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Research Article

DESIGN OF FAST DISSOLVING TABLET OF ATENOLOL USING NOVEL CO-PROCESSED SUPERDISINTEGRANT

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ABSTRACT

Atenolol is a recognized drug for hypertension therefore development of an FDT of Atenolol and to evaluate the effect of co-processed superdisintegrants on its disintegration time and release profile was the prime objective of this research work. Tablets were prepared by direct compression technique using two different superdisintegrants in combination by co-process mixing and by physical mixing. Croscarmellose sodium and Crospovidone were used as superdisintegrants in combinations in the different ratio (1:1, 1:2 & 1:3). The developed superdisintegrants were evaluated for angle of repose, Carr's index and Hausner's ratio in comparison with physical mixture of superdisintegrants. The angle of repose of the developed excipients was found to be < 25^0, Carr's index in the range of 10-15% and Hausner's ratio in the range of 1.11-1.14. Fast dissolving tablets of Atenolol were prepared using the co-processed superdisintegrants and evaluated for pre-compression and post compression parameters. Based on *in-vitro* dispersion time (approximately 20sec) CP1 formulation was tested for *in-vitro* drug release pattern in pH 6.8 Phosphate buffer and drug excipients interaction were studied with DSC. Among the designed formulations, the formulation (CP1) containing 4% w/w of co-processed superdisintegrants (1:1 mixture of Crospovidone and Croscarmellose sodium) emerged as the overall best formulation based on drug release characteristics in pH 6.8 phosphate buffer.

Keywords: Atenolol, Crospovidone, Croscarmellose sodium, Co-processed Superdisintegrants, Fast dissolving tablet

INTRODUCTION

Chemically Atenolol is 4-(2-Hydroxy-3-[(1-methyl ethyl) amino] propoxy) benzene acetamide [1] β1-blocker is prescribed widely in diverse cardiovascular diseases, eg, hypertension, angina pectoris, arrhythmias, and myocardial infarction. The drug is also frequently indicated in the prophylactic treatment of migraine [2]. Administration of conventional tablets of Atenolol has been reported to exhibit fluctuation in the plasma drug levels, resulting either in manifestation of side effects or reduction in drug concentration at the receptor site [3]. Oral bioavailability of Atenolol is around 50% and having half life 6 to 7 hrs [4]. For poorly soluble orally administered drugs the rate of absorption is often controlled by the rate of dissolution. The rate of dissolution can be increased by increasing the surface area of available drug by various methods (micronization, complexation, solid dispersion, etc). Another prerequisite for the fast dissolution may be the disintegration time of tablets because; faster disintegration of tablets delivers a fine suspension of drug particles and thus, greater dissolution of the drug[5]. Solid oral dosage forms, especially tablets, remain one of the most popular because of advantages like patient convenience, ease of storage and dispensing, dose accuracy and easy manufacturability.

Since the beginning of the pharmaceutical practices the oral route is rigorously checked for the delivery of drugs through tablet. Major challenge for tablets manufacturing comes from the flow properties of the materials to be compressed. Most of the formulations (> 70%) contain excipients at higher concentration than active drug [6]. In recent years drug formulation scientists have recognized that single component excipients do not always provide the requisite performance to allow certain active pharmaceutical ingredients to be formulated or manufactured adequately [7]. Hence, there is a need to have excipients with multiple characteristics built into them such as better flow, low/no moisture sensitivity, superior compressibility and rapid disintegration ability [8]. One such approach for improving the functionality of excipients is co-processing.

Co-processing is defined as combining two or more established excipients by certain defined processes. Co-processing is based on the novel concept of two or more excipients interacting at the sub particle level, the objective of which is to provide a synergy of functionality improvement as well as masking the undesirable properties of individual [9]. Co-processing of excipients could lead to the formation of excipients with superior properties compared with simple physical mixture of their components or with individual components. As such the Co-processing of superdisintegrants is totally unexplored. The widely used superdisintegrants include Crospovidone, Croscarmellose sodium (Ac-Di-Sol) [10].

In the present investigation, the preparation and evaluation of fast dissolving tablets by using co-processed superdisintegrants containing Crospovidone and Croscarmellose sodium was studied. The reasons for selection of Crospovidone are high capillary activity, pronounced hydration capacity and little tendency to form gels [11]. The concept of formulating fast dissolving tablets (FDT) of Atenolol using co-processed superdisintegrants helps to increase the water uptake with shortest wetting time and thereby decrease the disintegration time of the tablets by simple and cost effective direct compression technique. Main advantages of direct compression are low manufacturing cost and high mechanical integrity of the tablets [12].

