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DESIGN, DEVELOPMENT AND IN-VITRO EVALUATION OF METOPROLOL TARTRATE FAST DISSOLVING TABLETS

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Abstract:

The main objective of the study is to formulate and evaluate oro-dispersible tablets of Metoprolol tartrate with suitable superdisintegrantsMetoprolol Tartrate is effective β-blocker used in the second line treatment for angina and for myocardial infarction. Adult dose as conventional preparations is 25-100 mg daily in single or divided doses, as extended release 100-200 mg once daily. The bioavailability of the drug when formulated as conventional tablets is 40 % due to hepatic metabolism. The present investigation was undertaken with a view to develop a fast dissolving tablet of Metoprolol tartrate which offers a new range of product having desired characteristics and intended benefits prepared by direct compression method using different concentrations of superdisintegrant. Effect of superdisintegrant on wetting time, drug content, in-vitro drug release, disintegration time has been studied. Disintegration time increased with increase in the level of Croscarmellose while it decreased for Sodium starch glycolate, the release was dependent on the aggregate size in the dissolution medium. It is concluded that Metoprolol Tartrate fast dissolving tablets could be prepared using superdisintegrant with improved bioavailability and rapid onset of action.

***Keywords**: Fast dissolving tablets, Metoprolol Tartrate, Croscarmellose sodium, Sodium starch glycolate, disintegration time, in-vitro drug release.*

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INTRODUCTION:

A Solid dosage form containing medicinal substances, which disintegrates rapidly usually within a matter of seconds, when placed upon the tongue". According to European pharmacopoeia, "A tablet that is to be placed in the mouth where it disperses rapidly before swallowing [1].

Rapid Dissolving tablets are also known as Melt in Mouth tablets Mouth dissolving tablets (MDT) Fast disintegrating tablets (FDT) Orally disintegrating tablets Rapid disintegrating tablets (RDT) Oro dispersible tablets (ODT) Quick dissolving tablets. Fast Dissolving Tablets (FDT) disintegrates and/or dissolves rapidly in the mouth without the need for water. Some tablets are designed to dissolve in saliva remarkably fast within a few seconds. Others contain agents to enhance the rate of tablet disintegration in the oral cavity and are more appropriately termed Fast Dissolving Tablets (FDT) as they may take up to a minute to complete disintegration of these formulations is convenience. A major claim of the some Fast Dissolving Tablets (FDT) increased bioavailability compared to traditional tablets. Because of dispersion in saliva while still in the oral cavity, there can be pre-gastric absorption from some formulation in those cases where the drug dissolves quickly. Buccal, pharyngeal and gastric regions are all areas of absorption of the many formulations. However, other formulations show nearly identical plasma concentration profiles. Any pre-gastric absorption avoids first pass metabolism and can be a great advantage in drugs that undergo a great deal of hepatic metabolism.

Criteria for Fast Dissolving Drug Delivery System [16]:

The tablets should

Not require water to swallow, but it should dissolve or disintegrate in the mouth in matter of seconds.

Be compatible with taste masking.

Be portable without fragility concern.

Have a pleasant mouth feel.

Leave minimum or no residue in the mouth after oral administration.

Exhibit low sensitive to environmental condition as temperature and humidity.

Allow the manufacture of the tablet using conventional processing and packaging equipments at low cost.

Salient Feature Of Fast Dissolving Drug Delivery System [3,4]

Ease of Administration to the patient who cannot swallow, such as the elderly, stroke victims, bedridden patients, patient affected by renal failure and patient who refuse to swallow such as pediatric, geriatric & psychiatric patients.

No need of water to swallow the dosage form, which is highly convenient feature for patients who are traveling and do not have immediate access to water.

Rapid dissolution and absorption of the drug, which will produce quick onset of action.

Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach. In such cases bioavailability of drug is increased.

Pregastric absorption can result in improved bioavailability and as a result of reduced dosage; improve clinical performance through a reduction of unwanted effects.

Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patient.

The risk of chocking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety.

New business opportunity like product differentiation, product promotion, patent extensions and life cycle management.

Beneficial in cases such as motion sickness, sudden episodes of allergic attack or coughing, where an ultra rapid onset of action required.

An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tablets.

Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. So, it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.

Techniques for Preparing Fast Dissolving Tablets: [5]

Many techniques have been reported for the formulation of Fast dissolving tablets or Orodispersible tablets.

