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Formulation and evaluation of fast disintegrating tablets of metoprolol succinate using various superdisintegrants

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ABSTRACT

The aim of present work is to develop a fast disintegrating solid oral dosage form of Metoprolol succinate. The concept of fast dissolving drug delivery system emerged from the desire to provide patient with more conventional means of taking their medication. Problems associated with conventional tablets can be resolved by means of fast dissolving tablets when put on tongue these tablets disintegrate and dissolve rapidly in saliva without need of drinking water. The faster the drug disintegrates in to solution, the quicker the absorption and onset of clinical effect. Preformulation results reveal that the flow properties of the active pharmaceutical ingredient were found to be excellent as per IP limits. To perform drug-polymer compatibility FT-IR studies were carried out and observed that there was no interaction between the APl and excipients. Eight formulations were prepared with varying super disintegrating agent ratios and were found that as the level of super disintegrating agent decreased the drug release rates were found to be increased. Amongst all the formulations, formulation containing CCS (F4) as super disintegrant is fulfilling all the parameters satisfactorily. It has shown excellent in-vitro disintegration, in-vitro dissolution compared to other formulations. The prepared tablets disintegrate within few minutes without need of water; thereby enhance the absorption leading to its increased bioavailability. It was concluded that Fast Disintegrating tablets of Metoprolol can be prepared successfully as it satisfies all the criteria as a dispersible tablet and would be alternative to the currently available conventional tablets. Prepared formulations were stable during 90 days storage period at controlled 40°C and 75%RH.

Keywords: Metoprolol succinate; oral disintegration tablets; fast dissolving tablets; superdisintegrants.

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INTRODUCTION

Today drug delivery companies are focusing on solid oral drug delivery systems that offer greater patient compliance and effective dosages[1]. Tablet is the most popular among all dosage forms existing today because of its convenience of self-administration, compactness and easy manufacturing. Many patients find it difficult to swallow tablets and hard gelatin capsules and do not take their medication as prescribed. The difficulty is experienced in particular by pediatric and geriatric patients, but it also applies to people who are ill in bed and to those active working patients who are busy or traveling, especially those who have no access to water[2]. Over a decade, the demand for development of oral disintegrating tablets (ODTs) has enormously increased as it has significant impact on the patient compliance. ODTs with good taste and flavor increase the acceptability of bitter drugs by various groups of population. Oral disintegrating tablets are also called as orodispersible tablets, quick disintegrating tablets, mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets and rapimelts. However, of all the above terms, United States pharmacopoeia (USP) approved these dosage forms as ODTs[3]. Recently, European Pharmacopoeia has used the term orodispersible tablet for tablets that

disperses readily and within 3 min in mouth before swallowing.

MATERIALS AND METHODS

Metoprolol succinate was a gift sample from Cipla Labs, Chennai and Cross Carmellose Sodium, Sodium starch Glycollate, Carbopol, Polyvinyl pyrrolidone were obtained from Loba Chemie, Mumbai. All other chemicals used were of analytical grade.

Pre formulation parameters

Angle of Repose: The flow property was determined by measuring the Angle of Repose. In order to determine the flow property, the Angle of Repose was determined. It is the maximum angle that can be obtained between the free standing surface of a powder heap and the horizontal.

$$\text{Angle of repose} = tan^{-1}\frac{h}{r}$$

Where,

h = height of a pile (2 cm)

r = radius of pile base.

Bulk density: Bulk density is ratio of given mass of powder and its bulk volume. Bulk density was determined by measuring the volume of known mass of powder sample that has been passed through the screen in to graduated cylinder or through volume measuring apparatus in to cup.

$$\text{Bulk density} = \frac{M}{V_o}$$

Where M= mass of the powder

V0=bulk volume of the powder.

Tapped density: A known quantity of powder was transferred to a graduated cylinder and volume V0 was noted. The cylinder fixed to a density determination apparatus, tapped for 500 times then reading was observed. The density is achieved by mechanically tapped by a measuring cylinder containing the powder sample. After observing the initial volume the cylinder is mechanically tapped and volume reading were taken until little further volume changes is observed[4].

$$\text{Tap density} = \frac{M}{V_r}$$

Where M = mass of the powder,

Vr = final tapping volume of the powder.

