

Research Article

Formulation and evaluation of atenolol orodispersible tablets by co-processed super-disintegration process

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Abstract

Oral disintegrating tablet (ODT) is defined as “A solid dosage form containing medical substances or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue”. The aim of the present research is to formulate Atenolol oral disintegrating tablets. Atenolol is β_1 -cardio selective adrenergic receptor blocker, widely used in the treatment of hypertension, angina pectoris, arrhythmias and myocardial infarction. It works by slowing down the heart and reducing the work load of the heart. Atenolol was specifically developed so as to pass the blood brain barrier and overcome the side effects such as depression and nightmares. It has been reported that atenolol undergo extensive hepatic first pass metabolism following oral administration and has shorter biological half-life of 6 – 7 hours with oral bioavailability of 50%. The conventional tablets of atenolol are reported to exhibit fluctuations in the plasma drug levels after administration. Atenolol ODT's are prepared by novel co-processed super-disintegration process using Cross Povidone and Cross carmellose sodium, as the super disintegrants. The prepared tablets were characterized for their hardness, weight variation, disintegration time, wetting time, water absorption ratio friability, and in vitro dissolution studies. The ability of the tablet to release the drug faster depends on the concentration and type of super disintegrant. In this study the oral disintegrating tablets containing Cross carmellose sodium and Cross Povidone as the super disintegrant in the ratio of 1:1 shows better release of drug. About 99.5% of the drug was released from the tablets in 6 mins. Therefore, based on the physico chemical properties, in vitro drug release profile and mouth feel formulation F 1 containing 1:1 of Cross carmellose sodium and cros-povidone is optimised as the best formulation.

1. Introduction

The oral route of administration is considered as the most widely employed route of administration due to its wide range of advantages like stability, ease of administration, accurate dosage, self medication and patient compliance. Hence oral solid dosage forms are mostly preferred. Among all the dosage forms, the tablet dosage form is the most popular, because of ease of transportability and lower manufacturing cost [1]. The disadvantage of oral dosage forms such as Dysphasia or difficulty in swallowing can be overcome by developing rapidly disintegrating and dissolving tablet dosage forms which dissolve in saliva and does not require water for swallowing [2]. Recent development in novel drug delivery system to enhance the safety and efficacy of drugs during administration of conventional tablets led to the development of oral disintegrating tablets [3].

United States Food and Drug Administration (FDA) defined ODT as “A solid dosage form containing medical substances or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the

tongue” [4]. The disintegration time for ODTs generally ranges from few seconds to a minute [5].

Atenolol is β_1 - cardio selective adrenergic receptor blocker, widely used in the treatment of hypertension, angina pectoris, arrhythmias and myocardial infarction [6]. This is also used for prophylactic treatment of migraine. It was specifically developed to pass through the blood brain barrier. Atenolol being a cardio selective beta blocker does not show adverse effects when given to patients suffering from bronchial asthma and diabetes mellitus [7]. Patient compliance is better with atenolol because it is given once a day. It is also used to treat other conditions including dysautonomia, anxiety and hyperthyroidism. It has been reported that atenolol undergo extensive hepatic first pass metabolism following oral administration and has shorter biological half-life of 6 – 7 hours with oral bioavailability of 50% [8]. There are only conventional tablets of atenolol in the market and administration of these tablets has been reported to exhibit fluctuations in the plasma drug levels results either in manifestation of side effects like nausea, diarrhoea, ischemic colitis and mesenteric arterial thrombosis or reduction in drug concentration at receptor site. Therefore, the main aim of the present research is to formulate oral disintegrating tablets of Atenolol using a combination of super disintegrants such as Croscopovidone, Cross Carmellose [9].

2. Materials and Methods

The active ingredient Atenolol was received as a gift sample from Yarrow Chem Products, Mumbai, India. Microcrystalline cellulose received from Otto Kemi, Mumbai, India. Cross Povidone and Cross carmellose sodium are the super disintegrants received from Yarrow Chem Products, Mumbai, India.

All the other ingredients used in the formulation are of pharmaceutical analytical grade.

Table 1:-Formula of atenolol tablets

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	Normal (mg)	Control (mg)
Atenolol	50	50	50	50	50
Croscopovidone & Croscarmellose Sodium	12	12	12	12	-
Microcrystalline Sodium	108	108	108	108	120
Mannitol	5	5	5	5	5
Aspartame	15	15	15	15	15
Magnesium Stearate	4	4	4	4	4
Talc	6	6	6	6	6
Total Weight	200	200	200	200	200

2.1 Method

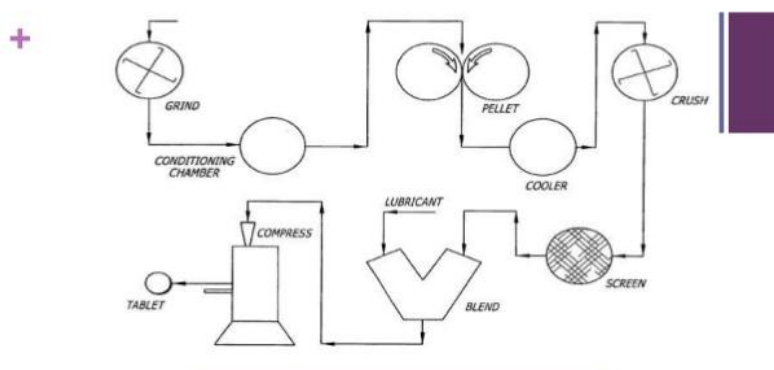
2.1.1 Preparation of Co-processed Super-disintegrants [10]:-

