Research Article

Design and Characterization of Fast Release Sublingual Tablets of Atenolol

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ABSTRACT

The present study aimed to Design and Characterization of Atenolol fast release sublingual tablets and it's prepared by using super disintegrants like cross Carmellose sodium, cross povidone, and sodium starch glycolate by direct compression method. All the batches were evaluated for weight variation, hardness, friability, drug content uniformity and *in-vitro* drug release characteristics as per USP monograph. The drug release rates from tablets [optimized formulation (F8 & F12)] were compared with pure drug of Atenolol and finally we have found that all formulations (F1 to F12), drug released up to 99% within 30 mints only. The formulation F12 was found to be drug released up to 99% within 15 mints because in this formulation drug, polymer and super disintegration ratios is present 5:1:1. The in situ interactions between the drug, polymers and excipients during direct compression process are also investigated by FT-IR examinations

Keywords: Atenolol (ATL), Cross Carmellose sodium (CCS), Crospovidone (CP), Low substituted hydroxy propyl cellulose (LHPC), Sodium starch glycolate (SSG).

INTRODUCTION

Tablets are solid dosage forms and each preparation containing a single dose of one or more active ingredients and are obtained by compressing uniform volumes of particles. Atenolol is a 2-(4-{2-hydroxy-3-[(propan-2 yl) amino] propoxy} phenyl) acetamide[1], and structure is show in Figure 1. It is a white or almost white powder with a molecular weight of 266.3361 gm/mol. It is slightly soluble in water and sparingly soluble in ethanol. It is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine.[2] The biological half life[3] of drug (6 to 8 h) also favors for the development of immediate release formulations. ATL is a β-blocker, is used widely in various cardiovascular diseases, e.g., hypertension, angina pectoris, arrhythmias, myocardial infarction and in prophylactic treatment of migrane.[4] It is one of the most commonly used β-blockers for hypertension and angina.[5] Recent advances in novel drug delivery system aims to enhance safety and efficacy of drug molecule by formulating a fast dissolving formulation for administration and to achieve better patient compliance. Pediatric and geriatric patients have difficulty in swallowing the conventional dosage forms. These dosage forms dissolve or disintegrate in the oral cavity within a minute without the need of water or chewing.[6]

The sublingual route usually produces a faster onset of action than orally ingested tablets and the portion absorbed through the sublingual blood vessels bypasses the hepatic first-pass metabolic processes. The purpose of this study was to develop a sublingual Atenolol tablet formulation having good Bio-availability.

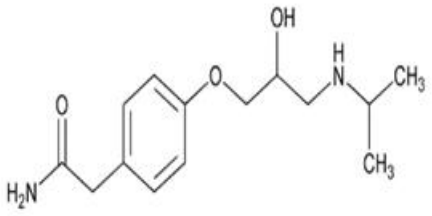


Figure 1: Structure of Atenolol

Direct compression is one of these techniques which require incorporation of a super disintegrant into the formulation, or the use of highly water soluble excipients to achieve fast tablet disintegration. Direct compression does not require the use of water or heat during the formulation procedure and is the ideal method for moisture and heat-labile medications.[7] Fast dissolving drug delivery can be achieved by various conventional methods like direct compression, wet granulation, moulding, spray drying, freeze drying, and sublimation[8] and The Main advantages of direct compression are low manufacturing cost and high mechanical integrity of the tablets.[9]

MATERIALS AND METHODS

Materials

Atenolol was obtained as a gift sample from Cipla Ltd., Mumbai. Low substituted hydroxy propyl cellulose (LHPC) obtained as a gift sample from M/S. Signet chemical corporation ltd., Mumbai. Cross povidone, Cross Carmellose Sodium, Sodium Starch Glycolate, Micro Crystalline Cellulose, Sodium Saccharine, Aerosil and Magnesium Stearate purchased from Strides Arcolab Ltd,. Bangalore. All the chemicals and solvents used were of analytical grade.

