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Formulation and Evaluation of Atenolol Fast Disintegrating Tablets using Co-processed Excipients

P. Nagalakshmi[1*], R. Rajkumar[1], K. Shashi[1], Jahirul Islam[1], T. Praveenkumar[2],V. Himabindu[2].
1. Department of Pharmacy, 2. Department of Pharmaceutics.
Anurag Pharmacy College, Affiliated to Jawaharlal Nehru Technological University, Hyderabad, Ananthagiri (V&M), Kodad, Suryapeta (D), Telangana, India, Pin 508206
Correspondence Author E-Mail: praveensuri1@gmail.com

ABSTRACT
Atenolol is commonly used to treat hypertension (high blood pressure) and stable angina (chest pain) either on its own or in combination with other antihypertensive medications like thiazide diuretics. The study focused on creating fast-disintegrating tablets of atenolol using different substances called super disintegrants. These included Sodium starch glycolate (SSG), Crosspovidone (CP), and Cross carmellose sodium (CCS) at a concentration of 10%. We tested co-processed super disintegrants, which were combinations of SSG with CP and SSG with CCS, at ratios of 1:1 and concentrations of 5% and 10%. Additionally, camphor was used at a concentration of 10% in formulations F1 to F7 as a subliming agent. We have studied the effects of these super disintegrants and co-processed super disintegrants, along with camphor, on various parameters such as wetting time, disintegrating time, drug content, and in-vitro release. The results indicated that there were no chemical interactions between them. The pre-compression parameters, which evaluate the flow properties of the prepared tablets, were found to be within the recommended limits, indicating good flow. Post-compressional parameters were also evaluated, and all of them met the prescribed limits, falling within the acceptable limits set by the Indian Pharmacopoeia (IP). Among all the formulations, F5 exhibited complete drug release within 6 minutes. Based on the findings of this study, it can be concluded that co-processed super disintegrants of SSG and CP are more effective than SSG and CCS co-processed super disintegrants.
Keywords: *Atenolol, co-processed, Crosscarmellose sodium, Crospovidone, Fast dissolving tablets, sodium starch glycolate.*

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INTRODUCTION

Oral disintegrating tablets (ODTs) are a fast-growing category of drug delivery systems that have gained significant attention in the field of pharmaceuticals due to their numerous advantages over conventional tablets [1]. ODTs are designed to rapidly dissolve or disintegrate upon contact with saliva, facilitating greater ease of swallowing for patients who may have difficulty swallowing traditional tablets or capsules [2]. In addition to their convenience, ODTs are often more stable than conventional tablets, largely due to the fact that they contain fewer ingredients and do not require as much processing [3].

Super disintegrants, on the other hand, work to enhance the disintegration and dissolution of tablets, resulting in faster absorption and improved bioavailability [4]. In recent years, pharmaceutical scientists have focused on the use of co-processed super disintegrants, which are a combination of two or more super disintegrants, to provide faster and more efficient disintegration of ODTs. Super disintegrants ensure rapid disintegration of the tablet in the mouth. Co-processed super disintegrants, which are a combination of two or more different disintegrants, are often used to achieve superior performance. These advantages make ODTs and super disintegrants particularly useful in contexts where quick drug action is critical, such as in emergency medicine or in treating conditions that require immediate relief [5].

Co-processing is a unique technique that involves mixing different types of disintegrants to create a synergistic effect, resulting in a more efficient and rapid disintegration profile in the tablet [6]. This method not only enhances the tablet's properties, such as hardness and friability, but also improves the dissolution rate, which is important for faster drug absorption in the body. Overall, co-processed super disintegrants have become an

essential tool for the pharmaceutical industry, offering flexibility in formulation design and improving patient compliance.

Atenolol belongs to the class of b-1 selective adrenoceptor antagonists. It has been used for the treatment of hypertension and stable angina either alone or with other antihypertensive drugs like thiazide diuretics [7-8]. AT is a highly soluble and has poor permeability (BCS class 3) with a log P value of 0.5. Due to incomplete intestinal absorption, the systemic bioavailability is about 50–60% in the human. The peak plasma concentrations occur about 2–4 h after an oral dose of 50–100 mg. It is reported that in the case of oral administration of atenolol, it can induce side effects such as diarrhea, nausea, mesenteric arterial thrombosis, ischemic colitis and dry mouth [9]. AT is reported to be subjected to extensive hepatic first-pass metabolism following the oral administration and has a short biological half-life of 6–7 h [10].