1. Freeze drying / lyophilization
2. Tablet Moulding
3. Spray drying
4. Sublimation
5. Direct compression
6. Mass extrusion

MATERIALS AND METHODS:

Table 1 shows the chemical/reagent and drugs and their source. And table 2 shows the source of instruments used for this study.

Table 1: Source of Chemicals and Ingredients

S. No.	Ingredients/chemicals/solvents	Manufacturer /supplier
1	Mannitol, Crosscarmellose	SD fine chemicals, Boisar
2	Sodium starch glycolate	SD fine chemicals, Boisar
3	Methanol	SD fine chemicals, Boisar
4	Lactose	. SD fine chemicals, Boisar
5	Magnesium stearate	SD fine chemicals, Boisar
6	Starch	SD fine chemicals, Boisar
7	Talc	SD fine chemicals, Boisar

All the chemical were of AR grade

Table 2: Manufacturers of Instruments/Apparatus

S. No.	Instrument/Apparatus	Manufacturer/ Supplier
1	Tablet Press (9 Station, Single Rotary)	ChamundaPharma, Ahmadabad.
2	Friabilator	Singhala Scientific, Ambala.
3	Dissolution Apparatus (USP Type II)	Electrolab, Mumbai.
4	Monsanto Hardness Tester	Singhala Scientific, Ambala.
5	U.V.Visible Spectrophotometer	Shimadju, Mumbai.
6	Digital VernierCaliperse	Digimate, Hyd.
7	pH meter	Systronic, Hyd.
8	Stability study chamber	Electrolab, Mumbai.

Formulation of Tablets:

Fast dissolving tablets of Metoprolol tartrate were prepared by direct compression. The term "direct compression" is defined as the process by which tablets are compressed directly from powder mixture of API with suitable excipients. No pretreatment of the powder blend by wet or dry granulation procedure is required it done by simple mixing of API with suitable additive and compress to tablets.

All the ingredients (except granular directly compressible excipients) were passed through 60-mesh separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 450 mg using 9 mm round flat punches on 9 - station rotary tablet machine.

Table 3: Formulation of Fabricated Oro Disintegration Tablets

Ingredients(mg)	FM-I	FM-II	FM-III	FM-IV	FM-V	FM-VI
Drug	50	50	50	50	50	50
Mannitol	150	150	150	150	150	150
MCC	94	92	90	94	92	90
Crosscarmellose Sodium	13	14	22	-	-	-
Sodium Starch glycolate	-	-	-	13	14	22
Magnesium Stearate	12	10	9	12	10	9
Flavouring ang Sweeting agent	31	32	33	31	32	33

Pre formulation studies

Bulk density:

Bulk Density is defined as weight per unit volume. Bulk density (pb) is defined as the mass of the powder divided by the bulk volume and is expressed as gm/ cm3. A sample of about 50 cm^3(blend) is carefully introduced in a 100ml graduated cylinder. The cylinder is dropped onto a hard wood surface three times from a height of 1 inch at two second interval. The bulk density is then obtained by dividing the weight of sample in gm by final volume in cm3.

Pb = M/ Vp

Pb = Bulk Density

M = Weight of sample in gm

Vp = Initial volume of blend in cm3

Bulk density is very important in designing the size of containers needed for handling, shipping, and storage of raw material and blend.

Tapped density:

It is the ratio of total mass of the product to the tapped volume of powder the volume was measured by tapping the powder for fifty times.

Dt = M/Vt

Where, M is the mass of the powder

Vt is the tapped volume of the powder

Compressibility index:

Is an important measure that can be obtained from the bulk and tapped densities.

CI = Tapped Density – Bulk Density /Tapped density*100

Angle of repose:

It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane. Fix the funnel at a distance of 6cm and pass the granules to fixed funnel and note down the height and radius of the pile.

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

Where, θ is the angle of repose

h is the height in cms and r is the radius in cms

Porosity:

The porosity € of powder is defined as the ratio of void volume to the bulk volume of the packaging. The porosity of the powder is given €= Vb - Vp/ Vp = 1- Vp/Vb

Porosity is frequently expressed in percentage and is given as

%€ = (1 - Vp/ Vb) X 100

The porosity of powder indicates the types of packaging a powder undergoes when subject to vibrations, when stored, or in tablet machine when passed through hopper or feed frame.