The Co-processed Super-disintegrants were by prepared solvent evaporation method. A blend of Croscarmellose Sodium and Croscopovidone in the ratio of 1:1, 1:2 and 1:3 was added to 10ml of methanol. The contents of the beaker were mixed thoroughly and stirred continuously till most of the methanol evaporated. The wet coherent mass was granulated through #44 mesh sieve. The wet granules were dried in hot air oven at 60°C for 20 minutes. The dried granules were passed through #44 mesh sieve and stored in airtight container till further use.

2.1.2 Preparation of tablets by Direct Compression Method [11]:-

Fast dissolving tablets of Atenolol were prepared by Direct Compression Method. 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 200mg by using 10-station Rotary minipress tablet machine.

Figure 1: Stepwise process for direct compression



2.2 Evaluation of tablets

2.2.1 Pre-compression characterization [12]:-

Bulk density

Bulk density of a powder is defined as the ratio of the mass of the powder and its bulk volume. For bulk density determination a weigh quantity of the powder material is introduced into a graduated measuring cylinder and volume of powder is determined.

$$\text{Bulk Density} = \frac{\text{Mass of the powder}}{\text{Bulk volume}}$$

Granule density

Granule density is the ratio of the mass of the granular powder and the volume occupied by the granular material together with its intra-particle spaces.

$$\text{Granule density} = \frac{\text{Mass of the granular powder}}{\text{Granule volume}}$$

Tapped density

For determination of the bulk density, a weigh quantity of the granular powder is introduced into a graduated measuring cylinder and is tapped mechanically either manually or using a tapping device till a constant volume is obtained.

$$\text{Tapped density} = \frac{\text{Mass of the granular powder}}{\text{Tapped volume of granules}}$$

Compressibility index or Carr's index:

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

Where B is the freely settled bulk density of the granules, and T is tapped bulk density of the granules.

Powders having Carr's index greater than 25 is considered to have poor flow and those powders having Carr's index 15 has good flow.

Angle of repose

The angle of repose is determined by allowing mass of powdered to flow freely through an orifice from a certain height and form a conical heap on the horizontal surface. The angle of repose is determined by the formula

$$\tan \theta = h/r$$

Where,

θ is the angle of repose,

h is the height of the heap of powder and

r is the radius of the base of the heap of powder.

2.2.2 Post compression characterization

Weight variation test [13]:

20 tablets were selected randomly from each formulation and their average weight was calculated using digital balance. All the 20 tablets were weighed individually and compared with the tablet to meet USP specifications if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

Table 2: Pharmacopeial specifications for tablet weight variation

Average weight of tablets (IP)	Average weight of tablets (USP)	Maximum % Difference allowed
Less than 80 mg	Less than 130 mg	10
80 mg-250 mg	130 mg-324 mg	7.5
More than 250 mg	More than 324 mg	5

Tablet Hardness [14]:-

Tablet hardness is termed as crushing strength and resistance to friability to withstand mechanical shocks of handling in manufacture, packaging and shipping. This can be tested by using one of the following hardness testers^[9] i.e. Monsanto hardness tester, Strong Cobb tester, Pfizer tester, Erweka and Varian tester.

Wetting time [15]:-

The wetting time of the tablets was measured by a simple procedure. A circular tissue paper of 10 cm diameter was placed in a Petri dish containing 10 ml of water containing Eosin blue. A tablet was carefully placed on the surface of tissue paper. The time required for developing blue colour on the upper surface of the tablet was noted as the wetting time.

Water Absorption Ratio [16]:-

A piece of tissue paper folded twice was placed in small Petridish containing 6ml of water. A tablet was put on the paper and the time required for complete wetting was measured. The wetting tablet was then weighed. Water absorption ratio R, was determined using the equation

$$R=10(W_a/W_b)$$

Where,

W_b is the weight of the tablet before water absorption,

W_a is the weight of the tablet after water absorption.

Friability [17]:-

It is used to measure the mechanical strength of tablets. Roche friabilator is used to determine the friability by following procedure.

Procedure: - Twenty tablets were weighed and placed in Roche Friabilator where the tablets were exposed to rolling and repeated shocks resulting from free falls within the apparatus. After 100 revolutions, tablets are removed, dedusted and weighed again. The friability was determined as the percentage loss in weight of the tablets.

$$\% \text{ Friability} = (\text{loss in weight} / \text{initial weight}) * 100$$

In vitro dissolution studies [18]:-

Freshly prepared pH 6.8 phosphate buffer (900ml) was placed in each dissolution vessel of dissolution test apparatus (USP, II Paddle method). The tablets were placed in the dissolution medium. The temperature of the dissolution medium was maintained at $37 \pm 0.5^\circ\text{C}$ and the paddle was rotated at 50 rpm. Five ml samples were withdrawn. The sample volume was immediately replaced with the same volume of fresh media as when a sample was taken. The samples withdrawn were filtered, diluted and estimated spectrophotometrically [16] at 225 nm. Cumulative amount of the drug released at each interval was calculated by using standard graph of Atenolol.