MATERIALS AND METHODS

Chemical and Drugs

Atenolol was procured as a gift sample from Shreya life sciences Pvt. Ltd. Aurangabad, Maharashtra. Croscarmellose sodium, Crospovidone, directly compressible Mannitol (Perlitol SD-200), Microcrystalline cellulose were procured as a gift sample from ICPA Health care products Ltd., Ankaleshwar, Gujrat. Magnesium sterate was procured as a gift sample from Navketan Pharma, Aurangabad, Maharashtra and all other chemicals and reagents used were Analytical grade.

Preparation of Co-processed Superdisintegrants

The co-processed Superdisintegrants were prepared by solvent evaporation method [13] . A blend of Croscarmellose sodium and Crospovidone (in the ratio of 1:1, 1:2 & 1:3) was added to 10 ml of ethanol. The contents of the beaker were mixed thoroughly and stirred continuously till most of ethanol evaporated. The wet coherent mass was granulated through # 44 mesh sieve. The wet granules were dried in a hot air oven at 60º C for 20 minutes. The dried granules were sifted through # 44 mesh sieve and stored in airtight container till further use.

Preparation of fast dissolving tablets

Fast dissolving tablets of atenolol were prepared by direct compression method [14] formula for tablet preparation is shown in Table 1. All the ingredients (except granular directly compressible excipients) were passed through # 60 mesh separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 150mg using 8.5mm concave flat punches on 12-station Karnavati Mini press-II tablet machine.

Table No.1 Formulation of Atenolol by Direct Compression Method

CONTENTS	Formulation batches						
	Co-processed			Physical Mixed			Control
	CP1(mg)	CP2 (mg)	CP3 (mg)	PM1 (mg)	PM2 (mg)	PM3 (mg)	C0 (mg)
Atenolol	25	25	25	25	25	25	25
Perlitol-SD-200	81	81	81	81	81	81	87
Crospovidone & Croscarmellose sodium	6	6	6	6	6	6	-
Avicel PH 102	30	30	30	30	30	30	30
Aspartame	3	3	3	3	3	3	3
Magnesium stearate	2	2	2	2	2	2	2
Colloidal silicon dioxide	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Strawberry flavour	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total Weight	150	150	150	150	150	150	150

Pre compression parameters [15-21]

Angle of repose

Angle of repose was determined using fixed funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone Height (h) was obtained. Radius of the heap (r) was measured and the angle of repose (ɵ) was calculated using the formula-

$$\tan \theta = h / r$$
$$\theta = \tan^{-1} (h / r)$$

Where,

θ is the angle of repose
h is the height in cms
r is the radius.

Bulk density

Bulk density was determined by pouring the blend into a graduated cylinder. The bulk volume (V_b) and weight of the blend (M) was determined. The bulk density is expressed in gm/ml and is given by

$$\text{Bulk density} = M / V_b$$

Where,

M = mass of powder taken
V_b= Bulk volume of the powder.

Tapped density

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml and is given by

$$\text{Tapped density} = M / V_t$$

Where,

M = Mass of powder taken
V_t = tapped volume of the powder

Carr's Index

It is also one of the sample methods to evaluate flow property of a powder by comparing the bulk density and tapped density. A useful empirical guide is given by the Carr's compressibility index. It indicates the ease with which a material can be induced to flow. It is expressed in percentage and is given by

$$\text{Compressibility index} = 100 (D_t - D_b) / D_t$$

Where,

D_t is the tapped density of the powder.
D_b is the bulk density of the powder.

Hausner ratio

Hausner ratio is an indirect index of ease of powder flow. It is calculated by following formula.

$$\text{Hausner's ratio} = D_t / D_b$$

Where,

D_t is the tapped density.
D_b is the bulk density.

Lower hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Post compression parameters [22-25]

All the batches of tablets were evaluated for various parameters like weight variation, friability, hardness, drug content, disintegration and dissolution study etc.

Weight variation:

Twenty tablets were taken and their weight was determined individually and collectively using single pan electronic balance. The average weight of the tablets was determined from collective weight. From the individual tablets weight, the range and percentage standard deviation was calculated. In direct compression of tablet, uniform weight of tablets represents appropriate powder flow and uniform die filling.

