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Formulation and Evaluation of Oral Disintegrating Tablets of Metaprolol

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A B S T R A C T

Oral disintegrating tablets of Metoprolol succinate, a ß1-adrenergic blocker and antihypertensive agent, have been prepared from Sodium Starch Glycolate, Crospovidone, Croscarmellose sodium, Microcrystalline Cellulose, D-Mannitol, Aerosil solution by direct compression method. In the present study, the oral disintegrating tablets of the drug was prepared using various super disintegrates such as Sodium Starch Glycolate, Crospovidone, Croscarmellose sodium, Microcrystalline Cellulose in various proportions following by direct compression technique. The tablets were evaluated for hardness, friability, weight variation, disintegration time, water absorption ratio and wetting time, in vitro dissolution studies. All the formulation showed rapid disintegration time along with rapid in vitro dissolution. It was concluded that the oral disintegration tablets of the poor soluble drug can be made by direct compression technique using selective super disintegrants showing enhanced dissolution, taste masking and hence better patient compliance and effective therapy.

Keywords: Metoprolol succinate, oral disintegrating, Superdisintegrants, Taste masking

A R T I C L E I N F O

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1. Introduction

Despite tremendous innovations in drug delivery, the oral route remains the preferred route for administration of therapeutic agents because of accurate dosage, low cost therapy, self medication, noninvasive method, and ease of administration leading to high level of patient compliance[1]. The most popular dosage forms are conventional tablets and hard gelatin capsules. One important drawback of such dosage forms is "dysphagia" or difficulty in swallowing for many patients; almost 50% of the population is affected by such problem. Hence, patients do not comply with prescription, which results in high incidence of noncompliance and ineffective therapy [2]. Recently, fast disintegrating drug delivery systems have started gaining popularity and acceptance as new drug delivery systems, because they are easy to administer and lead to better patient compliance[3]. In some cases such as motion sickness, sudden episodes of allergic attacks or coughing, and unavailability of water, swallowing conventional tablets may be difficult. Particularly the difficulty is experienced by pediatric and geriatric patients. To overcome such problems, fast disintegrating tablets or orally disintegrating tablets have emerged as an alternative dosage form [4]. Recent advances in novel drug delivery systems (NDDS) aim for enhancing the safety of a drug molecule while maintaining its therapeutic efficacy so as to achieve better patient compliance [5].

Metoprolol succinate which is used in the treatment of hypertension, angina and arrhythmia has an absorption window and is mainly absorbed from the upper parts of GIT, and good stability in the acidic environment of the stomach makes it a suitable candidate to formulate in an oral disintegrating tablet. Moreover it has a half-life of 3-7 hours[6], making repetitive dosing necessary. Therefore a fast disintegrating drug delivery system with less first pass metabolism effect i.e., oral disintegrating dosage form which improves the bioavailability of the drug was opted-for. The bioavailability of drugs may be increased due to absorption of drug in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. Moreover, the amount of drug that is subjected to first-pass metabolism is reduced as compared to standard tablet[7]. The target populations for these new fast-dissolving/ disintegrating dosage forms have generally been pediatric, geriatric, and bedridden or mentally disabled patients. Patients with diarrhea, persistent nausea, or vomiting,who are traveling, or who have little or no access to water are also good candidates for FDTs[8]. The aim of the proposed work was to formulate and characterize fast oral disintegrating tablets of metaprolol for rapid dissolution of drug and absorption, which may produce rapid onset of action in the management of hypertension in elderly patients.

2. Materials and Methods

Metoprolol succinate, [1-(Isopropylamino)-3-[4-(2-methoxyethyl) phenoxy] propan-2-ol] was a gift sample from Dr. Reddy's Laboratories (Hyderabad, India). Sodium Starch Glycolate, Crospovidone, Croscarmellose sodium, Microcrystalline Cellulose, D-Mannitol, Aerosil and citric acid were purchased from SD Fine chem, Mumbai. All other chemicals used were of analytical grade and purchased from SD Fine Chem. Mumbai.

Preparation of the oral disintegration tablets by direct compression method:

Each tablet (weight 200mg) consisted of Metaprolol, superdisintegrants such as cross povidone, sodium starch glycolate (SSG), croscarmellose sodium, mannitol, Micro crystalline cellulose, citric acid, talc and colloidal silicon dioxide (aerosil), prepared by direct compression method. The drug, diluent, superdisintegrant, Mannitol are passed through the sieve no. 40. All the ingredients are mixed well for 15 min in the motor. Then mixed with lubricant (4 mg) for 3 min in a mortar. The mixture was compressed by using 10 mm concave punches on eight station rotary tablet compression machine. Seven formulations (F1-F7) were prepared and their compositions were as shown in table 1.