MATERIAL AND METHODS

Atenolol, Sodium starch glycolate, cross-povidone, cross carmellose sodium, camphor, magnesium stearate, talc and aerosol were procured from yarrow chemicals limited. All other materials were of analytical reagent grade.

PREPARATION OF CO-PROCESSED SUPER DISINTEGRANTS [11]

To create co-processed super disintegrants, a combination of Sodium Starch Glycolate (SSG) and Crospovidone (CP) in a 1:1 ratio and SSG and Croscarmellose Sodium (CCS) in a 1:1 ratio was prepared using the solvent evaporation method. In a 250 ml beaker, a mixture of SSG:CP and SSG:CCS was taken, and 10 ml of ethanol was added. The contents of the beaker were thoroughly mixed, and stirring continued until the ethanol evaporated. The resulting wet cohesive mass was then granulated through a #44 mesh sieve. These wet granules were dried in a hot air oven at 60º C for 20 minutes. After drying, the granules were sifted through a #44 mesh sieve and stored in an airtight container until further use.

PREPARATION OF FAST DISSOLVING TABLETS BY DIRECT COMPRESSION METHOD [12]

Fast dissolving tablets of Atenolol were prepared using super disintegrants SSG (F1), CP (F2), CCS (F3) at a concentration of 10%, along with a subliming agent called camphor. Co-processed superdisintegrants, SSG:CP (1:1) and SSG:CCS (1:1), were also used at concentrations of 5% and 10%, combined with camphor (at 10% in F4 to F7), and only 20% camphor in F8. All the required ingredients were weighed according to the specified formula and mixed in a specific order. The mixing process took place in a polybag for 20 minutes. The resulting powder mass was then passed through a #60 mesh sieve. Subsequently, the ingredients were compressed into tablets weighing 120mg, using a direct compression method with 6 mm bi-convex punches on a 12-station rotary compression machine. The composition of the tablets is provided in Table 1.

Table 1: Formulation composition atenolol fast disintegration tablets

Formulation composition	Formulation codes							
	F1	F2	F3	F4	F5	F6	F7	F8
Atenolol	25	25	25	25	25	25	25	25
Microcrystlline Cellulose	60	60	60	66	60	66	60	60
SSG	12	---	---	---	---	---	---	---
CP	---	12	---	---	---	---	---	
CCS	---	---	12	---	---	---	---	---
SSG : CP (1:1)	---	---	---	6	12	---	---	---
SSG : CCS (1:1)	---	---	---	---	---	6	12	---
Camphor	12	12	12	12	12	12	12	24
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	120	120	120	120	120	120	120	120

EVALUATION OF ATENOLOL FAST DISINTEGRATING TABLETS

PRE-COMPRESSION PARAMETERS

Before compressing the tablet blends, various pre-compression parameters were evaluated to ensure their flow property. These parameters include bulk density, tapped density, Carr's index, and angle of repose. The evaluation was conducted according to the formula specified in the Indian pharmacopoeia.

POST-COMPRESSION PARAMETERS

After the tablets were compressed, several post-compression parameters were examined to assess their characteristics and adherence to quality standards.

WEIGHT VARIATION

To determine the weight uniformity of the tablets, 20 individual tablets were weighed. The average weight was calculated and compared to the weight of each individual tablet. The weight variation specification, as per the Indian Pharmacopoeia, was set at 7.5%.

HARDNESS TEST

The hardness of the tablets was measured using a Pfizer hardness tester and expressed in kg/cm^2. Six tablets were randomly selected from each formulation, and their hardness was measured. The mean and standard deviation values were then calculated.

FRIABILITY

Friability test was conducted using a Roche Friabilator. Twenty tablets were selected from each batch and weighed initially (W initial). These tablets were placed in the Friabilator, which rotated the drum at 25 rpm for 4 minutes. Afterward, the tablets were removed, dedusted, and weighed again (W final). The percentage of friability was determined using the formula F = [(W initial - W final) / W initial] x 100%.

