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Design and characterization of melt-in-mouth tablets of metoprolol tartarate

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Abstract

The purpose of the present research was to compare the effect of superdisintegrants on the Melt-in-mouth property of Metoprolol Tartrate tablets. Metoprolol tartrate is effective β-blocker which is having anti-anginal properties and used in the treatment of myocardial infarction. In the present work Melt-in-mouth tablets of metoprolol tartrate were prepared by direct compression method using superdisintegrants such as Isapgol husk, sodium starch glycolate and croscarmellose sodium. Among the formulations the most promising one is F3 containing 12% Isapgol husk with 10% camphor showing 99.45% drug release indicating better drug release and improved bioavailability. So it was concluded that sublimation method along with superdisintegrant addition was excellent method in formulation of Melt-in-mouth tablets of Metoprolol Tartrate which gives quick relief from Myocardial infarction.

Key-Words: Mouth-in-melt tablets, Metoprolol Tartrate, Isapgol husk, Sodium starch glycolate, Cross carmellose sodium

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, 3]. Over the last few years, a great deal of interest has been directed towards formulating solid oral dosage forms that disintegrate/melt rapidly in the mouth without the need for water.

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These dosage forms are known as rapid disintegrating or Melt-in-mouth tablets. Many patients find difficulty in swallowing tablets and hard gelatine capsules; consequently they do not take medications as prescribed. It is estimated that 30% of the population is affected by this problem which results in a high incidence of incompliance and ineffective therapy. For this reason the developments of Melt-in-mouth tablets have recently interested not only the pharmaceutical industry, but also academia[4]. Metoprolol tartrate is effective β-blocker which is having anti-anginal properties and used in the treatment of myocardial infarction[5].

The basic approach used in the development of the Melt-in-mouthtablets is the use of superdisintegrates. The main objective of this research is to study the effect of concentration of different superdisintegrants on drug release of Metoprolol Tartrate by direct compression method.

Material and Methods

Materials

Metoprolol tartrate was obtained as gift sample from Arabindo pharma, Hyderabad, India. SSG, CCS, Avicel ph 102, Talc and Magnesium stearate were procured from S.d fine chem. Pvt Ltd; Mumbai, India. All other chemicals and reagents used were of analytical grade.

Experimental methods[6, 7]

All the materials were passed through sieve no. 60. The weighed quantity of each ingredient (Table 1) was grinded to a required degree of fineness. (Except magnesium stearate and talc). The powdered blend was evaluated for flow properties. (Table -2).

Compression of tablets by using direct compression technique

To the blended powders finally sodium magnesium stearate and talc were added. The mixed blend of drug and excipients was compressed into tablets weighing 200 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). A minimum of 50 tablets were prepared for each batch.

Evaluation of metoprolol tartrate melt-in-mouth tablets

Pre compression parameters

Bulk density[8]

Apparent bulk density was determined by placing pre-sieved drug excipient blend in to a graduated cylinder and measuring the volume and weight as it is.

$$Db = M/Vb$$

Where, M = Weight of powder taken; Vt= tapped volume.

Tapped density[8, 9]

Tapped density was determined by USP method II tablet blend was filled in 100 ml graduated cylinder of tap density tester which was operated for fixed number of taps until the powder bed volume has reached a minimum, thus was calculated by formula

$$Dt = M/Vt$$

Where, M = Weight of powder taken; Vt= tapped volume.

Angle of Repose[14]

Angle of repose was determined by using funnel method. Tablet blend were poured from funnel, that can be raised vertically until a maximum cone height h was obtained diameter heap r, was measured. The repose angle θ was calculated by formula

$$\theta = \tan^{-1}\frac{h}{r}$$

Where, θ is the angle of repose, h is height of pile; r is radius of the base of pile.

Compressibility index and Hausner ratio [15, 16]

This was measured for the property of a powder to be compressed; as such they are measured for relative importance of interparticulate interactions.