Hardness

The resistance of tablets to shipping, breakage, under conditions of storage, transportation and handling before usage depends on its hardness. For each formulation, the hardness of tablets was determined using the Monsanto hardness tester. The tablet was held along its oblong axis in between the two jaws of the tester. At this point, reading should be zero kg/cm2. Then constant force was applied by rotating the knob until the tablet fractured. The value at this point was noted.

Thickness

Thickness and diameter of tablets were important for uniformity of tablet size. Thus the thickness of the tablets was determined using vernier caliper.

Friability

Roche Friabilator was used for testing the friability using the following procedure. This test subjects a number of tablets to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm, dropping the tablets to a distance of 6 inches in each revolution. A sample of preweighed tablets was placed in Roche friabilator which was then operated for 100 revolutions i.e. 4 minutes. The tablets were then dusted and reweighed. A loss of less than 1 % in weight in generally considered acceptable. Percent friability (% F) was calculated as follows.

$$\textbf{Friability} = \frac{\textbf{Initial weight - Final weight}}{\textbf{Initial weight}} \times 100$$

Drug content

The amount of active ingredient(s) is determined by the method described in assay and amount of active ingredient is calculated. New method was used for determination of drug content given below:

Twenty tablets were weighed and powdered. The blend equivalent to 25 mg of Atenolol was weighed and dissolved in sufficient quantity of PH 6.8 phosphate buffer. The solution was filtered through Whatmann filter paper (no.41), suitably diluted with pH 6.8 phosphate buffer and assayed at 224.2 nm, using a UV-Visible double beam spectrophotometer (UV-1700 Shimadzu).

Wetting time

This is carried out to measure the time, which is required for the complete wetting of tablet formulations. A piece of tissue paper folded twice was placed in small Petridish containing 6 ml of water. A tablet was placed on paper. When water completely wets tablet, the time was noted.

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 & the time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio, R, was determined using following equation,

$$\textbf{R=10 (wa/wb)}$$

Where,

wb is weight of tablet before water absorption & wa is weight of tablet after water absorption.

In vitro disintegration time

Disintegration of FDT was generally occurring due to water uptake by superdisintegrant via capillary action, which results in swelling of Superdisintegrants and tablet get disintegrated. It was also reported that increased compaction force may increase or decrease disintegration time. In the present study disintegration test was carried out on six tablets using the apparatus specified in USP (Electrolab Mumbai). The distilled water at 37⁰C ± 2⁰C was used as a disintegration media and time in second taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds.

In-vitro dissolution studies

Dissolution rate was studied by using USP type-II apparatus at 50 rpm (USP XXIII Dissolution Test Apparatus) using 900 ml of Phosphate buffer 6.8 as dissolution medium. Temperature of the dissolution medium was maintained at 37±0.5ºC, aliquot of dissolution medium was withdrawn (from a zone midway between the surface of dissolution medium and the top of rotating paddle not less than 1 cm apart from the vessel wall) were filtered through Whatmann filter paper (no.41) at fixed time interval and was replaced with fresh dissolution medium. The absorbance of filtered solution was checked by using UV-visible double beam spectrophotometer (UV-1700 Shimadzu) at 224.2nm and concentration of the drug was determined from standard calibration curve. The data presented is the average of 3 determinations. Dissolution rate was studied for all designed formulation and conventional tablet. The withdrawn samples were analyzed by an UV spectrophotometer at 224.2 nm using Phosphate buffer 6.8 as a blank.

Characterization of Atenolol tablets

Thermogram of pure drug Atenolol and the combination of drug with polymers was recorded on a TA-60 WS Thermal Analyzer (Shimadzu) as shown in Fig1-2. The samples were hermetically sealed in aluminium pans and heated at a constant rate of 10°C/min over temperature range of 40 to 300°C. Inert atmosphere was maintained by purging nitrogen gas at flow rate of 50 ml/min.

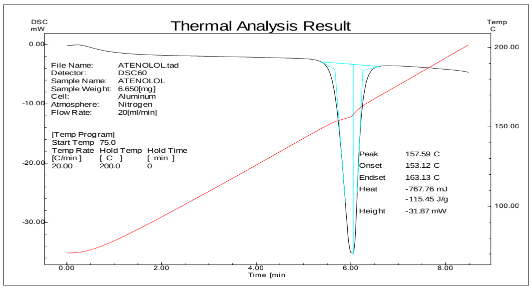

Figure 1: DSC thermogram of Atenolol the endothermic peak of Atenolol was seen at 157.59˚C with onset 153.12 ˚C. This complies with the reported literature value.