Evaluation of Tablets

Hardness Test:

The crushing strength of the tablets was measured using a Monsanto hardness tester. Three tablets from each formulation batch were tested randomly and the average reading noted.

Friability Test:

The friability test of a sample of 20 tablets was measured using a Roche Friabilator**.** Twenty pre weighed tablets were rotated at 25 rpm for 4 minutes. The tablets were then reweighed after removal of fines (using no. 60 mesh screen), and the percentage of weight loss was calculated.

Weight Variation:

Randomly, twenty tablets were selected after compression and the mean weight was determined. None of the tablets deviated from the average weight by more than ±10% (USPXX).

Drug Content

Twenty tablets were weighed and powdered. An amount of the powder equivalent to 100 mg of Metoprolol tartrate was dissolved in 100 ml of pH 6.8phosphate buffer, filtered, diluted suitably and analyzed for drug content at 243 nm using UV-

Visible spectrophotometer.

Wetting Time:
A piece of tissue paper folded twice was placed in a small petridish (ID=6.5 cm) containing 6 ml of simulated saliva pH 6.8, a tablet was put on the paper, and the time for complete wetting was measured.

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

Disintegration Time:
Disintegration time for MDTs was determined using USP disintegration apparatus with SSF (pH 6.2, 900 ml at 37°C) as the disintegrating medium. To comply the test all tablets should disintegrate within 3 minutes.

***In-vitro* Drug Release Studies:**
The *in vitro* dissolution study was carried out in USP dissolution test apparatus Type 2 (Electro lab,India) .The dissolution medium consisted of phosphate buffer (pH 6.8). An amount of 900 ml of the dissolution fluid was used at 37±0.5^{0}C with stirring speed of 50 RPM Samples were withdrawn at 2, 4, 8, 10,and16 minutes time intervals by replacing with same dissolution medium and samples were analyzed by measuring the absorbance at 254 nm by UV spectrophotometer.

RESULTS AND DISCUSSION:

Table: 4 Evaluation of granules:

Formulation Code	Bulk Density gm/cm^3	Tapped Density gm/cm^3	Compressibility Index (%)	Angle of Repose	% porosity
F-I	0.45 ± 0.04	0.57 ± 0.01	10.00 ± 0.04	32^{0}32’ ± 1.03	84.3 ± 0.88
F-II	0.52 ± 0.05	0.62 ± 0.02	13.33 ± 0.04	28^0 86’± 1.03	83.8 ± 0.98
F-III	0.45± 0.07	0.62 ± 0.01	25.21 ± 0.04	27^{0}42’ ± 1.25	92.6 ± 0.68
F-IV	0.42± 0.04	0.59 ± 0.01	19.20 ± 0.04	27^{0}34’ ± 1.15	91.3 ± 0.76
F-V	0.39± 0.03	0.45 ± 0.03	13.30 ± 0.04	29^{0}65’ ± 1.21	93.50 ±0.91
F-VI	0.47± 0.04	0.61 ± 0.04	21.66 ± 0.04	28^{0}23’ ± 1.16	92.80 ±0.55

Table: 5 Evaluations of Tablets

Formulation	Hardness Kg/cm^2	Friability %±SD	Weight Variation mg±SD	Drug Content (%)	Wetting time (sec ± SD	Disintegration time (Sec ± SD)	Thickness (mm ± SD)
FM – I	3.5 ± 0.02	0.66± 0.16	449 ± 0.41	98.51	21 ± 0.22	68 ± 0.12	4.19 ± 0.01
FM – II	3.5 ± 0.09	0.54 ± 0.16	451 ± 0.25	98.78	19 ± 0.12	72 ± 0.09	4.55 ± 0.01
FM – III	2.7 ± 0.10	0.56 ± 0.16	450 ± 0.39	99.81	38 ± 0.14	69 ± 0.11	4.65 ± 0.01
FM – IV	2.5 ± 0.05	0.52 ± 0.16	448 ± 0.35	99.21	56 ± 0.18	92 ± 0.12	4.32 ± 0.02
FM – V	3.0 ± 0.07	0.68 ± 0.16	450 ± 0.21	99.54	48 ± 0.18	83 ± 0.17	4.21 ± 0.01
FM – VI	3.7 ± 0.03	0.51 ± 0.16	451 ± 0.22	98.99	69 ± 0.19	91 ± 0.21	4.69 ± 0.02

The present investigation was undertaken to formulate and evaluate fast dissolving tablets of Metoprolol tartarate by direct compression method using Croscarmellose sodium and Sodium Starch Glycolate as a superdisintegrants. Superdisintegrant are generally used by formulation scientists for developing FDTs or for improvement of solubility for drugs. The primary requirement for both dosage forms is quicker disintegration. The amount of Super disintegrants was optimized in the formulation of FDTs. The total 6 formulation (FM-I–FM-VI) were prepared using different concentration of Croscarmellose sodium and Sodium Starch Glycolate to study its effect on disintegration time.