Table 1: Composition of oral disintegrating tablets prepared by direct compression method

Ingredients	F1	F2	F3	F4	F5	F6	F7
Metaprolol	50mg	50mg	50mg	50mg	50mg	50mg	50mg
Sodium starch glycolate	10mg	15 mg	-	-	-	-	-
Crospovidone	-	-	10mg	15mg	-	-	-
Crosscarmellose sodium	-	-	-	-	10mg	15mg	-
Mannitol	108mg	108mg	108mg	108mg	108mg	108mg	108mg
Aerosil	1mg	1mg	1mg	1mg	1mg	1mg	1mg
Citric acid	3mg	3mg	3mg	3mg	3mg	3mg	3mg
Microcrystlline cellulose	24mg	19mg	24mg	19mg	24mg	19mg	34mg
Talc	4mg	4mg	4mg	4mg	4mg	4mg	4mg
Total wt of tablet (mg)	200	200	200	200	200	200	200

Pre compression parameters:

Preformulation testing is the first step in the rational development of dosage forms of a drug. It can be defined as an investigation of physical and chemical properties of drug substance, alone and when combined with excipients. A complete evaluation of physicochemical properties may provide a rationale for designing the formulation or support the need for molecular modification or merely confirm that

there are no significant barriers to the compound development.

Angle of Repose

The angle of repose was measured by passing the prepared granules through a sintered glass funnel of internal diameter 27 mm on the horizontal surface. The height (h) of the heap formed was measured with a cathetometer, and the radius (r) of the cone base was also determined. The angle of repose (Θ) was calculated from equation

Angle of repose (Θ) = $\tan^{-1}h/r$

Bulk density

The term bulk density refers to a measure used to describe a packing of particles. It is expressed in gm/ml and was determined using a balance and measuring cylinder. Initially the weight of the measuring cylinder was tarred. Then, 4 gm presieved (40#) bulk drug were poured into the measuring cylinder using a funnel and weighed (M). Then volume of the powder (Vb) was taken. Bulk density of the granules was calculated using following formula.

Bulk density = M/Vb

Tapped density

Blend was tapped for a fixed number of taps. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density was calculated using following formula.

Tapped density = M/ Vt

Compressibility (Carr's) Index

An accurate weight of granules was poured into a volumetric cylinder to occupy a volume (V_0) and then subjected to a standard tapping procedure onto a solid surface until a constant volume was achieved (V_f). The Carr's index was calculated using equation

Hausner ratio

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

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

Drug polymer compatibility studies:

FTIR studies:

A physical mixture containing pure drug and pure polymers with ratio of 1:1was transferred into a screw capped bottle and stored at 40 ± 2^o C RH 65% for a period of 1 month. After the study period, the samples were subjected for FTIR analysis. The study was performed on Fourier transformer infrared spectrophotometer Bruker. The samples (drug, polymers and physical mixtures) were prepared on KBr-press. The samples were scanned over wave number range of 4000 to 400 cm^{-1}. Spectra were analyzed for drug polymer interactions and functional groups.

Post compression parameters

Hardness:

The tablet hardness, which is the force required to break a tablet in a diametric compression force. The hardness tester used in the study was Monsanto hardness tester, which applies force to the tablet diametrically with the help of an inbuilt spring. It is expressed in Kg / cm^2.

Friability:

Friability of the tablets was determined using Roche friability (Electrolab, Mumbai). This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Preweighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dedusted using a soft muslin cloth and reweighed.

The friability (f) is given by the formula.

$f = (1- W_0 / W) \times 100$

Where, W_0 is weight of the tablets before the test and

W is the weight of the tablet after the test

Weight variation test:

Weight variation test was carried out as per IP. Twenty tablets were randomly selected and individually weighed. The average weight and standard deviation was calculated.

***In vitro* disintegration time:**

The disintegration time of the tablet was measured in water (37±2°C) according to disintegration test apparatus with disk. The time in seconds taken for the complete disintegration of the tablet with no palpable mass in the apparatus was measured in seconds. Three tablets from each batch (formulation) were tested for the disintegration time calculations.

Wetting time:

The wetting time of the tablets can be measured using a simple procedure. Five circular tissue papers of 10 cm diameter are placed in a Petri dish with a 10 cm diameter. Ten millimeters of water containing Eosin, a water soluble dye, is added to Petri dish. A tablet 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.

Water absorption ratio:

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper and the time required for complete wetting was measured. The wetted tablet was then weighed. Results are shown in Table 14 and Fig. 19.Water absorption ratio (R) is calculated by using the equation.

$$R = 10 \times \frac{Wa - Wb}{Wb}$$

Where, Wa is the weight of the tablets before the test and

Wb is the weight of the tablet after water absorption.