Compressibility index and Hausner ratio: The compressibility index and Hausner ratio may be calculated using measured values of bulk density and tapped density as follows:

$$\text{Compressibility index} = \frac{Tapped\ density}{Bulk\ density} \times 100$$

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

Drug excipient compatibility studies

Standard calibration curve of the metoprolol succinate: 100 mg of Metoprolol was weighed accurately into 100 ml volumetric flask and dissolved in small quantity of pH 6.8 Phosphate buffer, the volume was made up with the pH 6.8 Phosphate buffer. Pipette 10ml of the solution into another 100ml volumetric flask and the volume was made with the pH 6.8 Phosphate buffer (i.e.: 100µg/ml in pH 6.8 Phosphate buffer). Aliquots of standard solution 1ml, 2ml, 3ml, 4ml, 5ml were pipette into 10ml volumetric flasks. The volume made up with pH 6.8 Phosphate buffer. The absorbance of each concentration was measured at 223 nm using UV-Visible spectrophotometer against pH 6.8 Phosphate buffer as a blank[5].

Fourier Transform Infrared Spectroscopy (FT-IR)

Infrared radiation can be worked in two different ways, either the radiation is absorbed by the sample or it can passed through the sample. FT-IR results represent the molecular absorption and transmission of the sample which gives a fingerprint image of the sample. So for different samples it carries unique spectra and gives the blue print of the sample. This characterization is very useful for analysis of number of samples[7]. In FTIR analysis sample has been analysed in the wave number between 4000-400 cm-1.KBr pallets is prepared for the FTIR analysis. KBr is added with the sample and finally pallet has been formed and submitted to the FTIR analysis. Potassium bromide (KBr) is the commonest alkali halide used in the pellets due to its high transparency. FT-IR analysis can be used for the identification of unknown materials, determination of quality and compatibility of the sample in a mixture.

Formulation of Metoprolol succinate Fast Dissolving Tablets

Micro crystalline cellulose, Crosscarmellose sodium, sodium starch glycolate, Crosspovidone, and PVP were weighed and sifted through 40 mesh. To the above blend Metoprolol succinate, saccharin was added and sifted through 18 mesh. The sifted material was placed in poly bag and mixed for 5 min. To the above blend add Magnesium stearate and Aerosil, and this lubricated blend was added to mint flavor and placed in poly bag and mixed for 2-3 min. The lubricated blend was compressed using 8 mm round punches[6].

Post compression parameters

Physical Appearance: The general appearance of a tablet, its identity and general elegance is essential for consumer acceptance, for control of lot-to-lot uniformity and tablet-to-tablet uniformity. The control of general appearance involves the measurement of size, shape, colour, presence or absence of odour, taste etc.

Size& Shape: It can be dimensionally described & controlled. The thickness of a tablet is only variables. Tablet thickness can be measured by micro-meter or by other device. Tablet thickness should be controlled within a ± 5% variation of standard value.

Weight variation test: Twenty tablets were weighed individually and the average weight was calculated. The individual tablet weights are then compared to the average weight. Not more than two tablets should differ in their average weight by more than percentages stated in USP. No tablet must differ by more than double the relevant percentage.

Content Uniformity: Randomly select 30 tablets. 10 of these assayed individually. The Tablet pass the test if 9 of the10 tablets must contain not less than 85% and not more than 115% of the labeled drug content and the 10th tablet may not contain less than 75% and more than 125% of the labeled content. If these conditions are not met, remaining 20 tablets assayed individually and none may fall outside of the 85 to 115% range.

Thickness and diameter: The thickness and diameter of 10 tablets were recorded during the process of compression using vernier calipers.

Hardness: Hardness, which is the force required to break the tablet is measured in kilograms. The small and portable hardness tester measures the force required to break the tablet when the force generated by a coil spring is applied diametrically to the tablet.

Friability: A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked.