Methods

Atenolol calibration curve

Calibration curve of Atenolol was constructed by using pH 6.8 phosphate buffer in the concentration range of 1–10 µg/ml. The drug was analyzed spectrophotometrically (Elico Double beam UV-Visible Spectrophotometer) at 225 nm (regression coefficient r^2 = 0.9999) and graph is shown in Graph 1.

Fabrication of Atenolol sublingual tablets

Atenolol sublingual tablets were prepared by the direct compression method using different polymers with different ratios of polymers. All the ingredients of the sublingual tablets of Atenolol were accurately weighed and mixed in mortar with the help of pestle, and then finally 0.6 mg of magnesium stearate, Aerosil was added for lubrication and triturated well. Then the blended material was compressed on the tablets by using SISCO tablet compression machine, Mumbai (using 6 mm flat-faced punches). The total weight of the all formulation was maintained at 100 mg. The compositions of Atenolol tablets prepared by direct compression are shown in Table 1, 2, and 3.

Table 1: Composition of Atenolol Sublingual tablets by using Direct Compression with SSG

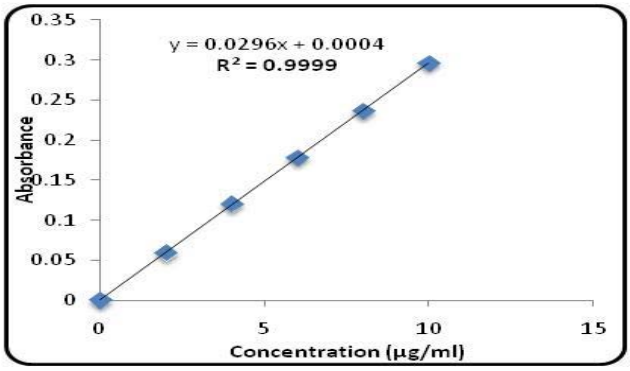
Ingredients (mg/tablet)	Formulations			
	F1	F2	F3	F4
Atenolol	25	25	25	25
SSG	2	3	4	5
LHPC	5	5	5	5
MCC	56.8	55.8	54.8	53.8
Aerosil	0.6	0.6	0.6	0.6
Magnesium Stearate	0.6	0.6	0.6	0.6
Sodium Saccharine	10	10	10	10
Total weight	100	100	100	100

Table 2: Composition of Atenolol Sublingual tablets by using Direct Compression with CCS

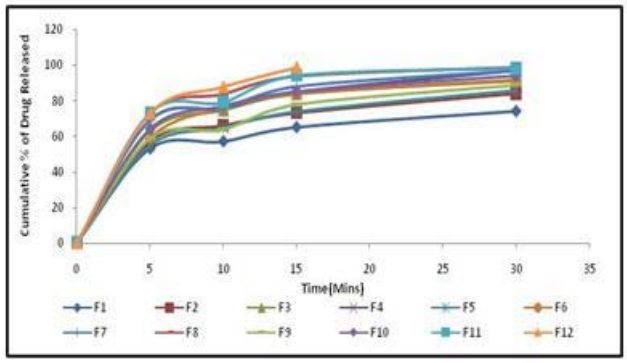
Ingredients (mg/tablet)	Formulations			
	F5	F6	F7	F8
Atenolol	25	25	25	25
CCS	2	3	4	5
LHPC	5	5	5	5
MCC	56.8	55.8	54.8	53.8
Aerosil	0.6	0.6	0.6	0.6
Magnesium Stearate	0.6	0.6	0.6	0.6
Sodium Saccharine	10	10	10	10
Total weight	100	100	100	100

Table 3: Composition of Atenolol Sublingual tablets by using Direct Compression with CP