***In vitro* dissolution profile:**

In-vitro drug release study was performed at 37±0.5°C using eight station USP type-II apparatus with paddle rotating at 50 rpm. The drug release study was carried out in Phosphate buffer pH 6.8 by taking about 900ml of the dissolution medium. The drug release study was performed in Phosphate buffer pH 6.8 to demonstrate the availability of Sumatriptan succinate. About 5 ml of sample was withdrawn at specified time intervals from the dissolution medium and replaced with equal volume of fresh medium. Samples were filtered through whattmann filter paper and analyzed using UV spectrophotometer (T60,PG Instruments) at 222 nm.

Stability studies:

The tablet formulations were packed in aluminum foil and were exposed to 40°C ± 2°C / 75% ± 5% RH in humidity control oven as per ICH guidelines118 Q1C: "Stability

testing of new dosage forms." Sampling was done at predetermined time intervals of 0, 30 and days.

3. Results and Discussion

The results of physicochemical evaluation of tablets are given in table 2 and 3. As the material was free flowing, tablets were obtained of uniform weight due to uniform die filling. Hardness of tablets was between 2.5-2.9 kg/cm^2 for all the formulations. The thickness was found in range of 2.20-2.43 mm. Friability was found in between 0.64-0.82%. The friability value below 1% was an indication of good mechanical resistance of the tablet. The drug content was found to be 98.23-99.62% which was within the acceptable limits. The results of pre formulation analysis was shown in table 2. Drug excipients were determined by FTIR studies and found to be compatible.

Table 2: Determination of flow properties of powder

Code	Bulk density g/cm^3	Tapped density g/cm^3	Angle of repose (Ɵ)	Carr's index %	Hausner's ratio
F1	0.56 ± 0.24	0.62 ± 0.08	21.70 ± 1.63	13.96 ±2.08	1.10±0.71
F2	0.55 ± 0.01	0.60 ± 0.06	22.88 ± 1.77	12.93 ±0.77	1.09±0.09
F3	0.55 ± 0.04	0.64 ± 0.12	20.76 ± 0.78	10.54 ±0.98	1.16±0.36
F4	0.56 ± 0.02	0.67 ± 0.04	22.94 ± 1.51	11.93± 0.98	1.17±0.64
F5	0.56 ± 0.01	0.68 ± 0.18	24.56 ± 0.70	13.86 ±1.42	1.13±0.42
F6	0.56 ± 0.24	0.65 ± 0.14	23.11 ± 0.44	12.20 ±0.42	1.16 ± 0.07
F7	0.53 ± 0.01	0.59 ± 0.02	22.70 ± 1.63	13.60 ±0.14	1.11 ± 0.32
Pure Drug	0.41 ± 0.14	0.55 ± 0.14	26.19 ± 0.48	23.54 ± 0.26	1.34 ± 0.82

Mean ± S.D (n=3)

Table 2: Evaluation of physico chemical properties

Formulation	Uniformity of Content (%)	Wetting time (sec)	Water absorption ratio (%)	Disintegration time (sec)
F1	98.78±0.14	26.93 ± 0.12	72.91±0.96	37.14 ± 0.17
F2	98.48±0.13	21.14 ± 0.27	76.48±0.59	29.01 ± 0.13
F3	99.62±0.23	19.93 ± 0.18	80.58±0.45	26.55 ± 0.21
F4	98.23±0.06	24.78 ± 0.31	75.98±0.49	21.16 ± 0.25
F5	99.57±0.01	23.82 ± 0.26	83.32±0.48	28.34 ± 0.12
F6	98.83±0.02	22.93 ± 0.12	81.25±0.75	26.34 ± 0.17
F7	98.52±0.05	20.14 ± 0.27	80.62±0.98	26.01 ± 0.13

Mean ± S.D (n=3)

The most important parameter that is needed to optimize during the development of oral dispersible tablets is disintegration time. Disintegration time is very important for ODT which is desired to be less than 60 sec. This rapid disintegration assists swallowing and also plays a role in drug absorption in buccal cavity. Dissolution of a tablet is dependent on wetting time and disintegration time. Measurement of wetting time may be another confirming test for evaluation of ODT thus promoting bioavailability. Wetting time is related to inner structure of tablet and hydrophobicity of components. Disintegration time is used as an indication from the ease of tablet disintegration in buccal cavity. The disintegration time is shorter with quick wetting properties at the core of the tablets. The wetting time decreases with increase in the concentration of superdisintegrants. It was observed that as the concentration of super disintegrants increases water absorption ratio increases and disintegration time decreases. Wetting time and water absorption ratio was influenced by nature of diluent and super disintegrants. Water absorption ratio was inversely proportional to disintegration time. CCS and CP when comes in contact with water it quickly wicks water into the tablet through capillary action to create internal pressure that disintegrates tablet. SSG has swelling tendency with a longer wetting time results in slower disintegration of tablets. The investigated superdisintegrants can be ranked according to ability to wick/swell in water as CP> CCS > SSG. The finding is in agreement with the results obtained from wetting time. The tablets prepared by crospovidone have disintegrated in 21.16 sec considered to be best formulation.