ESTIMATION OF DRUG CONTENT

To determine the drug content in the tablets, five tablets were weighed and crushed in a mortar. The equivalent weight of 100 mg of the drug was transferred to 100 ml of pH 6.8 phosphate buffer, resulting in a concentration of 1000 µg/ml. From this solution, 10 ml was pipetted and diluted up to 100 ml with pH 6.8 phosphate buffer, yielding a concentration of 100 µg/ml. Further dilution was performed by pipetting 1 ml of this solution and diluting it up to 10 ml with pH 6.8 phosphate buffer, creating a concentration of 10 µg/ml. The absorbance of the resulting solution was measured at 224 nm using a UV-Visible Spectrophotometer [13].

DISINTEGRATION TIME

The disintegration time of the tablets was determined using an Electrolab USP disintegration test apparatus. One tablet was placed in each tube, and the basket rack was immersed in 900 ml of pH 6.8 phosphate buffer at a temperature of 37°C ± 1°C. The time required for complete disintegration of the tablets was recorded [14].

WETTING TIME

To assess the wetting ability of the tablets, a petri dish with a 10 cm diameter was filled with 10 ml of distilled water containing a water-soluble dye. The tablets were carefully placed in the center of the petri dish, and the time it took for the water to reach the upper surface of the tablet was noted as the wetting time. The test results were presented as the mean value of three determinations [15].

IN VITRO DISPERSION TIME

The in vitro dispersion time was determined by placing one tablet in a beaker containing 10 ml of pH 6.8 phosphate buffer at a temperature of 37±0.5°C. The time required for complete dispersion of the tablet was measured using a stopwatch. To ensure reproducibility, the measurements were conducted in triplicates.

IN-VITRO RELEASE

The release of the tablets' active ingredient in an artificial environment was examined through in-vitro dissolution studies. These studies were conducted using a pH 6.8 phosphate buffer at a temperature of 37±0.5°C, employing the USP II paddle method at 50 rpm. At predetermined time intervals, 5 ml samples were withdrawn and replaced with 5 ml of fresh buffer at the same temperature to maintain a sink condition. The samples were then analyzed at 224 nm using a UV spectrophotometer [16].

FOURIER TRANSFORM INFRARED SPECTROSCOPY (FTIR)

FTIR studies were conducted on the drug and the optimized formulation using a Shimadzu FTIR instrument (Prestige, India). The samples were analyzed within the wave number range of 4000 to 400 cm^{-1} to determine their molecular characteristics.

RESULTS AND DISCUSSION

The pre-compression parameters were evaluated and found to be within the prescribed limits, indicating good flow properties (Table 2). The bulk density of all formulations ranged from 0.505±0.03 to 0.568±0.05, while the tapped density fell within the range of 0.606±0.02 to 0.709±0.02. The Carr's index and Hausner's ratio were calculated based on the tapped density and bulk density. The powder blend of all six formulations exhibited excellent flowability, as indicated by Hausner's ratio ranging from 1.161±0.001 to 1.262±0.002 and Carr's index

ranging from 13.846±0.2 to 20.787±0.5. Additionally, the angle of repose values obtained for all powder blends demonstrated excellent flow properties, ranging from 28.51 to 24.28.

The results of the post-compression parameters are shown in Table 3. All evaluated post-compression parameters met the prescribed limits and were within the acceptable limits specified in the Indian Pharmacopoeia. The hardness test indicated good mechanical strength for all formulations, ranging from 3.9±0.4 to 3.2±0.4 kg/cm^2. The friability, ranging from 0.4% to 0.8%, was well below the approved limit of 1%, indicating the tablets' favorable mechanical resistance. The weight variation among the designed formulations fell within the range of 120.1±2.5 to 120.5±2.6, and all tablets passed the weight variation test, as the average percentage weight variation was within the 7.5% limit set by the pharmacopoeia. The standard deviation values confirmed that all formulations were within the acceptable range. The drug content uniformity ranged from 98.4±0.6 to 99.3±0.2%. Wetting time for all formulations ranged from 76±8 to 145±15 seconds. Comparing the three super disintegrants (SSG, CP, CCS) and coprocessed mixtures, it was found that a 1:1 mixture of SSG + CP at a concentration of 10% exhibited the best disintegration among the super disintegrants. All formulations showed rapid disintegration within a few minutes. The in-vitro disintegration time of the fast-dissolving tablets ranged from 15±5 to 85±10 seconds, meeting the official requirements. The addition of super disintegrants significantly increased the disintegration time of the tablets. The detailed results are provided in Table 3.