Mannitol because of its negative heat of solution gives cooling sensation and mask after bitter taste of aspartame. Microcrystalline cellulose has also been used as a diluent which helps in enhancing the disintegration of the tablet. Magnesium stearate is used as lubricant. The sweetener combination aspartame and mannitol gives long lasting sweet taste to the formulation. Vanillin acts as a flavouring agent.

The present investigation was planned to formulate and evaluate Metoprolol tartrate fast dissolving tablets (FDT), using different excipients and super disintegrates in various proportions prepared by direct compression technique. The preparation process in direct compression tablets includes co-grinding of all the excipients before compression resulting, the increase in the solubility due to the reduction in the effective particle size of the drug following increase in the wetting of drug particle by the excipients and improved dissolution of drugs. The precompression and postcompression evaluations were taken over for the prepared granules and tablets respectively. The *in-vitro* drug release studies have been carried out pH 6.8. The values of pre-compression parameters evaluated were within prescribed limits and indicated good free flowing property is given in Table 5.

Bulk density was found to be between 0.39 ± 0.03 and 0.52 ± 0.05 and tapped density between 0.45 ± 0.03 and 0.62 ± 0.02 for all the formulations. The percentage compressibility was calculated and was found to be in the range of 10.00 ± 0.04 and 25.21 ± 0.04 which indicates a fairly good flowbility of the powder blend. The good flowability of the powder blend was also evidenced with angle of repose (range of 27^0 34’ ± 1.15 to 32^0 32’ ± 1.03) which is below 40^o indicating good flowability. The percentage porosity was found to be in the range of 83.8 ± 0.98 to ± 93.50 ± 0.91. All the formulation shows the good blend properties for direct compression and hence tablets were prepared by direct compression technology.

The values of post compression parameters evaluated were given in Table 6&7. Percent weight variation was observed between 448± 0.35 and 451 ± 0.25 which were well within the acceptable limit for uncoated tablets as per United States Pharmacopoeia. It is well known to formulation scientists that the tablets with more hardness show longer disintegration time. Since mechanical integrity is of paramount importance in successful formulation of FDTs, hence the hardness of tablets was determined and was found to be in the range of 2.5 ± 0.05 to 3.7 ± 0.03Kg/cm^2. Friability was observed between 0.51 ± 0.16 and 0.68± 0.16, which were below 1% indicating sufficient mechanical integrity and strength of prepared tablets. The disintegration time for all formulations was found to be 68 ± 0.12 – 92± 0.12 seconds and wetting time was 19 ± 0.12 to 69 ± 0.19 seconds. The thickness of the tablet ranges from 4.19 ± 0.01 to 4.69 ± 0.02.

The drug release studies were performed on the prepared formulations (FM I-FM VI) using phosphate buffer pH 6.8 for 20min. Table No. 6 enlists the comparatives *In vitro* drug release data for formulations FM – I to FM– VI. The percentage release of Metaprolol tartarate at 20 min for formulations FM- I to FM- VI showing 79.03%, 83.06%, 93.06%, 78.89%, 81.15%, and 83.44% respectively. From the above results, the formulation FM - III showed faster and maximum drug release than the other formulations.

