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Formulation and Evaluation of Metoprolol Fast Disintegrating Tablets Using Coprocessed Excipients

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Abstract: Metoprolol is a medication primarily used for managing conditions like high blood pressure, chest pain (angina), irregular heart rhythms, and heart attacks. This study aimed to develop fast-dissolving tablets of metoprolol using coprocessed superdisintegrants, consisted of sodium starch glycolate (SSG) with either crospovidone (CP) or croscarmellose sodium (CCS) in different ratios (1:1 and 1:2). The study investigated the effects of these coprocessed superdisintegrants on various aspects of the tablets, such as wetting time, disintegrating time, drug content, and release of the medication in laboratory tests. The pre-compression parameters, which assess the properties of the materials before tablet formation, were within the recommended limits, suggesting that the materials flowed well during the manufacturing process. All the parameters met the acceptable limits specified by the Indian Pharmacopoeia (IP), indicating satisfactory tablet quality. The in-vitro disintegration time, which measures how quickly the tablets break down in a simulated environment, ranged from 8 ± 4 to 86 ± 14 seconds. Notably, the addition of coprocessed superdisintegrants significantly reduced the disintegration time, indicating their effectiveness. The tablets achieved complete drug release in 6 minutes for formulation F6 and 8 minutes for formulation F5, respectively. Among all the formulations, the tablets containing a combination of SSG and CP in a 1:1 ratio demonstrated the highest drug release, reaching 99.79% within 4 minutes. Based on the findings of this study, it was observed that the coprocessed superdisintegrants consisting of SSG and CP were more superior compared to SSG and CCS. Increasing the concentration of coprocessed superdisintegrants resulted in longer disintegration time and decreased drug release for both combinations. In conclusion, the researchers determined that the tablets formulated with SSG and CP in a 1:1 ratio exhibited the most favorable properties in terms of disintegration time and drug release.

Keywords: Fast dissolving tablets, Montelukast sodium, sodium starch glycolate, Crosscarmellose sodium, Crospovidone, co-processed.

I. INTRODUCTION

Oral disintegrating tablets (ODTs) have gained much interest in the pharmaceutical industry due to their ability to provide rapid onset of drug action, improved patient compliance, and convenience¹. Oral disintegrating tablets offer several advantages over conventional solid dosage forms. They are easier to swallow, especially for individuals who have difficulty swallowing tablets or capsules. They provide a convenient dosing option for patients on the go, as they do not require water to be ingested². They offer improved bioavailability, as they dissolve quickly in the mouth and bypass first-pass metabolism in the liver. They have the potential to increase patient compliance, as they are more palatable and convenient to take³. They may be useful in treating certain populations such as children, seniors, and patients with mental disabilities who have difficulty swallowing traditional tablets. Co-processed super disintegrants have been introduced to ODT formulations to enhance disintegration and dissolution properties of the tablet, thereby improving drug bioavailability⁴. This study aims to explore the use of co-processed super disintegrants in the preparation of ODTs. With the current drive towards personalized medicine, ODTs provide a viable alternative to conventional dosage forms and offer a patient-centric approach for drug delivery. Co-processed super disintegrants have gained popularity in the development of orally disintegrating tablets due to their enhanced disintegration properties. These super disintegrants are formed through the physical and/or chemical interaction between two or more individual excipients with different modes of disintegration, resulting in improved disintegration and dissolution properties⁵. They provide faster disintegration time, good stability and excellent moisture resistance. Each of these super disintegrants has its unique characteristics, which make them suitable for different formulations⁶.

Metoprolol is a cardio selective b-blocker. It is used in the management of hypertension, angina pectoris, cardiac arrhythmias and myocardial infarction. It is almost completely absorbed after oral administration, although the systemic bioavailability varies (40% to 50%) widely owing to extensive presystemic metabolism. The immediate release formulations of metoprolol present a half-life of about 3-7 hours. Metoprolol is a beta-1-adrenergic receptor inhibitor specific to cardiac cells with negligible effect on beta-2 receptors. This inhibition decreases cardiac output by producing negative chronotropic and inotropic effects without presenting activity towards membrane stabilization nor intrinsic sympathomimetics⁷⁻⁹.

II. MATERIALS AND METHODS

Metoprolol, Sodium starch glycolate, croscopolvidone, cross carmellose sodium, magnesium stearate, aspartame, orange flavor, talc and aerosil were procured from yarrow chemicals limited. All other materials were of analytical reagent grade.

