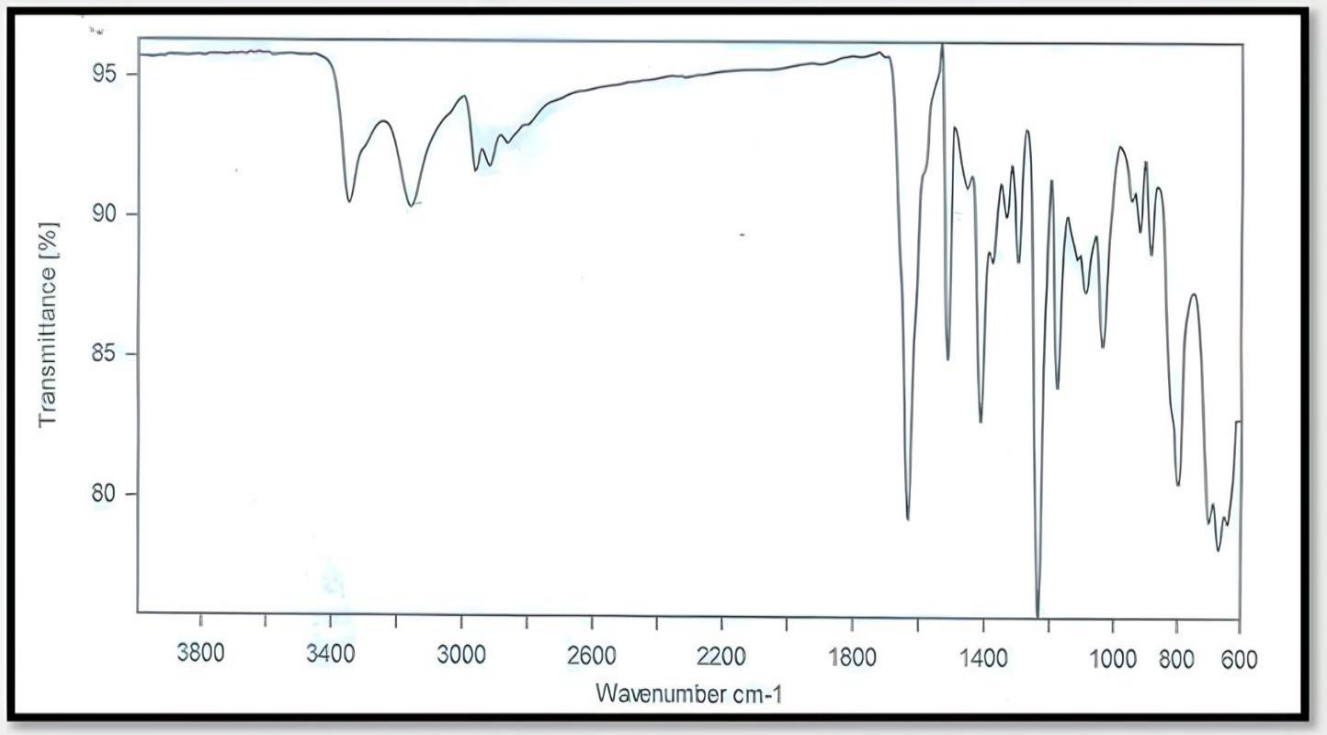

Figure 01: IR spectra of atenolol

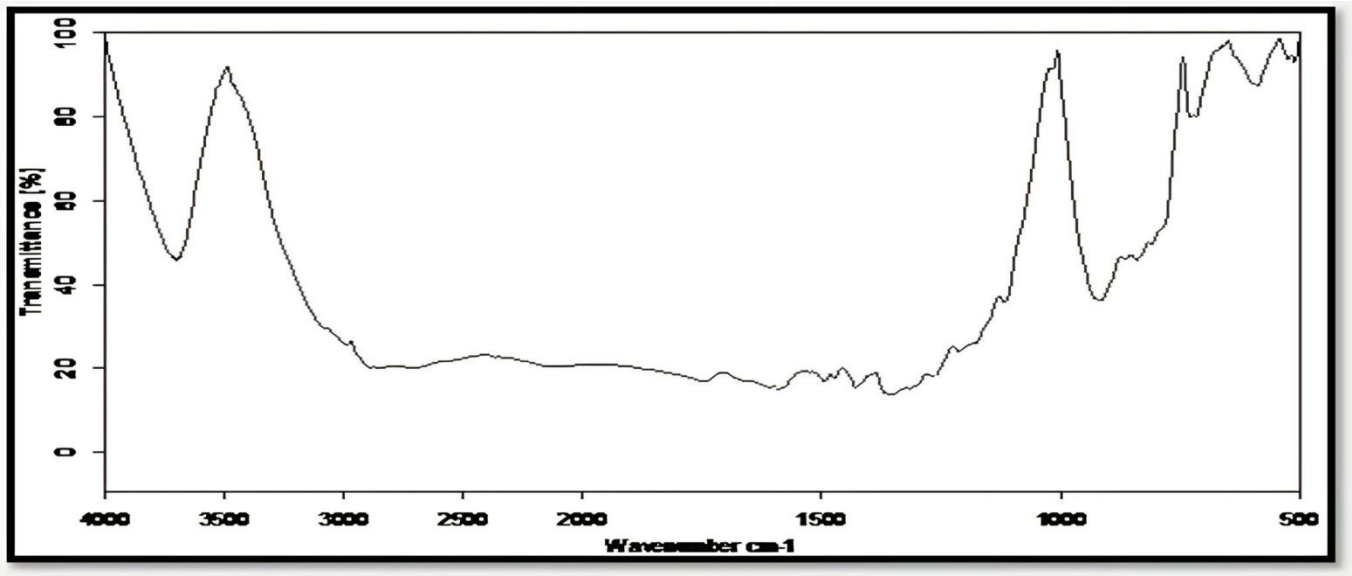

Figure 02: IR spectra of SSG

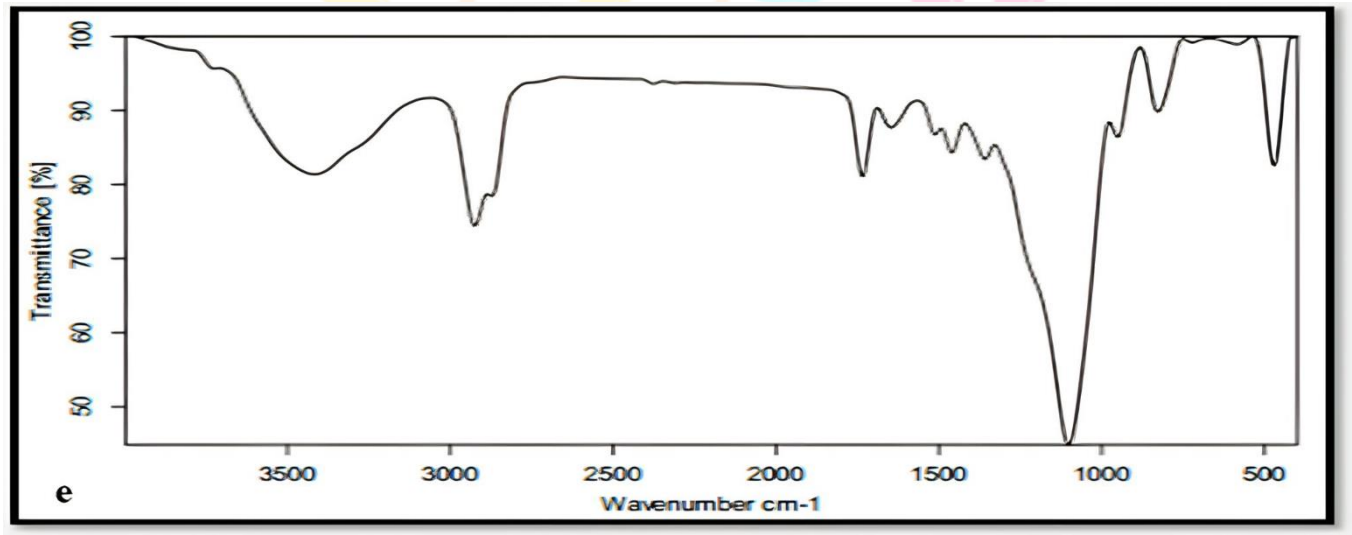

Figure 03: IR spectra of Aerosil

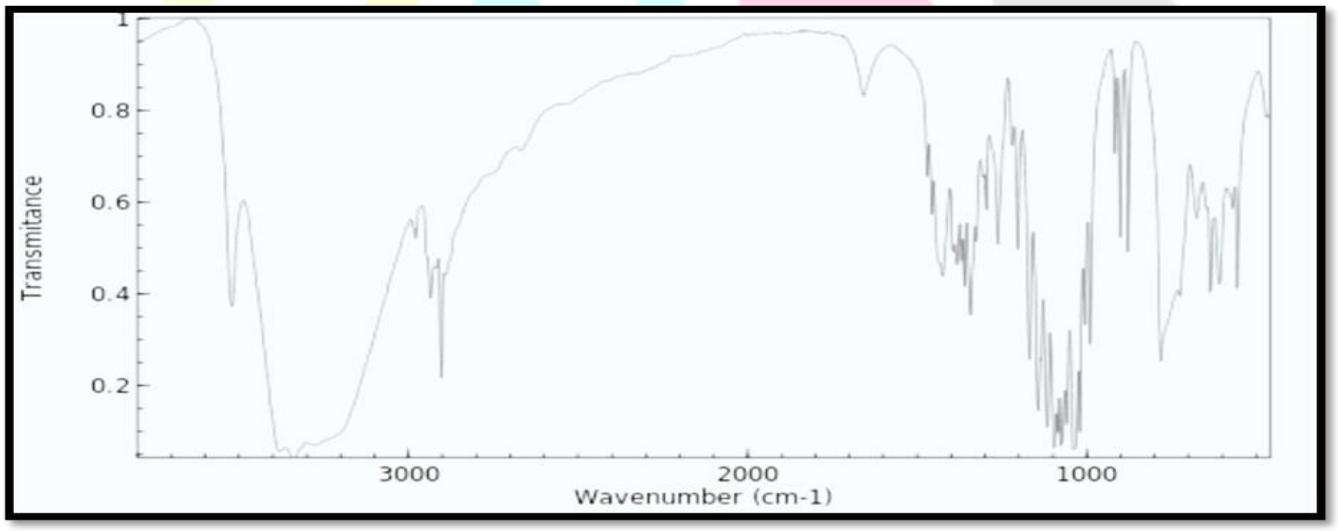

Figure 04: IR spectra of Lactose

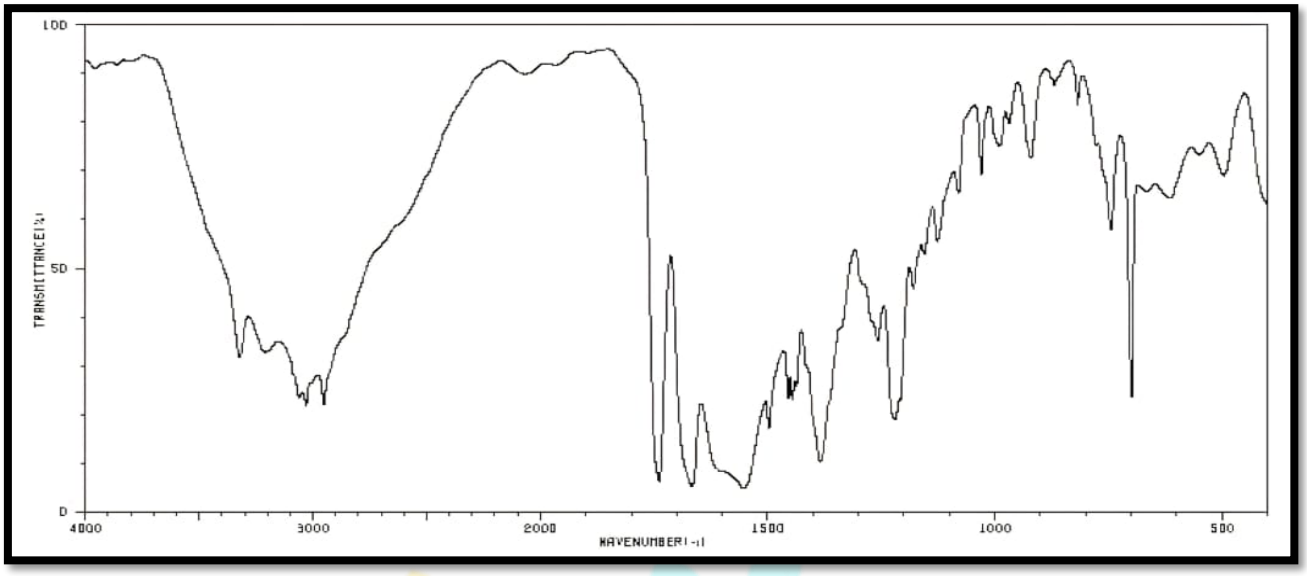

Figure 05: IR spectra of Aspartame

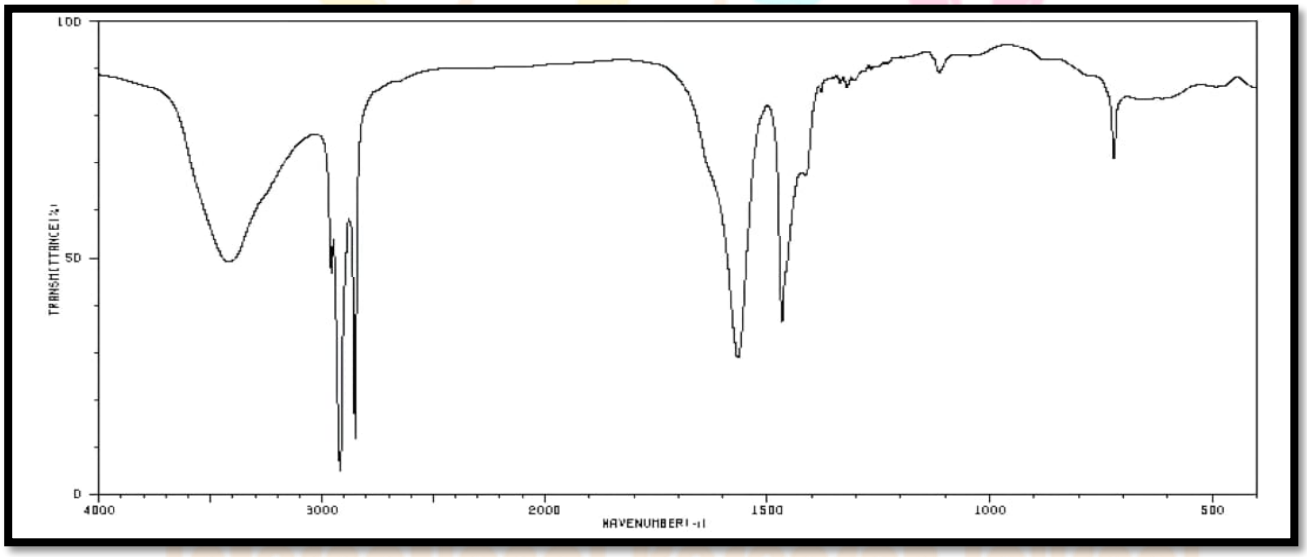

Figure 06: IR spectra of Magnesium stearate

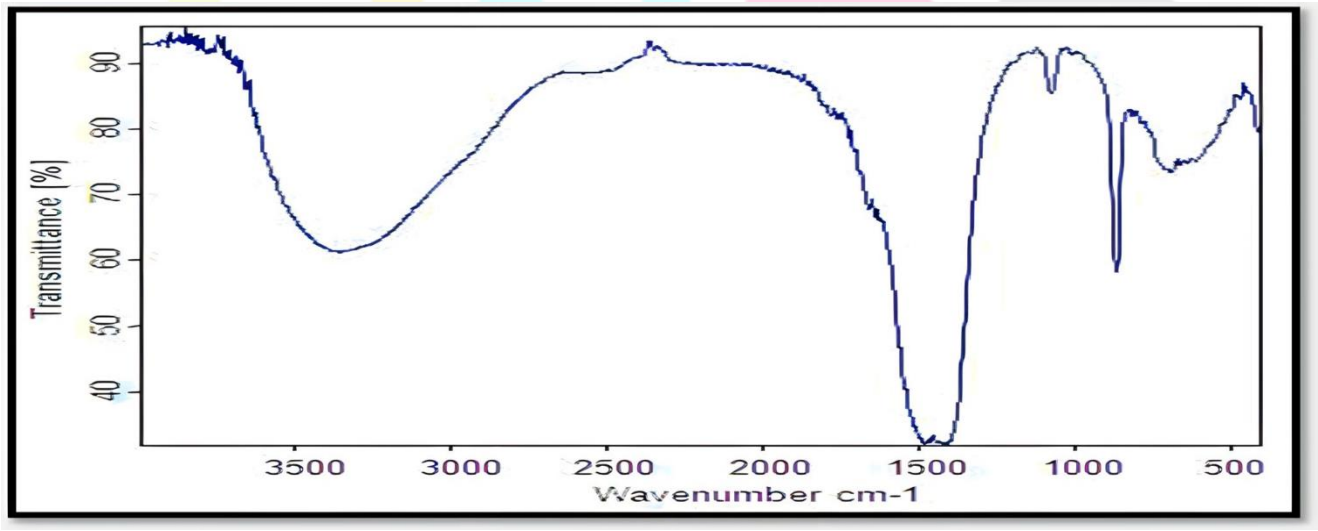

Figure 07: IR spectra of mixture of atenolol, crosspovidone, aerosil, lactose and Mg stearate

Standard calibration curve of Atenolol in Phosphate buffer (ph 7.4)

The absorbance of standard solutions of clotrimazole ranging from 2-10µg/ml in Phosphate buffer (ph 7.4)

. The curve was found to be linear in the range of 2-10µg/ml at λmax 226nm. The regression value was found to be 0.999 as shown in Figure 8.