3. Results**Table 2:-Pre compression parameters**

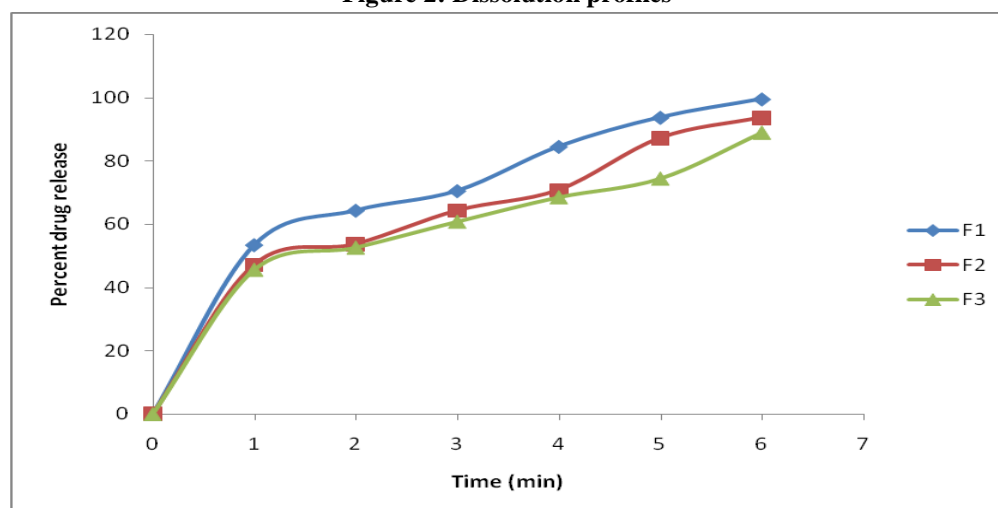
Formulation Code	Angle Of Repose	Bulk Density (Gm/MI)	Tapped Density (Gm/MI)	Carr's Index (%)	Hausner's Ratio	Flowability
F1	24.98	0.276	0.285	10.25	1.11	Excellent
F2	26.88	0.267	0.307	13.08	1.12	Good
F3	25.27	0.256	0.299	14.38	1.15	Good
Normal	28.80	0.318	0.401	20.69	1.17	Good
Control	29.62	0.320	0.400	20.00	1.18	Good

Table 3:-Post compression parameters

Formulation Code	F1	F2	F3	Normal	Control
Weight Variation	Pass	Pass	Pass	Pass	Pass
Hardness (kg/cm ²)	2.66	2.66	2.66	3.40	4.50
Friability (%)	0.413	0.433	0.437	0.465	0.524
Water Absorption Ratio (%)	25.22	24.10	22.90	8.40	5.59
Wetting Time (sec)	120	150	135	210	300

Table 4:- In-vitro dissolution data of co-processed super-disintegrant formulations of atenolol

TIME (min)	Cumulative percentage drug release		
	F1	F2	F3
1	73.4	73.2	72.6
2	84.3	83.7	79.6
3	85.0	84.3	80.8
4	94.5	90.8	89.5
5	97.7	97.2	94.4
6	99.5	98.7	97.9

Figure 2: Dissolution profiles

4. Discussion

Atenolol Oral dispersible tablets were developed with an aim to improve patient's compliance. The development was initiated with standard calibration curve using UV spectrophotometric methods for analysis of the drug. The UV spectrophotometric method was developed in 0.1N HCl at 225nm. The method shows linearity in the concentration range of 5-40µg/ml with a correlation coefficient of 1.

The Atenolol Oral disintegrating tablets were developed by co-processing of super disintegrants such as Croscopovidone, and Cross carmellose sodium in the ratios 1:1, 1:2 and 1:3. All the 3 formulations prepared with different ratios of Croscopovidone and Cross carmellose releases 90 to 100% of the drug within 6mins. Based on the physico chemical properties, in vitro drug release profile, water absorption ratio and wetting time F 1 containing Cross carmellose sodium and Cross Povidone in the ratio 1:1 is optimised as the best formulation.

5. Conclusion

Oral disintegrating tablets of Atenolol were successfully prepared by using different superdisintegrants by direct compression method. The present investigations helped in studying the effect of formulation process variables especially the concentration of different super disintegrants on the dispersion time and drug release profile. The rapid disintegration of Atenolol tablets formulated in this investigation may possibly help in administration of Atenolol in a more palatable form without water, thus, the "patient-friendly dosage form especially for geriatric, bedridden, and non cooperative patients which makes it a promising candidate for further studies, including stability studies, on the way to achieving intraoral formulations.

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