Among the formulations, F5 containing a 10% w/w concentration of co-processed super disintegrants (1:1 mixture of SSG + CP) showed promising results, with an in-vitro dispersion time of 45±3 seconds, wetting time of 76±8 seconds, and disintegrating time of 15±5 seconds. Formulation F4, containing a 5% w/w concentration of co-processed super disintegrants (1:1 mixture of SSG + CP), also exhibited promising properties, with an in-vitro dispersion time of 64±8 seconds, wetting time of 93±10 seconds, and disintegrating time of 39±11 seconds. Formulation F6, with a 10% w/w concentration of co-processed super disintegrants (1:1 mixture of SSG + CP), showed an in-vitro dispersion time of 81±6 seconds, wetting time of 115±11 seconds, and disintegrating time of 48±10 seconds. Formulation F7, containing a 10% w/w concentration of co-processed super disintegrants (1:1 mixture of SSG + CP), displayed an in-vitro dispersion time of 67±5 seconds, wetting time of 108±10 seconds, and disintegrating time of 30±8 seconds.

The dissolution profiles of atenolol from the tablets are illustrated in Figure 1, showing the t50% and t90% values of the release profiles. These values varied with different formulations. Among all the formulations, F5 demonstrated 99% drug release within 6 minutes. F5 exhibited rapid disintegration and improved drug dissolution. Formulations F1 to F3 achieved complete drug release between 14 to 16 minutes, while F6 and F7 accomplished complete drug release between 8 to 12 minutes. Formulation F8, containing camphor, displayed complete drug release in 16 minutes. The results indicated that increasing the concentration of co-processed super disintegrants led to decreased disintegration time and increased drug release. It can be concluded that co-processed super disintegrants of SSG+CP exhibited superior properties compared to SSG+CCS co-processed super disintegrants containing camphor and tablets prepared with camphor alone.

FTIR RESULTS

The FTIR spectra of pure drug, super disintegrant and optimized formulation (F5) are taken for the characterization studies. Similar peaks were obtained in FTIR analysis indicating absence of interactions (Figure 2).

Table 2: Pre compression parameters of atenolol fast disintegration tablets

Formulation codes	Precompression parameters				
	Bulk density (g/ml)	Tapped density (g/ml)	Carrs Index (%)	Hausners ratio	Angle of repose (θ)
F1	0.549±0.02	0.667±0.05	17.582±0.3	1.213±0.003	26.12
F2	0.505±0.03	0.606±0.02	16.667±0.4	1.200±0.004	27.16
F3	0.535±0.04	0.641±0.06	16.578±0.3	1.199±±0.003	25.31
F4	0.541±0.04	0.641±0.06	15.676±0.2	1.186±0.002	25.36
F5	0.513±0.02	0.595±0.04	13.846±0.2	1.161±0.001	24.28
F6	0.513±0.04	0.610±0.03	15.897±0.6	1.189±0.001	25.24
F7	0.568±0.05	0.680±0.04	16.477±0.6	1.197±0.005	26.45
F8	0.562±0.04	0.709±0.02	20.787±0.5	1.262±0.002	28.51

Table 3: Post compression parameters of atenolol fast disintegration tablets

Post compression parameters	Formulation codes							
	F1	F2	F3	F4	F5	F6	F7	F8
Weight Variation	120.2±1.4	120.1±2.5	120.4±2.1	120.3±2.2	120.5±1.1	120.4±2.6	120.3±2.4	120.5±2.6
Thickness	2.2±0.03	2.2±0.02	2.3±0.03	2.4±0.04	2.1±0.02	2.4±0.05	2.3±0.04	2.2±0.03
Hardness	3.6±0.3	3.4±0.2	3.7±0.4	3.5±0.2	3.2±0.4	3.4±0.5	3.5±0.3	3.9±0.4
% Friability	0.7	0.5	0.6	0.5	0.4	0.6	0.7	0.8
Drug content	98.5±0.7	98.6±0.5	99.1±0.4	98.4±0.6	99.2±0.2	99.3±0.2	99.1±0.3	98.7±0.4
Disintegration time	66±12	55±8	85±10	39±11	15±5	48±10	30±8	70±13
Wetting time	135±15	121±11	145±12	93±10	76±8	115±11	108±10	134±15
In vitro dispersion time	114±10	86±7	95±10	64±8	45±3	81±6	67±5	108±8