Table-2: Standard calibration curve of atenolol in Phosphate buffer (ph 7.4) at 226nm

Sl no	Concentration (µg/ml)	Absorbance
1	0	0.0
2	2	0.15
3	4	0.32
4	6	0.49
5	8	0.667
6	10	0.82

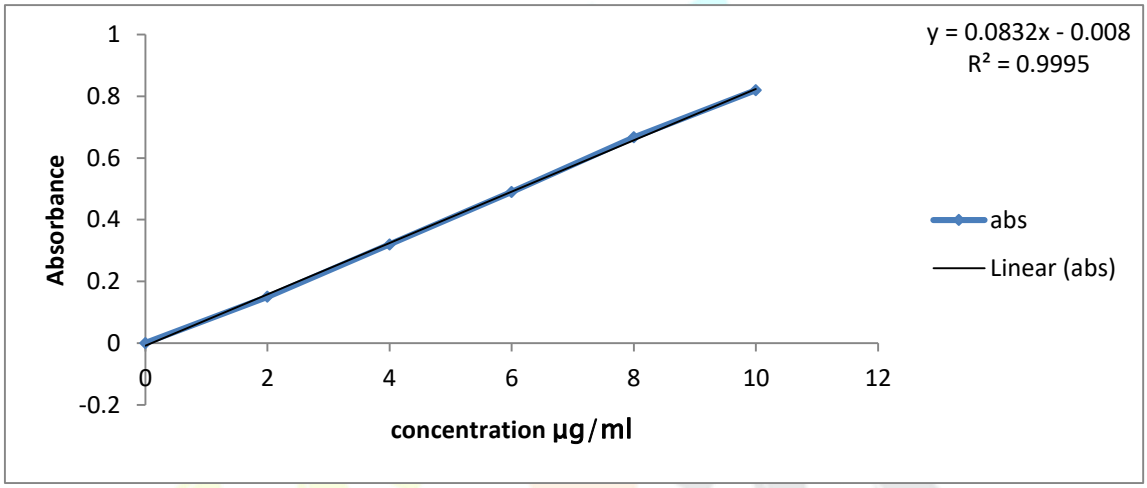

Figure 08: Calibration curve of atenolol

IV. EVALUATION OF ATENOLOL MOUTH DISSOLVING TABLETS

Evaluation was done on tablets of all formulations batches considering following parameters and results were reported in Table no.3

1) Weight variation test [14]

Twenty tablets were selected randomly and average weight was determined. Then individual tablets were weighed and was compared with average weight. If the variation is within the I.P limits, the tablets pass the weight variation test.

2) Tablet hardness [14]

The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm2. 3 tablets were chosen randomly and tested for hardness. The average hardness of 3 determinations was recorded.