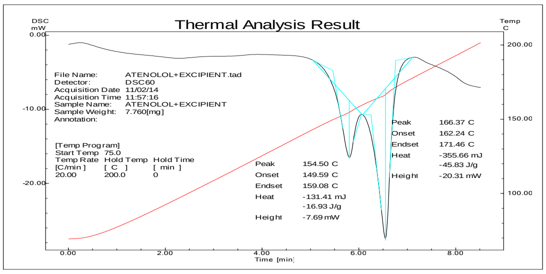

Figure 2: DSC thermograms of the pure drug and in combination with the polymers

RESULTS AND DISCUSSION

The co-processed and Physical method (non co-processed) superdisintegrants which was ready for compression, was examined for Angle of repose, Bulk density, Tapped density, Compressibility index, Hausner's ratio and the values for which are as reported in Table no. 2.

Table:2 Preformulation parameters of co-processed and non co-processed superdisintegrants

Formulation batches	Evaluation Parameters					
	Angle of Repose	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Compressibility Index (%)	Hausner's Ratio	Flowability
CP1	24.77	0.256	0.285	10.25	1.11	Good
CP2	24.28	0.244	0.277	12.17	1.13	Good
CP3	25.11	0.263	0.303	13.14	1.15	Good
PM1	28.60	0.537	0.662	18.88	1.23	Good

PM2	28.39	0. 537	0. 660	18.63	1. 23	Good
PM3	27.59	0.518	0.645	19.69	1.24	Good

According to literature survey powders with Compressibility index values below 16% were suitable for producing tablets via direct compression and those with HR values below 1.25 and angle of repose below 30 indicate good flow properties of powders. The bulk density of both co-processed and non co-processed excipients was found to be in the range of 0.244 to 0.537 gm/ml, whereas the tapped density was observed between 0.277 to 0.662 gm/ml. From the values of bulk density and tapped density the values for Compressibility index and Hausner's ratio were calculated. The values for Compressibility index were found between 10.25 to 19.69. The values for Hausner's ratio were found to be less 1.11 to 1.24. Angle of repose was found to be less than 30 which indicate good flow of powder. All these values indicate good flow properties of powder blend, uniform die fill and better compression ability. Therefore, from this data so obtained, it was decided to go for direct compression of tablets from the powder blends. The blended mixture which was ready for compression was also examined for Angle of repose, Bulk density, Tapped density, Compressibility index, Hausner's ratio and the values for which are as reported in Table no.3.

Table 3: Preformulation parameters of formulations powder blend.

Formulation batches	Evaluation Parameters					
	Angle of Repose	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Compressibility Index (%)	Hausner's Ratio	Flowability
CP1	25.11	0.409	0.462	11.48	1.06	Good
CP2	25.96	0.438	0.5	12.3	1.14	Good
CP3	26.56	0.403	0.45	10.49	1.11	Good
PM1	25.86	0.378	0.434	12.88	1.14	Good
PM2	26.36	0.416	0.476	12.51	1.14	Good
PM3	28.32	0.454	0.526	13.64	1.15	Good
C0	29.25	0.53	0.59	10.16	1.11	Good

The bulk density of all formulations powder blend containing both non co-processed and co-processed excipients was found to be in the range of 0.378 to 0.53 gm/ml, whereas the tapped density was observed between 0.434 to 0.59 gm/ml. From the values of bulk density and tapped density the values for Compressibility index and Hausner's ratio were calculated. The values for Compressibility index were found between 10.16 to 13.64 %. The values for Hausner's ratio were found to be less than 1.25. Angle of repose was found to be less than 30 which indicate good flow of powder. Overall these values indicate good flow properties of powder blend, uniform die fill and better compression ability and also the DSC study reveals that their exist a compatibility between drug and excipients. Therefore, from this data so obtained, it was decided to go for direct compression of tablets from the powder blends. The weight of all formulations batch tablets was found to be in the range of 148 to 155. None of the tablet was found to deviate from the average weight of tablets. Hardness test for all formulations was carried out and observations obtained were in the range of 3.0 to 4.5 kg/cm2. Test for friability was conducted for all formulations, % friability was found to be in the range of 0.212 to 0.564. *In vitro* disintegration time for all formulations was found to be in the range of 20 to 140 sec. whereas the thickness of all formulations containing both excipients was found to be uniform as it was obtained in the range of 3.3 to 3.4 mm. Drug content of all formulations was observed between 99.19 to 101.83. Wetting time of tablets are found in the range of 22 to 142 sec. and the water absorption ratio was found in the range of 54.08 to 92.11 %. The values for thickness and diameter signify uniformity and it was due to uniformity in die fill, good flow properties, uniform pressure and appropriate punch movement. Drug content for all formulations showed uniformity which indicated that there was an uniform flow and uniform distribution of drug. Weight variation tests for all formulations showed weight variation with deviation less than ± 7.5, which complies with I.P specification and signifies that there is uniformity in flow of powder blend which leads to uniform die fill. Hardness for all formulations was observed to be proper, which signify that tensile strength of all formulations was maintained after direct compression. Friability test for all formulations indicated that % friability was less than 1%, which complies the I.P specification and reveals that all formulations have possessed good physical strength and can withstand the mechanical shocks that can be observed during handling, shipping and transportation. *In vitro* disintegration study explained that there was decrease in disintegration time with successive increase in concentration of Crospovidone in both types of formulations but comparatively co-processed formulations take least time for disintegration with respect to their physical mixture formulations. Such a difference in disintegration time between both of these formulations indicates that in co-processed formulation there might be increase in capillary action of Superdisintegrants which might have led to improved water uptake. Wetting time and water absorption ratio was determined for all formulations. It was revealed that due to co-processing comparatively wetting time and water absorption ratio showed by co-processed formulations was better than non co-processed formulations due to improved capillary mechanism. Results are shown in Table no.4.