Compressibility index was calculated by following equation

$$\text{Compressibility index} = \{(Dt - Db)/Dt\} \times 100$$

Where, Dt= tapped density; Db= bulk density;

Hausner ratio was calculated by following equation

$$\text{Hausner ratio} = Dt/Db$$

Where, Dt= tapped density; Db= bulk density

Post compression parameters

All prepared Metoprolol tartarate tablets were evaluated for its uniformity of weight, hardness, friability and thickness, *in vitro* drug release according to official methods shown in Table 3.

Weight variation[17]

Twenty tablets were randomly selected from each batch weighed individually and compared with average weight and calculate the standard deviation.

Thickness[17]

The thickness of the tablet was measured by using digital verniercaliper, twenty tablets from each batch were randomly selected and thicknesses were measured.

Hardness[18]

Hardness was measured using Pfizer hardness tester, for each batch three tablet were tested.

Friability[19]

Ten tablets were weighed and placed in a Roche friabilator and the equipment was rotated at 25 rpm for 4 min. The tablets were taken out, dedusted and reweighed. The percentage friability of the tablets was measured as per the following formula,

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

Wetting time[16, 17]

Wetting time is an important step in the disintegration process. Wetting is closely related to the inner structure of tablet and to the hydrophilicity of excipients. The method reported by Yunexia was used to measure tablet wetting time.[8] A piece of tissue paper folded twice was placed on the distilled water (6ml) which was taken in a small petridish (6.5cm diameter).One tablet was placed on the paper and the time for complete wetting of the tablet was measured.

Water absorption ratio[17]

A piece of tissue paper folded twice was placed in a small petri dish containing6ml of water. A tablet was put on the paper and time required for complete wetting wasmeasured. The wetted tablet was then weighed. Water absorption ratio, R was determinedusing following equation.

$$R = 100\ (Wa - Wb)/Wb$$

Where, Wb – weight of tablet before absorption

Wa – weight of tablet after absorption

Three tablets from each formulation were performed and standard deviation was also determined

***In vitro* Disintegration Test [17, 18]**

The process of breakdown of a tablet into smaller particles is called as disintegration. The *in vitro* disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specifications. Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using pH 6.8 phosphate buffer maintained at 37 ±2 °C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the pH 6.8 phosphate buffer maintained at 37 ±2 °C. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

***In vitro* drug release studies[19]**

In Vitro dissolution studies for all the prepared tablets were carried out using USP paddle method at 50 rpm in 900 ml of 6.8 pH phosphate buffer as dissolution media, maintained at 37 ± 0.5º. 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 223nm. An equal volume of pre warmed (37ºC) 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 (Figure-2 & 3).

Results and Discussion

Twelve formulations of Metoprolol Tartrate were prepared with concentration of three superdisintegrants: Isapgol husk, Croscarmellose sodium, Sodium Starch glycolate and Avicel 102 were used as a direct compressible vehicle. For each formulation, blend of drug and excipients were prepared and evaluated for various parameters as explained earlier. The powder blend was compressed using direct compression technique. The power blends were evaluated for their flow and compression properties in comparison. The angle of repose of co-processed superdisintegrant was found to be $<30^0$ which indicate good flow in comparison to physical mixture of excipients ($<30^0$) due to granule formation, bulk density in the range of 0.49 to 0.54 g/cc, tapped density in the range of 0.61 to 0.65 g/cc, Carr's index in the range of 13 to 17 % and Hausner's ratio in the range of 1.15 to 1.21 these results data shown in table no 2.