The percentage friability was determined by the formula:

$$\% \text{ Friability} = \frac{(W_1 - W_2)}{W_2} \times 100$$

W_1 = Weight of tablets before test

W_2 = Weight of tablets after test

Disintegration test: The U.S.P. device to test disintegration uses 6 glass tubes that are open at the top and 10 mesh screen at the bottom end. To test for disintegration time, one tablet is placed in each tube and the basket rack is positioned in a 1-L beaker of water, simulated gastric fluid or simulated intestinal fluid at 37 ± 2^0C such that the tablet remain 2.5 cm below the surface of liquid on their upward movement and not closer than 2.5 cm from the bottom of the beaker in their downward movement. Move the basket containing the tablets up and down through a distance of 5-6 cm at a frequency of 28 to 32 cycles per minute. Floating of the tablets can be prevented by placing perforated plastic discs on each tablet. According to the test the tablet must disintegrate and all particles must pass through the 10 mesh screen in the time specified. If any residue remains, it must have a soft mass. If one or two tablets fail to disintegrate, the test is repeated using 12 tablets[7].

Disintegration time: Uncoated tablet: 5-30 minutes.

Coated tablet: 1-2 hours

Table 1: Results of Pre-Compression Parameters

S.No	Parameter	Result
1	Angle of repose	28.98 ± 0.13
2	Bulk density	0.463 ± 0.31
3	Tap density	0.509 ± 0.27
4	Compressibility index	9.03 ±0.63
5	Hausner ratio	1.09 ± 0.12

Dissolution studies

The dissolution test was carried out in USP Apparatus Type II (paddle) with 0.1 N Hydrochloric acid as the dissolution medium. The samples were drawn at 5, 10, 15, 20 and 30 min. Fresh volume of the medium were replaced with the withdrawn volume to maintain the sink conditions. Samples withdrawn were analyzed for the percentage of drug released.

Dissolution Parameters

Dissolution Apparatus	USP Apparatus Type II (Paddle)
Dissolution Medium	0.1N Hydrochloric acid
Volume	900 ml
Temperature	37±2°C
Rpm	50
Sampling Intervals (min)	5, 10, 15, 20 &30min

RESULTS AND DISCUSSION

Pre-formulation study: Weight variation has shown almost similar to all the formulations as the total weight taken is 200 mg for the tablets. Friability percentage varies according to the concentrations of the super disintegrants and F4 has shown the value of 0.74. Hardness is compared all the formulations where F4 has shown the best result of 3.82 as it gives the optimum hardness which facilitates the disintegration of oral disintegration tablet. Thickness measured using Vernier calipers which varies among all the formulations and optimized formulation is F4.

Wetting time is calculated as per the IP for all the formulations and more time taken for the formulation F1 i.e. 22 sec as it implies to the disintegration and dissolution. Best result is obtained for the formulation F4 which has shown 15 sec which facilitates the disintegration. Assay is calculated for all the formulations F4 has shown the good result. The most im

Table 2: Formulation Developmental Trails

Ingredients (%)	F1	F2	F3	F4	F5	F6	F7	F8
Metoprolol (mg)	25	25	25	25	25	25	25	25
CCS	5	-	-	7.5	10	12.5	-	-
SSG	-	5	-	-	-	-	10	-
CP	-	-	5	-	-	-	-	10
Aerosil	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
PVP	5	5	5	5	5	5	5	5
Sodium saccharin (mg)	5	5	5	5	5	5	5	5
Magnesium Stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
MCC	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Mint Flavor	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total (mg)	200	200	200	200	200	200	200	200

portant parameter which is evaluated for oral disintegration tablet is disintegration time which compared for all the formulations. Its ability to perform effectively as an ODT should be justified based on product performance. For such products, the extent of component solubility (e.g., tablet residue, need for liquids) can influence the acceptability of the product being labeled as an ODT. Disintegration time for ODT generally ranges from few sec to less than a minute. Dissolution studies were carried out for all the formulations a s per IP and among all the formulations F4 formulation which is composed of Crosscarmellose sodium as a superdisintegrant has shown the best release in 30 sec.