A. Preparation of Co-processed Superdisintegrants¹⁰

Co-processed super disintegrants were prepared using SSG:CP (1:1 and 1:2) and SSG:CCS (1:1 and 1:2) ratio by solvent evaporation method. A blend of SSG:CP and SSG:CCS was taken in 250 ml beaker and 10 ml of ethanol is added to the mixture. The contents of the beaker were mixed thoroughly and stirring was continued until ethanol was evaporated. The wet coherent mass obtained was granulated through # 44 mesh sieve. The wet granules were dried in a hot air oven at 60° C for 20 mins. The dried granules were sifted through # 44 mesh sieve and stored in airtight container till further use.

B. Preparation of fast dissolving tablets by direct compression method¹¹

Metoprolol fast disintegrating tablets were prepared with coprocessed super disintegrants SSG:CP (1:1 and 1:2 ratio) in F1 to F4 , SSG:CCS (1:1 and 1:2 ratio) in F5 to F8 in 5% and 10% concentration. All the ingredients were weighed as per the formula and mixed in geometrical order. The ingredients were mixed in polybag for 20 mins. The powder mass was passed through # 60 mesh. Then the ingredients were compressed into tablets of 120mg by direct compression method using 6 mm bi concave punches on a 12 station rotary compression machine. The composition of the tablets were given in Table 1.

Table 1: Formulation composition of Metoprolol Fast Disintegrating Tablets

Formulation composition	Formulation codes							
	F1	F2	F3	F4	F5	F6	F7	F8
Metoprolol	25	25	25	25	25	25	25	25
Microcrystalline Cellulose	87.5	81	87.5	81	87.5	81	87.5	81
SSG : CCS (1:1)	6.5	13	----	----	----	----	----	----
SSG: CCS (1:2)	----	----	6.5	13	----	----	----	----
SSG : CP (1:1)	----	----	----	----	6.5	13	----	----
SSG: CP (1:2)	----	----	----	----	----	----	6.5	13
Aspartame	3	3	3	3	3	3	3	3
Orange flavour	2	2	2	2	2	2	2	2
magnesium stearate	1	1	1	1	1	1	1	1
Talc	3	3	3	3	3	3	3	3
Aerosil	2	2	2	2	2	2	2	2
Total weight	130	130	130	130	130	130	130	130

III. EVALUATION OF ATENOLOL FAST DISINTEGRATING TABLETS

A. Pre-Compression Attributes¹²

The tablet mixtures were examined for pre-compression characteristics, such as bulk density, tapped density, Carr's index, and flow properties, following the Indian Pharmacopoeia's specified formula.

B. Post-Compression Attributes

1) Weight Variation

To determine weight variation, 20 tablets were weighed individually. The average weight was determined and compared to the individual tablet weights. According to the I.P., the weight variation criterion is 7.5%.

2) Tablet Hardness Test

The tablet hardness was measured using a Pfizer hardness tester and reported in kg/cm². Six tablets were chosen at random from each sample to determine the mean and standard deviation values.

3) Friability¹³

A Roche Friabilator was used for the friability test. Twenty tablets were chosen from each batch and weighed initially (W initial). After placing them inside the Friabilator and rotating the drum at 25 rpm for 4 minutes, they were removed, dedusted, and reweighed (W final). The percentage friability was calculated using the formula:

$$F = [(W_{\text{initial}} - W_{\text{final}}) / W_{\text{initial}}] \times 100\%$$

4) Drug Content Estimation¹⁴

Five tablets were weighed and crushed. The equivalent weight of 100 mg of drug from the powdered sample was mixed in 100 mL of pH 6.8 phosphate buffer to obtain a concentration of 1000 µg/mL. This solution was then diluted accordingly with pH 6.8 phosphate buffer to obtain concentrations of 100 µg/mL and 10 µg/mL. Finally, absorbance was measured at 224 nm using a UV-Visible Spectrophotometer.

5) Disintegration Time¹⁵

An Electrolab USP disintegration test device was used to evaluate disintegration time. Each tablet was placed in a separate tube containing 900 mL of pH 6.8 phosphate buffer at 37°C ± 1°C, and the disintegration process was timed.

6) Wetting Time

A petri dish, with a diameter of 10 cm, was filled with 10 mL of distilled water containing water-soluble dye. Each tablet was carefully positioned at the center of the dish, and the time it took for the water to reach the top surface of the tablet was recorded as the wetting time. This procedure was done in triplicate, and the average result was calculated.