The data obtained from post-compression parameters such as hardness, friability, thickness, drug content, water absorption ratio, wetting time, and *in-vitro* disintegration time. The results are shown in table no. 3 and 4. In all the formulations, hardness test indicated good mechanical strength results were ranges from 2.6 to 3.8 kg/cm^2, friability is less than 1%, ranges from 0.56 to 0.77% indicated that tablets had a good mechanical resistance. Thickness of the tablets range from 2.55 to 3.62 mm. Drug content was found to be in the range of 97.47 to 100.59 %, which is within acceptable limits. The 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 71 to 85% and 35 to 68 sec respectively. The *in-vitro* disintegration time were found to be in the range of 18 to 46 sec. The graphical representation of comparison of *in-vitro* disintegration time and wetting time were shown in Figure no. 1. Among all the designed formulations, formulation F4 was found to be promising and was displayed an *in-vitro* dispersion time, which facilitates its faster dispersion in the mouth. The formulations F4 containing 12% Isapgol husk was found to be promising and has shown an *in-vitro* disintegrating time of 18 sec, wetting time of 35 sec when compared to the other formulations. The dissolution profile of prepared formulations shown in figure no. 2 and 3.

Conclusion

In the present work Melt-in-mouth tablets of Metoprolol tartrate were prepared by direct compression methods using superdisintegrants such as Isapgol husk, sodium starch glycolate and cross carmellose sodium**.** Among the formulations the most promising one is F4 containing 12% Isapgol husk showing 99.45% drug release indicating better drug release and improved bioavailability. So it was concluded that sublimation method along with superdisintegrant addition was excellent method in formulation of fast dissolving tablets of Metoprolol Tartratewhich gives quick relief from Myocardial infarction.

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Table 1: Composition of Melt-in-mouth tablets of Metoprolol Tartrate

Ingredients (Mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Metoprolol Tartrate	25	25	25	25	25	25	25	25	25	25	25	25
Isapgol husk	6	12	18	24	-	-	-	-	-	-	-	-
CCS	-	-	-		6	12	18	24	-	-	-	-
SSG	-	-	-	-	-	-	-		6	12	18	24
Lactose	45	45	45	45	45	45	45	45	45	45	45	45
Aspartame	5	5	5	55	5	5	5	5	5	5	5	5
Talc	4	4	4	4	4	4	4	4	4	4	4	4
Mg. stearate	2	2	2	2	2	2	2	2	2	2	2	2
Avicel ph 102	113	107	101	95	113	107	101	95	113	107	101	95
Total weight	200	200	200	200	200	200	200	200	200	200	200	200

Table 2: **Pre-compression parameters of powder blend**

Formulation code	Bulk density (g/cc) ±SD, n=3	Tapped density (g/cc) ±SD, n=3	Angle of repose (degree) ±SD, n=3	Carr's Index (%) ±SD, n=3	Hausner's Ratio ±SD, n=3
F1	0.49 ± 0.007	0.65 ± 0.01	29.25 ± 1.56	17 ± 1	1.30 ± 0.03
F2	0.52 ± 0.007	0.62 ± 0.01	28.02 ± 1.20	16 ± 1.51	1.19± 0.04
F3	0.53 ± 0.007	0.61 ± 0.02	29.11 ± 1.70	13 ± 1.20	1.15 ± 0.03
F4	0.53 ± 0.007	0.64 ± 0.01	30.20 ± 0.88	17 ± 2.51	1.20 ± 0.03
F5	0.50 ± 0.007	0.63 ± 0.01	26.43 ± 1.48	20 ± 1.58	1.26 ± 0.03
F6	0.54 ± 0.007	0.65 ± 0.02	27.72 ± 1.22	16 ± 1.55	1.20 ± 0.04
F7	0.52 ± 0.007	0.63 ± 0.38	29.87 ±1.32	17 ± 1.39	1.21 ± 0.04
F8	0.51 ± 0.007	0.62 ± 0.02	29.04 ± 1.34	17 ± 2.20	1.21 ± 0.03
F9	0.52 ± 0.007	0.62 ± 0.02	30.03 ± 1.56	16 ± 1.20	1.19 ± 0.04
F10	0.53 ± 0.007	0.63 ± 0.01	29.72 ± 1.41	15 ± 1.67	1.18 ± 0.02
F11	0.51 ± 0.007	0.62 ± 0.02	28.85 ± 1.33	17 ± 1.41	1.21 ± 0.03
F12	0.53 ± 0.007	0.64 ± 0.02	28.14 ± 1.67	17 ± 2.51	1.20 ± 0.03