Table 4: Evaluation parameters of Atenolol FDT

Evaluation Parameters	Formulation batches						
	C0	**CP1**	**CP2**	**CP3**	**PM1**	**PM2**	**PM3**
$Weight Variation(mg)	150±5	150±5	150±5	150±5	150±5	150±5	150±5
Hardness (Kg/cm²)	4.0–4.5	3.0–3.5	3.0–3.5	3.0–3.5	3.0–3.5	3.0–3.5	3.0–3.5
Thickness (mm)	3.4	3.4	3.4	3.3	3.3	3.4	3.4
Friability (%)	0.212	0.332	0.451	0.325	0.538	0.564	0.517
Drug Content (%)	100.12	99.19	99.92	99.75	99.57	101.83	100.13
Water Absorption Ratio (%)	54.08	92.11	85.51	82.08	78.59	74.75	68.14
***Wetting Time (seconds)**	142±2	22±2	34±2	45±4	32±4	42±4	47±4
***In vitro* DT (seconds)**	140	20±10	32±20	43±30	30±10	40±10	45±25

$All values are mean ± SD, (n = 20), *All values are mean ± SD, (n = 3).

Dissolution rate was studied for all designed formulations. Among the various formulations of fast dissolving tablet of Atenolol, the formulation containing co-processed superdisintegrants Crospovidone and Croscarmellose sodium in 1:1 Proportion (Batch CP1) is the best formulation having 100.54% drug release in least time and the least time for tablet disintegration. The Dissolution Graph of Atenolol FDT is shown in fig. 3.

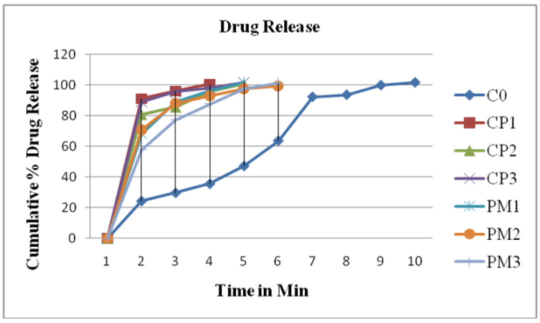

Figure 3: Graph of % Drug Release for individual Batch

CONCLUSION

From the present work it concludes that the co-processing of excipients could lead to the formation of excipients granules with superior properties such as better flow, low moisture sensitivity, superior compressibility and rapid disintegrating ability compared with physical mixture. Among the various formulations of fast dissolving tablet of Atenolol, the formulation containing co-processed Superdisintegrants Crospovidone and Croscarmellose sodium in 1:1 Proportion (Batch CP1) is the best formulation having 100.54% drug release in least time and the least time for tablet disintegration . Thus from the present work it reveals that the co-processed Superdisintegrants gives the better results than the physical mixture. Increasing the concentration of Crospovidone there is decrease in disintegration time of tablet. The results of a revealed that the amount of Croscarmellose sodium and Crospovidone significantly affect the dependent variables, disintegration time and also percentage friability. DSC study reveals that their no interaction between drug and excipients and can be used for preparation of fast dissolving tablet of Atenolol by direct compression method.

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