7) In Vitro Dispersion Time

A single tablet was placed in a beaker containing 10 mL of pH 6.8 phosphate buffer at a temperature of 37 ± 0.5°C, and the time required for complete dispersion was recorded using a stopwatch. This measurement was taken three times (n=3) for consistency.

8) In-vitro release^{16,17}

The FDT in-vitro dissolution tests were conducted at 37 ± 0.5°C using a pH 6.8 phosphate buffer with the USP II paddle method at 50 rpm. At predetermined intervals, 5 mL aliquots were removed and replaced with the same amount of fresh buffer of the same temperature to maintain a stable environment. A UV spectrophotometer was used to analyze the samples at 224 nm.

IV. RESULTS AND DISCUSSION

This study aimed to develop orally disintegrating tablets (ODTs) of metoprolol via direct compression method, using different super disintegrants in various concentrations while keeping other excipients constant. Three super disintegrants were utilized – croscarmellose sodium, sodium starch glycolate, and crospovidone – with the primary goal for all dosage forms to disintegrate rapidly.

A. Pre-compression parameters

Pre-compression parameters were assessed according to standard procedures and fell within acceptable limits, indicating good flow properties (table 2). All evaluated post-compression parameters were also within acceptable limits according to IP standards. The drug-excipient blend for each formulation was prepared and evaluated for various precompression parameters. Bulk density values ranged from 0.51 ± 0.03 to 0.56 ± 0.05, while tapped density values ranged from 0.59 ± 0.03 to 0.70 ± 0.02.

Carr's index and Hausner's ratio were calculated based on tapped and bulk densities. The excellent flowability of all powder blends was demonstrated by Hausner's ratios (1.16 ± 0.005 to 1.26 ± 0.003) and Carr's indexes (13.84 ± 0.4 to 20.78 ± 0.5). Angle of repose values, ranging from 24.47 to 27.23, further confirmed the superior flow properties of the blends compared to the pure drug.

B. Post-compression parameters

Post-compression parameter results are displayed in Table 3. In all formulations, hardness tests revealed satisfactory mechanical strength ranging from 3.2 ± 0.6 to 3.6 ± 0.3 kg/cm². Friability values between 0.4% and 0.8% were within the acceptable range (<1%), signifying good mechanical resistance. Weight variations in all formulations were in the range of 130.2 ± 1.1 to 130.9 ± 1.5 .

All tablet formulations passed the weight variation test, with average percentage weight variations being within 7.5%, meeting pharmacopoeia requirements.

Standard deviation values indicated that all formulations fell within acceptable ranges. Drug content uniformity ranged between $97.6 \pm 0.8\%$ and $99.2 \pm 0.4\%$. Wetting time for all formulations ranged from 62 ± 6 to 152 ± 5 seconds, while in vitro dispersion time ranged from 39 ± 3 to 120 ± 4 sec.

All tested formulations underwent rapid disintegration within mere minutes. The in-vitro disintegration time for the fast-dissolving tablets fell within the official requirements, ranging from 8 ± 4 to 86 ± 14 seconds. The addition of super disintegrants led to a significant decrease in disintegration time. Table 3 contains all pertinent results.

The promising F6 formulation consisted of a 10% w/w co-processed super disintegrant mix (1:1 ratio of SSG and CP), boasting an in-vitro dispersion time of 39 ± 3 seconds, wetting time of 62 ± 6 seconds, and disintegration time of 8 ± 4 seconds. Comparing co-processed super disintegrant blends (SSG+CP, SSG+CCS), we discovered that the best disintegration was achieved through a 10% concentration (1:1 ratio) SSG and CP mixture.

The F8 formulation, containing a 10% w/w co-processed super disintegrant mix (1:2 ratio of SSG and CP), showed an in-vitro dispersion time of 54 ± 8 seconds, wetting time of 91 ± 6 seconds, and disintegration time of 24 ± 5 seconds. Meanwhile, the F2 formulation, with a 10% w/w co-processed super disintegrant mix (1:1 ratio of SSG and CCS), displayed an in-vitro dispersion time of 75 ± 8 seconds, wetting time of 113 ± 12 seconds, and disintegration time of 40 ± 9 seconds. Lastly, the promising F3 formulation consisted of a 5% w/w co-processed super disintegrant mix (1:2 ratio of SSG and CCS). This blend exhibited an in-vitro dispersion time of 112 ± 10 seconds, wetting time at 148 ± 8 seconds, and disintegration time of 80 ± 12 seconds.