3) Wetting time [14]

The wetting time of the tablets can be measured using a simple procedure. Five circular tissue papers of 10 cm diameter were placed in a petri dish with a 10 cm diameter. 10 ml of water was poured on the tissue paper placed in the petridish. A table is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time.

4) Tablet friability [14]

Five tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. Then tablets were removed from the friabilator, dusted off the fines and again weighed and the weight was recorded.

Percentage friability was calculated by using
the formula:

$$\frac{\text{Initial weight - Final weight}}{\text{Initial weight}} \times 100$$

5) *In-Vitro* Disintegration time [14]

The test was carried out on 6 tablets using tablet disintegration tester ED – 20, Electrolab. Distilled water at 37° C ± 2° C was used as a disintegration media and the time in second taken for complete disintegration of the tablet with no mass remaining in the apparatus was measured in seconds.

6) Thickness and Diameter [15]

The thickness and diameter of individual tablets was measured using vernier calipers, which permits accurate measurements and provides information of the variation between tablets.

7) Drug content uniformity [16]

Ten tablets were weighed and taken in mortar and crushed to make powder. A quantity of powder weighing equivalent to 25 mg of Atenolol was taken in 100 ml volumetric flask and 0.1 N HCl was added. Then the solution was filtered using membrane filter 0.45 µ m and then the solution was diluted up to 10 µ g and absorbance was measured at 224.2 nm. Then the amount of drug present was calculated using standard graph.