Table 3: Calibration table of Metoprolol Succinate

Concentration(µg/ml)	Absorbance at 223 nm
2	0.112
4	0.224
6	0.312
8	0.416
10	0.518
12	0.614
14	0.708

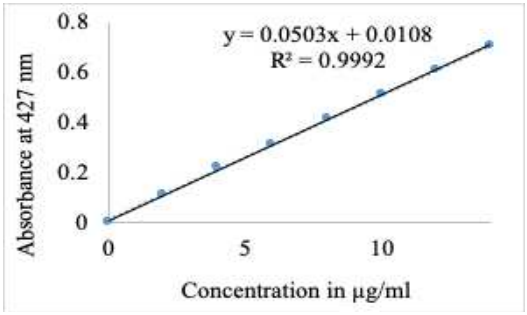

Figure 1: Calibration graph of Metoprolol Succinate

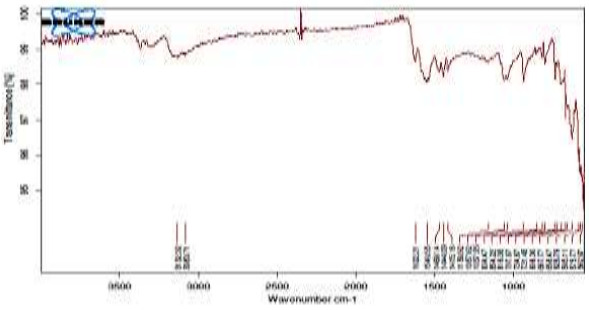

Figure 2: FT-IR spectrum of Metoprolol Succinate

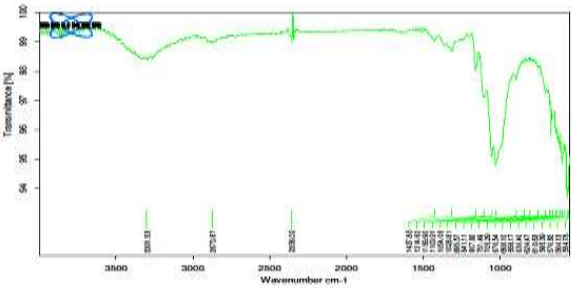

Figure 3: FT-IR spectrum of Metoprolol Succinate and MCC

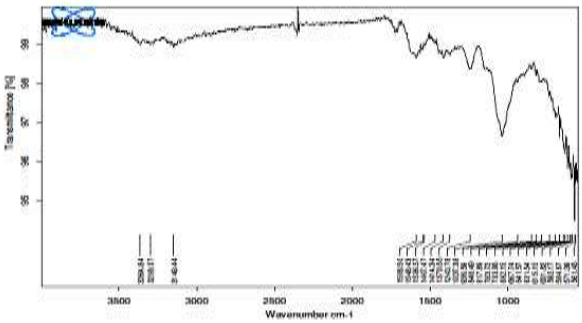

Figure 4: FT-IR spectrum of Metoprolol Succinate and CCS

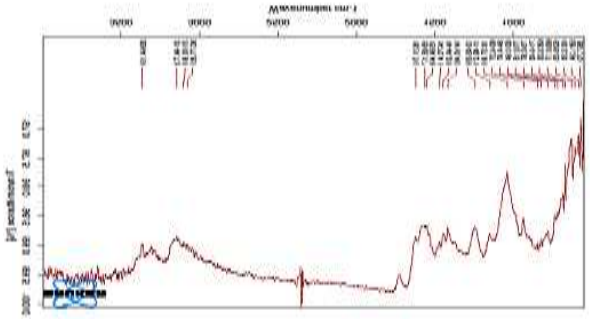

Figure 5: FT-IR spectrum of Metoprolol Succinate and CP

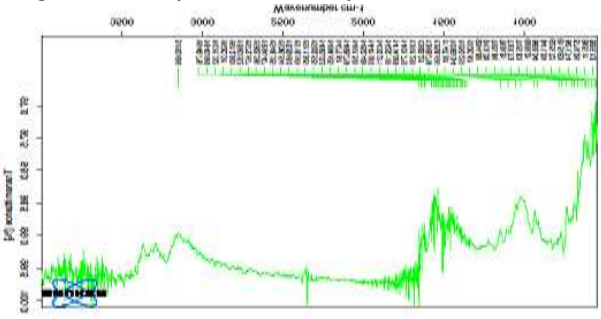

Figure 6: FT-IR spectrum of Metoprolol Succinate and SSG

Table 4: Results of post compression parameters

Parameters	F1	F2	F3	F4	F5	F6	F7	F8
Weight variation	200±0.92	201±0.91	200±0.92	200±0.92	201±0.91	201±0.91	200±0.92	200±0.92
Friability	0.65	0.59	0.90	0.74	0.70	0.65	0.87	0.64
Hardness	4.26±0.68	4.12±0.94	4±0.53	3.82±0.54	3.7±0.62	3.6±0.37	3.4±0.37	3.36±0.37
Thickness	4.32±0.42	4.24±0.36	4.1±0.26	3.93±0.28	3.82±0.62	3.61±0.48	3.42±0.32	3.21±0.26
Wetting time	38±1.5	28±1.3	22±1.4	15±1.8	32±1.3	34±1.2	33±1.4	26±1.6
Disintegration time	46±1.1	45±1.4	40±1.7	35±1.3	31±2.6	35±3.8	22±4.2	20±1.2
Assay	93.6±0.99	93.8±0.98	94.2±1.0	98..6±0.91	95.1±0.98	93.2±0.98	93.8±0.92	98.3±092

Table 5: Dissolution time

Time	F1	F2	F3	F4	F5	F6	F7	F8
5	89.2	89.8	91.2	91.7	91.9	92.3	92.3	92.9
10	91.6	91.9	92.6	92.8	93.8	94.2	94.6	94.9
15	92.2	92.6	92.8	93.1	93.2	94.4	94.6	95.2