* mean ± S.D., n=3 (all the values are the average of three determinations)

Table 3: Post compression parameters of prepared formulations

Formulation code	Weight variation ±SD, n=3	Hardness (Kg/cm^2) ±SD, n=3	Friability (%) ±SD, n=3	Thickness (mm) ±SD, n=3
F1	200±1.05	3.3±0.14	0.69±0.03	2.92±0.12
F2	201±1.02	3.0±0.11	0.75±0.07	3.35±0.09
F3	200±0.99	2.8±0.16	0.71±0.05	3.50±0.05

F4	200±1.15	2.6±0.15	0.77±0.03	3.62±0.08
F5	198±1.32	3.5±0.13	0.64±0.01	2.78±0.05
F6	199±1.10	3.6±0.15	0.59±0.06	2.70±0.02
F7	199±1.32	3.2±0.12	0.67±0.05	3.05±0.09
F8	200±1.14	3.0±0.20	0.75±0.06	3.34±0.10
F9	202±1.15	3.8±0.28	0.56±0.08	2.55±0.26
F10	201±1.33	3.5±0.19	0.63±0.05	2.75±0.15
F11	198±1.52	3.3±0.09	0.68±0.03	2.90±0.07
F12	202±1.18	3.3±0.17	0.68±0.09	3.13±0.12

* mean ± S.D., n=3 (all the values are the average of three determinations)

Table 4: Post compression parameters of prepared formulations

Formulation Code	Drug content* (%) ±SD, n=3	*In vitro* disintegration time* (sec) ±SD, n=3	Wetting time* (sec) ±SD, n=3	Water absorption ratio* (%) ±SD, n=3
F1	98.31±0.94	26±1.4	55±1.05	70±0.15
F2	99.11±1.7	22±2.7	48±1.6	76±1.14
F3	97.65±1.3	21±1.5	41±1.4	80±1.07
F4	100.59±1.1	18±1.3	35±1.3	85±0.20
F5	98.62±0.52	39±1.4	63±0.3	71±0.15
F6	97.47±0.22	33±2.0	54±1.1	74±0.12
F7	98.86±1.6	27±1.3	47±1.3	76±1.18
F8	99.19±0.74	23±1.8	43±1.6	81±0.14
F9	99.58±1.8	46±1.5	68±1.3	68±1.03
F10	97.90±0.51	40±1.1	60±1.5	64±0.50
F11	98.53±0.11	36±1.8	55±1.6	73±1.14
F12	99.65±1.70	29±1.03	50±1.2	78±1.20

* mean ± S.D., n=3 (all the values are the average of three determinations)