8) Dissolution studies [16]

In Vitro dissolution studies for all the prepared tablets and the marketed available tablets was carried out using USP paddle method at 50 rpm in 500 ml of 0.1 N HCl(pH 1.2) as dissolution media, maintained at 37 $\pm$ 0.5°. 5 ml of samples, were withdrawn from the dissolution medium at the specified regular intervals, filtered through Whatmann filter paper and release of the drug was determined spectrophotometrically at 224.2 nm. An equal volume of pre warmed (37° C) fresh medium was replaced into the dissolution medium after each sampling, to maintain the constant volume of the dissolution medium throughout the test. Then the cumulative percentage of drug release was calculated and represented graphically.

Assay:

Twenty tablets from each batch were weighed accurately and powdered powder equivalent to 100 mg Atenolol was shaken with 100ml of 0.1N Hydrochloric acid in 100 ml amber coloured volumetric flask and from this 10 ml was pipette out and then dilute up to 100 ml. From standard solution again 10 ml pipette out and diluted up to 100 ml in 100 ml amber coloured volumetric flask. Resulting solution was filtered and assayed at 225 nm and content of Atenolol was calculated.

Table-2: **Evaluation of the Powder Blend**

	F1	**F2**	**F3**	**F4**	**F5**	**F6**
Weight variation	25	25	25	25	25	25
Friability(%)	0.4026	0.399	0.6019	0.49	0.4995	0.4004

	Angle of repose	**Bulk density**	**Tapped density**	**Carr`s index**	**Hausners ratio**
F1	26.65± 0.055	0.3978	0.4625	14.44	1.1626
F2	28.32± 0.225	0.4002	0.4669	14.28	1.1666
F3	25.36± 0.055	0.3997	0.4612	13.33	1.1538
F4	27.43± 0.273	0.4043	0.4751	14.81	1.6664
F5	28.50 ±0.462	0.4073	0.4807	12.13	1.1802
F6	22.54 ±0.137	0.4157	0.4923	15.15	1.1842

9) DSC studies

Differential scanning colorimetry is a technique in which the difference in the amount of required to increase the sample and reference is measured as a function of temperature. Both the sample and reference are maintained at nearly the same temperature throughout the experiment. Generally, the temperature program for a DSC analysis is designed such that the sample holder temperature increases linearly as a function of time. The reference sample should have a well-defined over the range of temperatures to be scanned.

DSC studies were carried out for pure drug with polymer. DSC scans were performed by using an automatic thermal analyzer system. (DSC60 Shimadzu Corporation, Japan). 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 for the sample was used as a reference. The entire samples were run at a scanning rate of 10°C/min from 50-250°C. The figures are shown below.