20	94.4	94.6	95.1	95.3	95.6	96.1	96.2	96.3
25	95.2	95.5	95.8	96.9	96.1	96.3	96.6	98.1
30	96.2	96.5	96.8	98.9	97.1	97.3	97.6	97.8

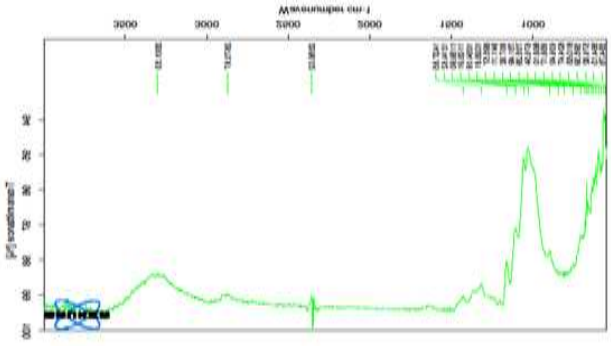

Figure 7: FT-IR spectrum of Metoprolol Succinate and PVP

CONCLUSION

Fast disintegrating Tablets of Metoprolol succinate using super disintegrating agents were found to be good without chipping, capping and sticking. The drug content was uniform in all the formulations of tablets prepared. FT-IR studies indicated that the drug is compatible with the disintegrants. The drug and super disintegrating agent ratio was found to influence the release of drug from the formulations. As the level of super disintegrating agent decreased the drug release rates were found to be increased. Amongst all the formulations, formulation containing CCS as super disintegrant is fulfilling all the parameters satisfactorily. It has shown excellent *in vitro* disintegration, *in vitro* dissolution, compared to other formulation. The prepared tablets disintegrate within few minutes without need of water; thereby enhance the absorption leading to its increased bioavailability. It was concluded that Fast Disintegrating tablets of Metoprolol can be prepared successfully as it satisfies all the criteria as a dispersible tablet and would be alternative to the currently available conventional tablets. Prepared formulations were stable during 90 days storage period at controlled 40°C and 75%RH.

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