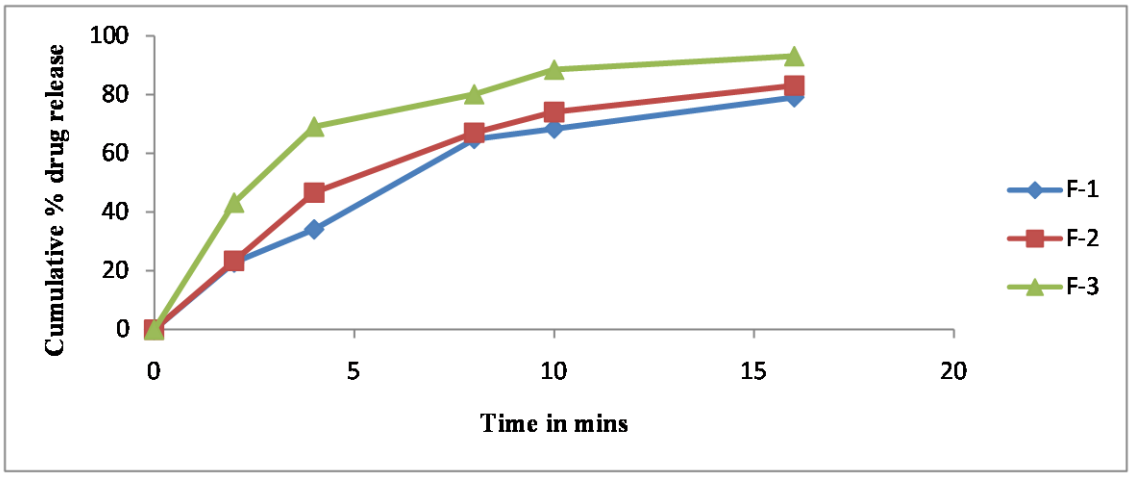

Fig 1: Comparison of *In vitro* Drug Release of Formulation-1,2 and 3

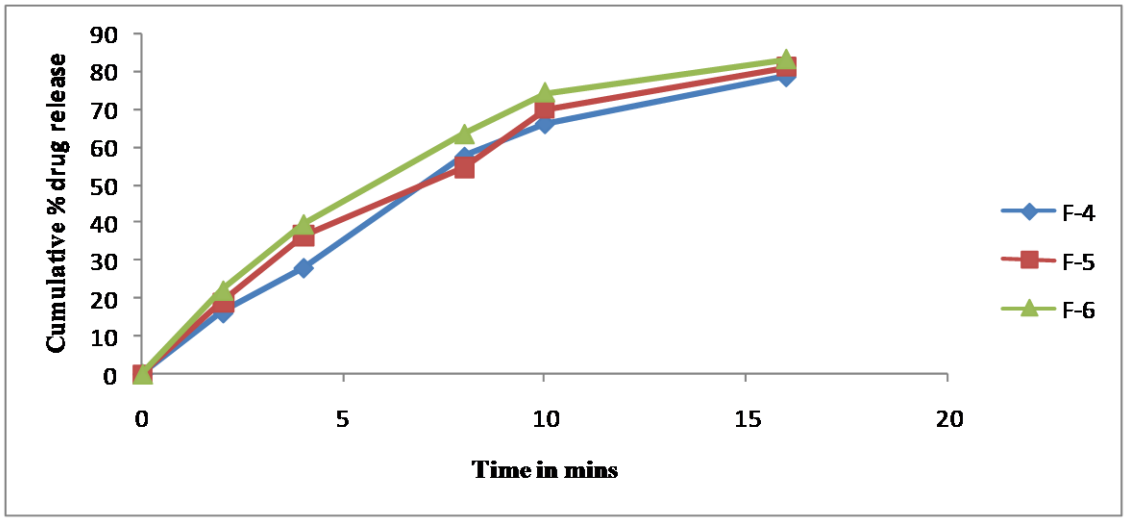

Fig 2: Comparison of *In Vitro* Drug Release of Formulation-4, 5 and 6

CONCLUSION:

Fast oro-dispersible tablet is a promising approach with a view of obtaining faster action of the drug and would be advantageous in comparison to currently available conventional forms. Fast dissolving tablets of Metoprolol tartrate were prepared by direct compression method using Croscarmellose sodium and Sodium Starch Glycolate as a superdisintegrant. The dosage form had a good balance over disintegration time and mechanical strength.

In vitro drug release from the tablets shows significantly improved drug dissolution. It was concluded that in direct compression method, Crosscarmellose sodium (5 %w/w) act as a best and suitable superdisintegrant. Fast dissolving tablets of Metaprolol tartarate is successfully prepared by using direct compression method, will surely enhance the patient compliance, low dosing, rapid onset of action, increased bioavailability, low side effect, good stability and its popularity in the near future. Further investigations are needed to confirm the in vivo efficiency.

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