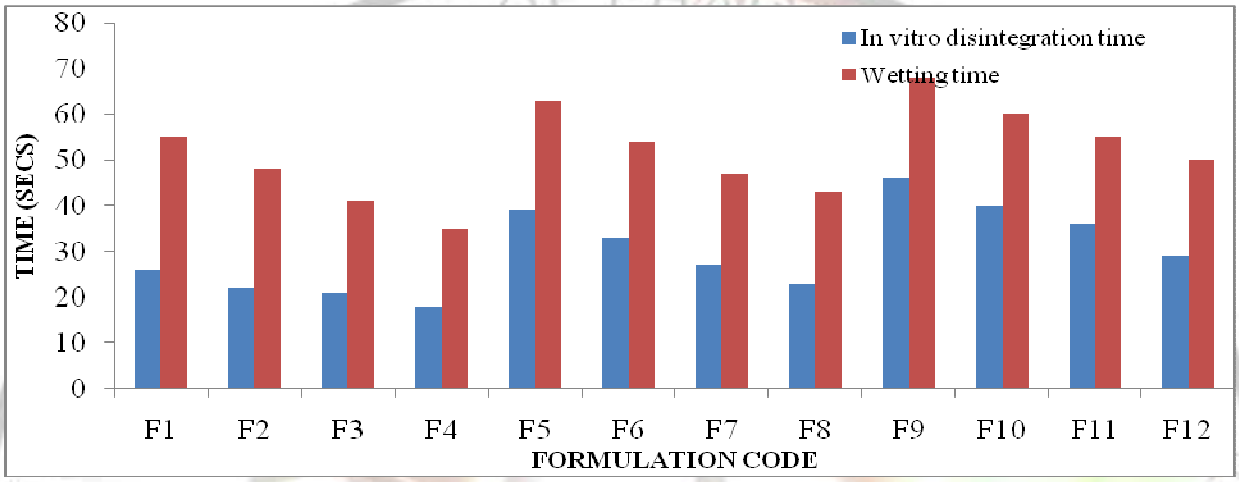

Fig. 1: Comparison between *in vitro* disintegration time and wetting time of Metoprolol Tartrate

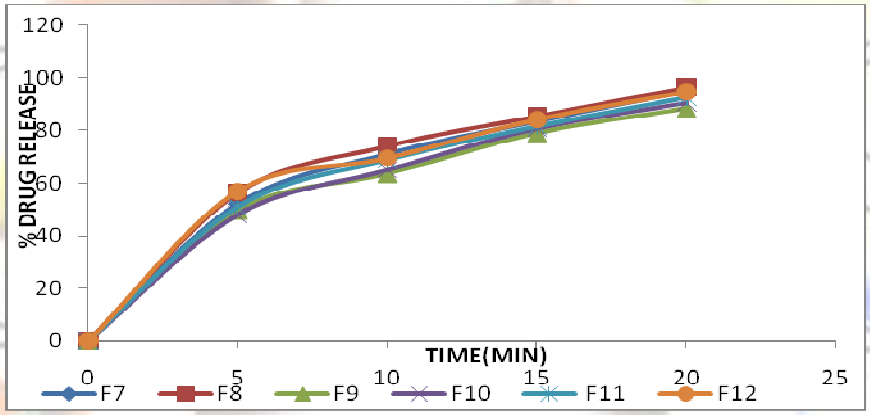

Fig. 2: Cumulative % drug Release Vs Time in min from prepared batches F-1, F-2, F3, F-4 F-5 & F-6 of Melt-in-mouth tablets of Metoprolol Tartrate prepared by direct compression method

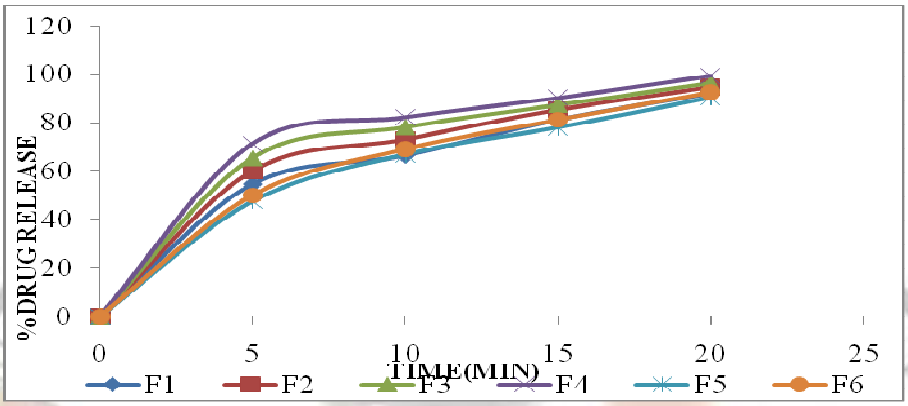

Fig. 3: Cumulative % drug Release Vs Time in min from prepared batches F-7, F-8, F-9, F-10, F-11 & F-12 of Melt-in-mouth tablets of Metoprolol Tartrate prepared by direct compression method.