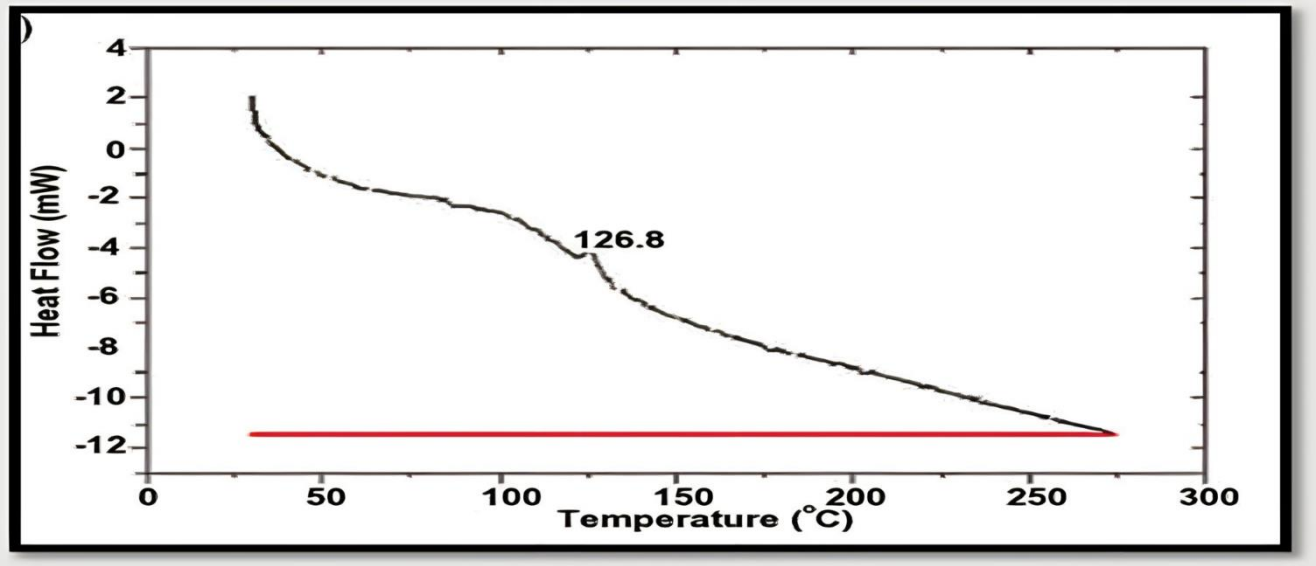

Figure 09: DSC of atenolol and cross povidone

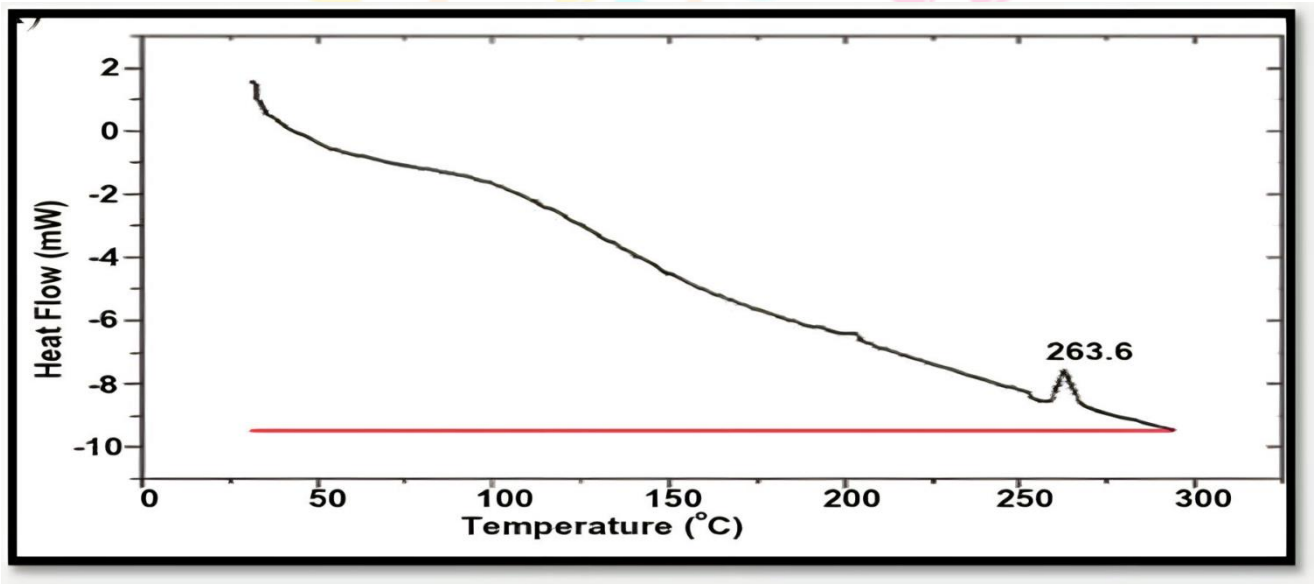

Figure 10: DSC of atenolol and MCC

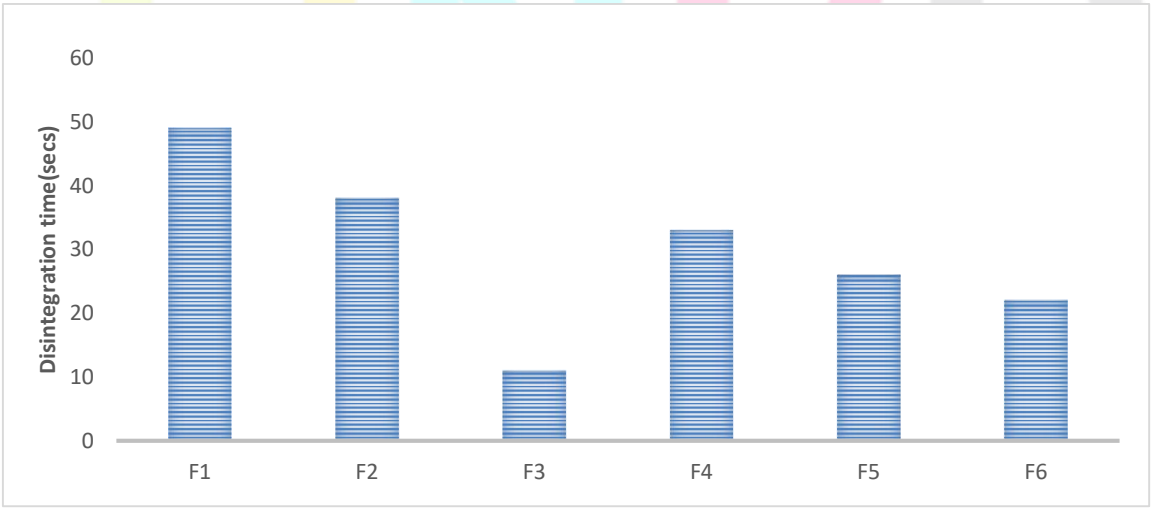

Figure 11: Column graph of the Disintegration time (Sec) of various batches.

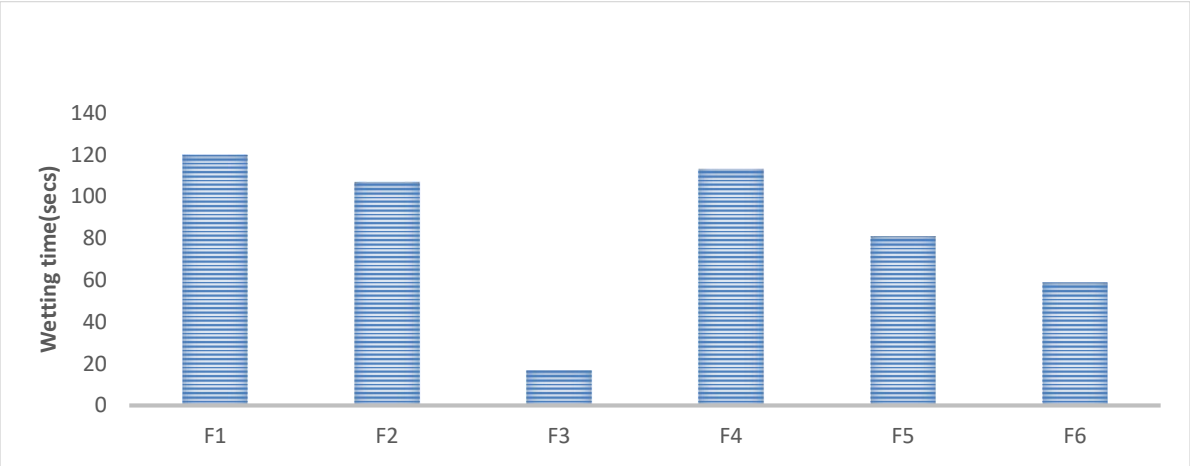

Fig 12: Column graph of the Wetting time (Sec) of various batches.