***In-vitro* release study:**

The *in-vitro* dissolution of Metaprolol tablets was studied in Phosphate buffer pH 6.8 using USP (Type-II) dissolution test apparatus by paddle method. Results showed that dissolution of tablets was proportionate with super disintegrant concentration. Also the results indicated that the dissolution profiles of tablet containing SSG, CCS and CP are in agreement with disintegration time. The rapid increase in the dissolution of Metaprolol with increase in polymer concentration of CP and CCS may be due to rapid wicking and disintegration of the tablet into primary particles. SSG exhibits swelling tendency with longer wetting time resulting in larger masses of aggregated particles leading to slower dissolution.

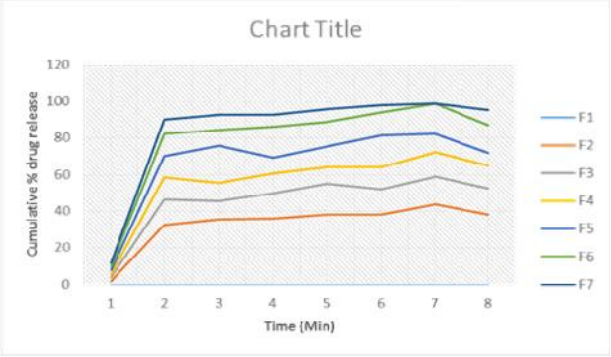

Figure 1: Cumulative % Drug release of Formulations (F1 – F7)

In-vitro release of Metaprolol orodispersible tablets of SSG (F1-F2) was proportionate to the concentration of super disintegrants. The release profile of orodispersible tablets containing 5%and7.5% of super disintegrant SSG were 90.1%, 92.65% respectively at the end of 12 min (Fig 1).

In-vitro release of Metaprolol oral dispersible tablets of CCS (F3-F4) was proportionate to the concentration of super disintegrants. The release profile of orodispersible tablets containing 5% and 7.5% of super disintegrant CCS were 92.66%, 95.78% respectively at the end of 12 min (Fig 1).

In vitro release of Metaprolol orodispersible tablets of CP(F5-F6) was proportionate to the concentration of superdisintegrants. The release profile of orodispersible tablets containing 5% and 7.5% w/w of super disintegrant CP were 97.78%, 98.93% respectively at the end of 12 min (Fig 1). The investigated super disintegrants can be ranked based on overall *in-vitro* release profile of Metaprolol ODT tablet i.e. CP > CCS > SSG. The results of dissolution profile of ODT were in accordance with that of disintegration data. Hence overall release data of ODT was proportionate with that of disintegration data irrespective of super disintegrants.

Stability Studies

The fabricated mouth dissolving formulation (optimized formulation F-4) was subjected to stability studies at 40^{o}c± 2^{o}c/75% RH ±5 % for 30 days. The product was evaluated for appearance and hardness. Drug excipient compatibility, drug content and drug release studies were conducted. Table 3 shows the storage conditions.

Table 3: Storage condition at 40 ^{o} c ±2^{o} c & 75% RH ±5%

Test	Inference after 30days
Wetting Time	17.93±0.18
Water Absorption Ratio	84.58±1.86
Disintegration Time	21.46±0.25

Table 4: Dissolution data of stability sample F7at accelerated condition

Time in (min)	(0days)	(30days)
0	0	0
2	43.98	42.83
4	59.16	58.02
6	72.5	72.45
8	82.44	81.79
10	98.56	98.45
12	98.93	98.69

The stability studies were carried out for selected tablet (F4) at 40^{o}C ± 2^{o}C / 75% RH ± 5% for one month. The orodispersible tablets were evaluated for their drug content, wetting time, water absorption ratio, disintegration time and *in vitro* drug release. The studies indicated that no significant change in drug content, wetting time, water absorption ratio, dispersion time, disintegration time and *in vitro* drug release as shown in Table 24. The tablets were considered to be stable at 40^{o}C ± 2^{o}C / 75% RH ± 5%.

4. Conclusion

Oro-dispersible tablets of metaprolol can be successfully prepared by direct compression techniques using selected super disintegrants for the better patient compliance and effective therapy. The relative efficiency of these superdisintegrants to improve the disintegration and dissolution rate of tablets was found in order i.e. Crospovidone > Croscarmellose sodium.

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