Our study revealed that increasing the concentration of co-processed super disintegrants resulted in delayed tablet disintegration. This phenomenon may be attributed to certain super disintegrants, such as sodium starch glycolate or croscarmellose sodium, forming gels upon water exposure. These gels can obstruct fluid penetration into tablet matrices, subsequently slowing down the disintegration process.

Dissolution rates were examined using a USP type-II Dissolution Test Apparatus at 50 rpm, with 900ml pH 6.8 phosphate buffer serving as the dissolution medium. The dissolution medium temperature remained at $37 \pm 0.5^\circ\text{C}$. A 5ml aliquot was removed every two minutes and filtered. UV spectrophotometry measured the filtered solution's absorbance at 224 nm, and drug concentrations were identified via standard calibration curves.

The release patterns of atenolol from the tablets can be observed in Figure 1, which demonstrates the $t_{50\%}$ and $t_{90\%}$ values. These figures vary depending on the formulation used. Out of all the formulations, F6 exhibited a 99% drug release within six minutes, providing rapid disintegration and enhanced drug dissolution. Formulations F1 to F4 displayed complete drug release in 16 minutes, while formulations F5 and F8 achieved it between 8 to 12 minutes. Formulation F4, which contained a 10% concentration of SSG:CCS (1:2), demonstrated weak disintegration and drug release performance.

It was noted that with an increased concentration of co-processed super disintegrants, disintegration time decreased and drug release increased for SSG:CP but led to poor results in SSG:CCS.

Consequently, the research indicated that co-processed super disintegrants SSG:CP offered better properties than SSG:CCS. The conclusion drawn was that Metoprolol fast-disintegrating tablets could be effectively prepared utilizing co-processed super disintegrants comprising SSG+CP. The overall ranking for disintegrating capability among the tested disintegrants was as follows: SSG : CP (1:1) > SSG : CP (1:2) > SSG : CCS (1:1) > SSG : CCS (1:2).

Regarding FTIR results, the analysis included pure drug, super disintegrant, and optimized formulation (F5) spectra for characterization studies. The similar peaks identified in FTIR analysis suggest no interactions took place (Figure 2).

Table 2: Precompression parameters of Metoprolol Fast Disintegrating Tablet

Formulation codes	Precompression parameters				
	Bulk density (g/ml)	Tapped density (g/ml)	Carrs Index (%)	Hausners ratio	Angle of repose (θ)
F1	0.54 \pm 0.03	0.66 \pm 0.02	17.58 \pm 0.3	1.21 \pm 0.003	26.25
F2	0.50 \pm 0.02	0.60 \pm 0.04	16.66 \pm 0.5	1.20 \pm 0.002	25.36
F3	0.56 \pm 0.04	0.68 \pm 0.05	16.47 \pm 0.2	1.19 \pm 0.004	26.48
F4	0.51 \pm 0.03	0.59 \pm 0.03	13.84 \pm 0.4	1.16 \pm 0.005	26.53
F5	0.56 \pm 0.05	0.70 \pm 0.02	20.78 \pm 0.5	1.26 \pm 0.003	28.21
F6	0.54 \pm 0.03	0.64 \pm 0.05	15.67 \pm 0.3	1.18 \pm 0.002	24.47
F7	0.51 \pm 0.06	0.59 \pm 0.04	13.84 \pm 0.4	1.16 \pm 0.005	27.23
F8	0.53 \pm 0.02	0.64 \pm 0.03	16.57 \pm 0.2	1.19 \pm 0.004	26.54