10)*In-vitro* drug release studies

The drug release from the microsponge hydrogel were studied by Franz diffusion cell method. The *in-vitro* release profiles of Clotrimazole and Beclomethasone dipropionate from Ethyl cellulose microsponges are shown in **Table 3 and Fig 13**. The cumulate percentage release of Atenolol varied from14.80 to 91.92 and 50.6 to 90.3 respectively depends on the drug polymer ratio.

TABLE 3: *In vitro* drug release for clotrimazole F1 to F6

Time (min)	Batch code					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	18.212	17.845	18.312	23.412	25.675	20.515
2	22.623	20.676	21.345	29.645	37.769	33.212
3	29.315	25.849	24.824	36.487	40.342	39.924
4	35.169	29.628	26.709	45.672	47.701	47.413
5	41.204	32.151	30.236	53.128	49.802	53.621
6	45.673	36.182	34.190	63.750	61.507	59.457
7	51.324	41.024	39.925	65.418	68.915	66.012
8	62.597	55.683	54.628	67.746	71.212	75.129
9	71.645	59.355	56.159	73.687	75.854	83.910
10	74.896	67.802	60.924	79.504	83.158	91.927

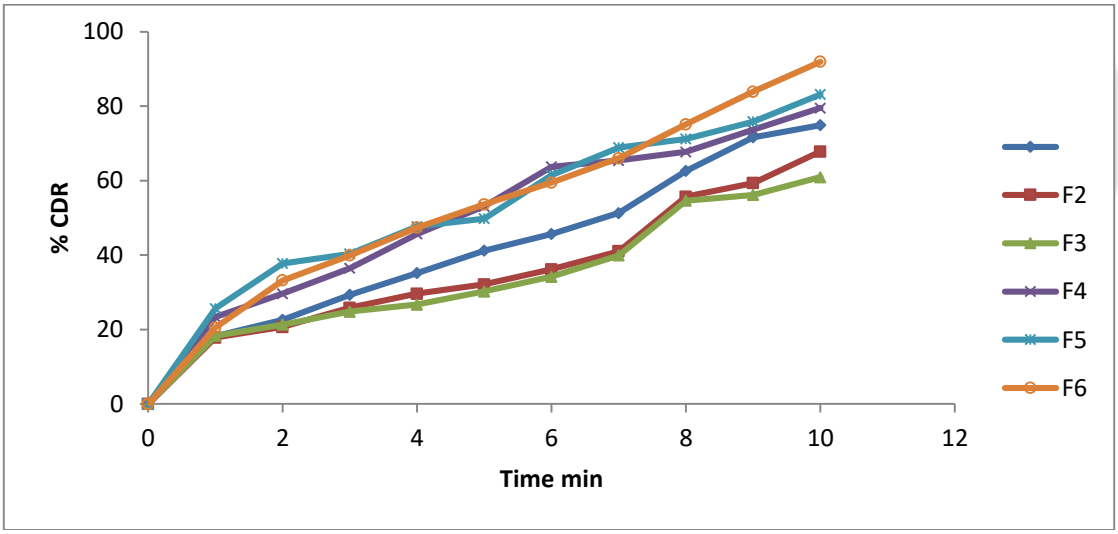

Fig 13: *Invitro* drug release for Atenolol from F1 to F6

11) Scanning Electron Microscopy

The determination of shape and surface morphology was done by scanning electron microscope HITACHI SU 1500, Japan. Scanning electron photomicrographs of the formulation F6 are shown in Figure 13 and 14 respectively. The surface topography reveals that the microsponges were porous due to the rapid escape of the volatile solvents during formulation. Inward dents were seen on the surface probably due to collapse of the walls of the microsponges during the in situ drying process.