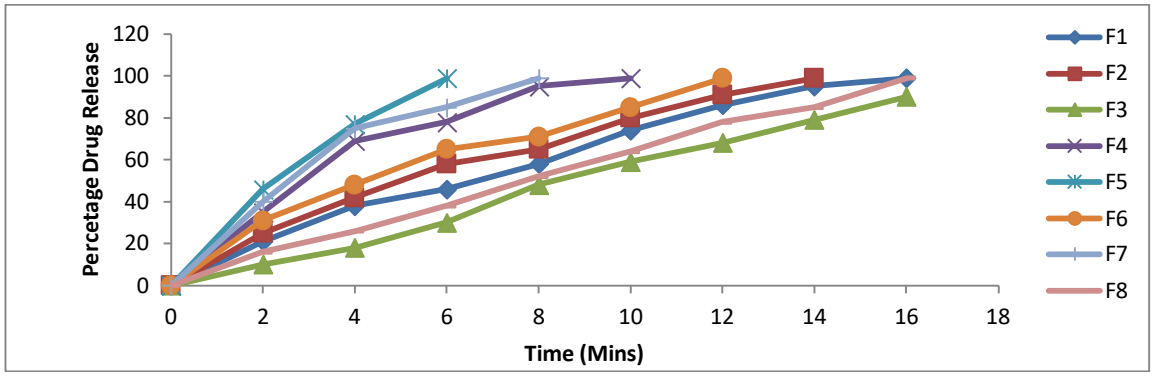

Figure 1: Percentage drug release profile of atenolol fast disintegration tablets

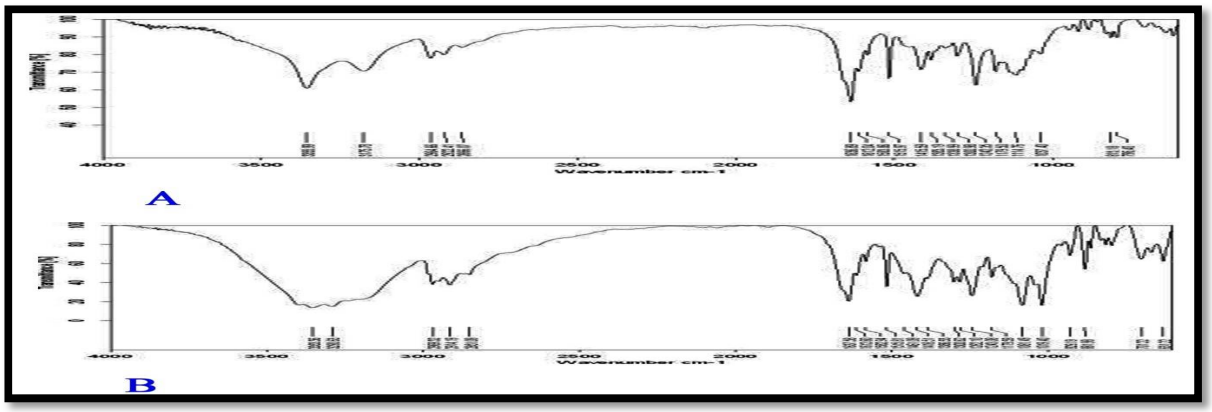

Figure 2: A- FTIR spectra of pure drug, B- FTIR spectra of optimized formulation F5

CONCLUSION

A b-1 selective adrenoceptor antagonist atenolol is used alone or in combination with other antihypertensive medications such thiazide diuretics to treat hypertension and stable angina. In the current study, super disintegrants SSG, CP, and CCS at 10% concentration, as well as co-processed super disintegrants made up of SSG with CP and SSG with CCS in different ratios (1:1 at 5% and 10% concentration), were used to make fast disintegrating tablets of atenolol. Super disintegrants used in co-processing show fast disintegration and better drug dissolution in atenolol tablets. The results of this study support the conclusion that co-processed super disintegrants of SSG and CP are superior than mixture of SSG and CCP, super disintegrants by themselves, and formulations incorporating camphor.

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CONFLICT OF INTEREST
Authors of this publication declare no conflict of interest.

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