Table 3: Post compression parameters of Metoprolol Fast Disintegrating Tablet

Post compression parameters	Formulation codes							
	F1	F2	F3	F4	F5	F6	F7	F8
weight variation	130.5 \pm 1.2	130.9 \pm 1.5	130.6 \pm 1.8	130.4 \pm 1.2	130.7 \pm 1.3	130.2 \pm 1.1	130.8 \pm 1.6	130.3 \pm 1.5
Thickness	2.3 \pm 0.05	2.3 \pm 0.03	2.4 \pm 0.02	2.4 \pm 0.05	2.5 \pm 0.04	2.3 \pm 0.08	2.2 \pm 0.06	2.3 \pm 0.05
Hardness	3.2 \pm 0.6	3.3 \pm 0.4	3.6 \pm 0.2	3.4 \pm 0.4	3.3 \pm 0.6	3.5 \pm 0.5	3.4 \pm 0.2	3.6 \pm 0.3
% Friability	0.8	0.6	0.5	0.7	0.5	0.4	0.6	0.8
Drug content	99.5 \pm 0.4	97.6 \pm 0.8	98.1 \pm 0.6	98.4 \pm 0.5	98.2 \pm 0.7	99.2 \pm 0.4	98.2 \pm 0.5	98.8 \pm 0.3
Disintegration time	50 \pm 7	40 \pm 9	80 \pm 12	86 \pm 14	18 \pm 6	8 \pm 4	30 \pm 8	24 \pm 5
Wetting time	102 \pm 10	113 \pm 12	148 \pm 8	152 \pm 5	84 \pm 7	62 \pm 6	97 \pm 9	91 \pm 6
Invitro dispersion time	83 \pm 5	75 \pm 8	112 \pm 10	120 \pm 4	50 \pm 5	39 \pm 3	63 \pm 6	54 \pm 8

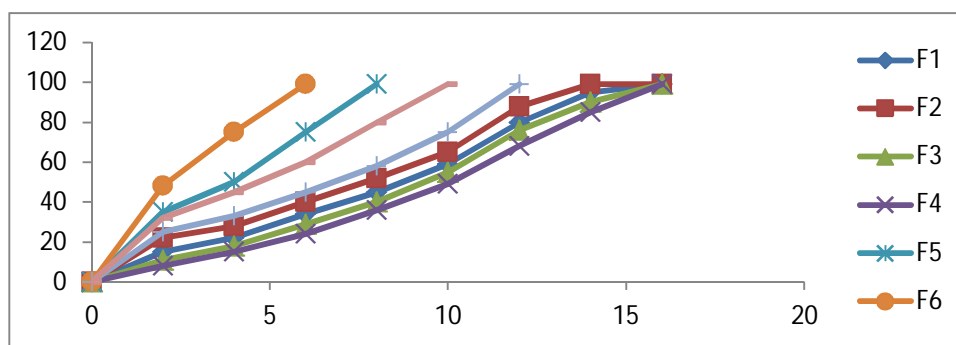


Fig 1: Dissolution profile of Metoprolol Fast Disintegrating Tablet

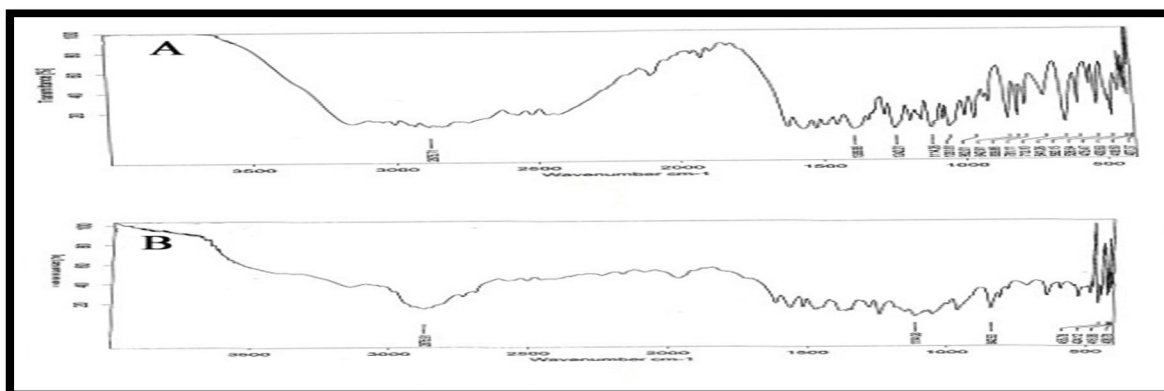


Fig 2: A. FTIR spectra of pure drug, B. FTIR spectra of optimized formulation F5

V. CONCLUSION

Metoprolol, a cardio-selective beta-blocker, is commonly utilized for treating hypertension, angina pectoris, heart rhythm disorders, and heart attacks. In this study, fast-dissolving atenolol tablets were created using a combination of co-processed super disintegrants – SSG with CP and SSG with CCS – in various proportions (1:1 and 1:2 at 5% and 10% concentrations). The metoprolol tablets with co-processed super disintegrants displayed rapid disintegration and enhanced drug dissolution. This research suggests that combining SSG and CP as co-processed super disintegrants proves to be more effective than mixing SSG and CCS.

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Conflict Of Interest

Authors of this publication declare no conflict of interest.

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