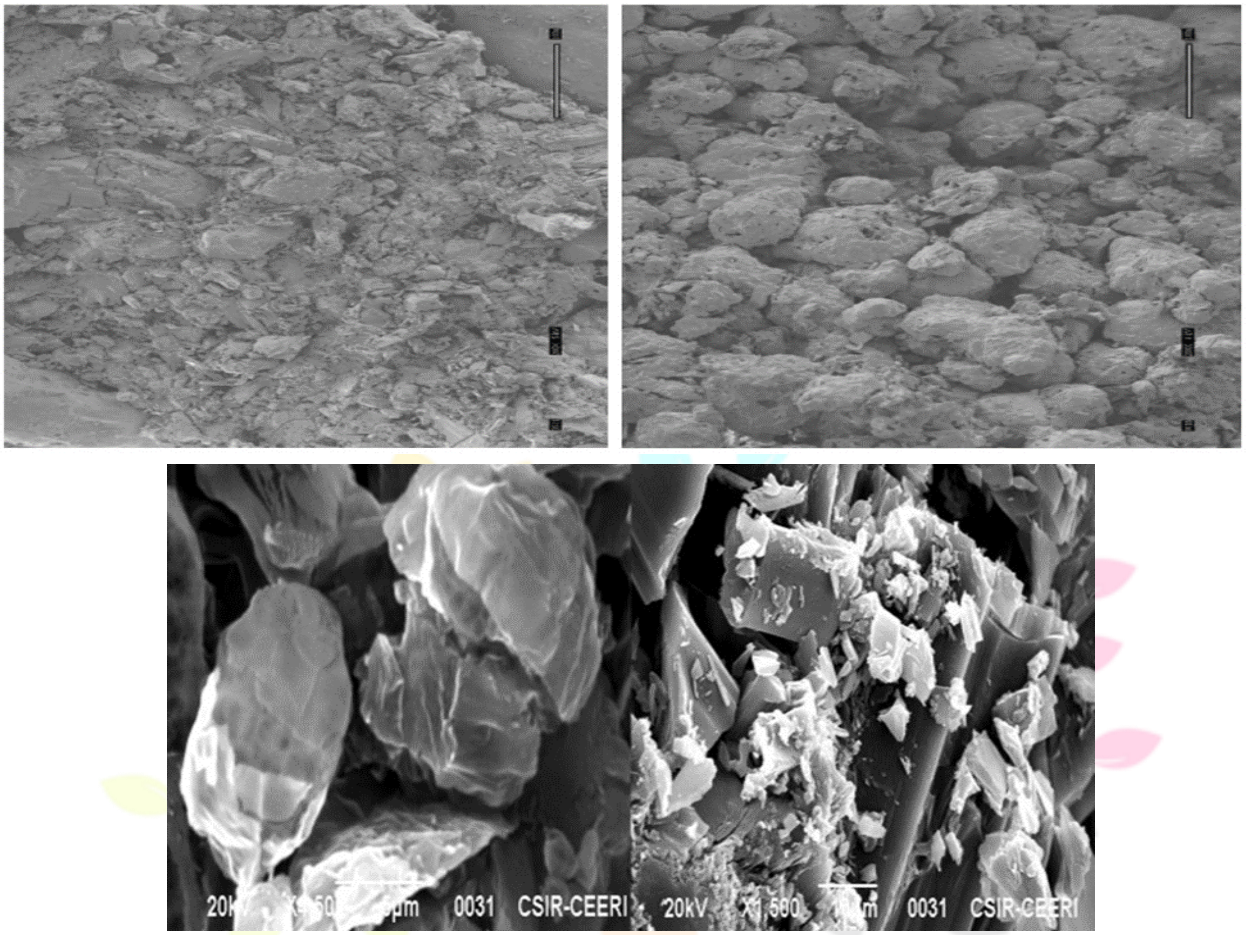

Fig 14: SEM images of F6 formulation

I. RESULTS AND DISCUSSION

Six formulations of Atenolol were prepared with combination of different concentrations of superdisintegrants crospovidone, sodium starch glycolate. For each formulation, blend of drug and excipients were prepared and evaluated for various parameters as explained earlier. The formulated blends were evaluated and the results are shown in the table 2. The angle of repose was in the range of 22.54 ± 0.137 to 28.50±0.462 indicating good flow property. The bulk density and tapped density was in the range of 0.3978 ± 0.005 to 0.4157 gm/cc and 0.4612 ± 0.009 to 0.4923 ± 0.011 gm/cc. The compressibility index and Hauser's ratio was in the range of 13.33 ± 1.89 to 15.15 ±1.62% and 1.15 ± 0.003 to 1.18 ± 0.023 indicating good flow property. The powder blend was compressed using direct compression technique. The compressed tablets were evaluated for physical properties and the results are tabulated in table 3. The hardness was in the range of 3.1to 3.83 kg/cm2. Uniformity of weight was found to be in the range of 200.3 ± 1.02 to 202.45 ±0.045 mg. The friability of all the formulation was within 1%, and was in the range of 0.399 to 0.6019 % indicating a good mechanical resistance of tablets. The wetting time for all the formulated tablets was in the range of 17 ± 0.64 to 120 ± 0.46 sec. The disintegration time of all the formulated tablets was found to be in the range of 11.66 ± 1.15 to 49 ± 1.60 sec. **The drug content was in the range of 98.23 ± 0.29 to 101.76 ± 1.28%. The thickness and diameter was in the range of 2.83 ± 0.04 to 2.95 ± 0.04 and 7.97 ± 0.02 to 8.00 ± 0.05.** All the formulations in-vitro drug release results were mentioned in the Table no.3. The results revealed that the increase in proportion of superdisintegrants was associated with increase in the overall cumulative drug release rate. Release profile of F-6 having 4% crospovidone and prepared, using mannitol (DC), micro crystalline cellulose and aspartame was found to have maximum release of 91.92% at the end of 10 minutes. The drug release from all batches was found to be concentration dependent.

VI. CONCLUSION

In the present work efforts have been made to prepare and evaluate fast dissolving tablets of atenolol with combination of different concentrations of superdisintegrants crospovidone, sodium starch glycolate by direct compression technique. The results revealed that the increased proportion of various superdisintegrants were associated with increase in the overall cumulative drug release rate. Release profile of F-6 having Crospovidone and prepared using Mannitol (DC), Microcrystalline cellulose, Aspartame was found to have maximum release of 91.92 % at the end of 10 minutes. The drug release from all batches was found to be concentration dependent. The mouth dissolving tablets (MDT) found to have excellent physical characters. The superdisintegrants were also found to be compatible with the other excipients of the formulation as well as with drug, which is evident from the drug content values. Hence the formulation of F-6 fulfills the objective of the present study. Undoubtedly the availability of various technologies and

the manifold advantages of MDT will surely enhance the patient compliance, low dosing, and rapid onset of action, increased bioavailability, low side effect, good stability and its popularity in the near future.

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