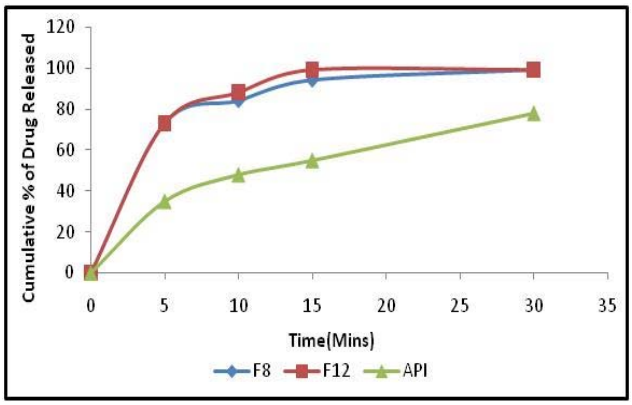
Ingredients (mg/tablet)	Formulations			
	F9	F10	F11	F12
Atenolol	25	25	25	25
CP	2	3	4	5
LHPC	5	5	5	5
MCC	56.8	55.8	54.8	53.8
Aerosil	0.6	0.6	0.6	0.6
Magnesium Stearate	0.6	0.6	0.6	0.6
Sodium Saccharine	10	10	10	10
Total weight	100	100	100	100



Graph 1: Calibration Curve of Atenolol



Graph 2: *In-vitro* Drug Release Profile of Atenolol Sublingual Tablets (F1-F12)



Graph 3: Comparison of *In-vitro* Drug Release Profile of Optimized Formulation (F8, F12) with Pure Drug (Atenolol)

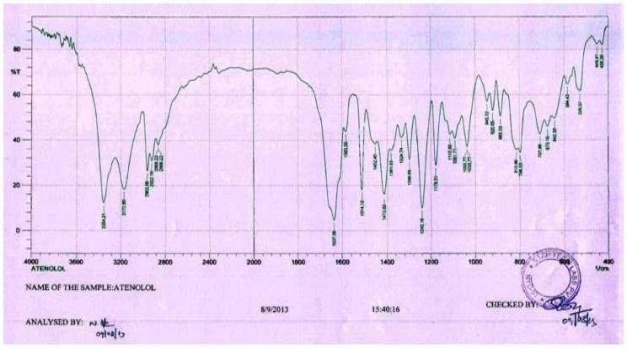


Figure 2: FT-IR Spectra of Pure drug (Atenolol)

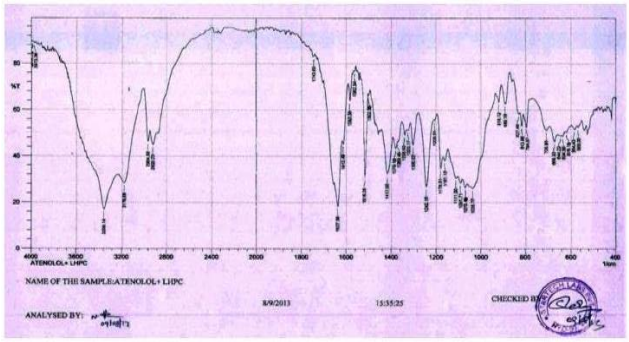


Figure 4: FT-IR Spectra of Atenolol & LHPC

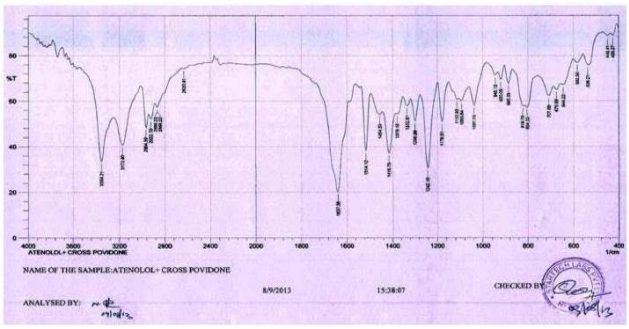


Figure 3: FT-IR Spectra of Atenolol & Cross Povidone

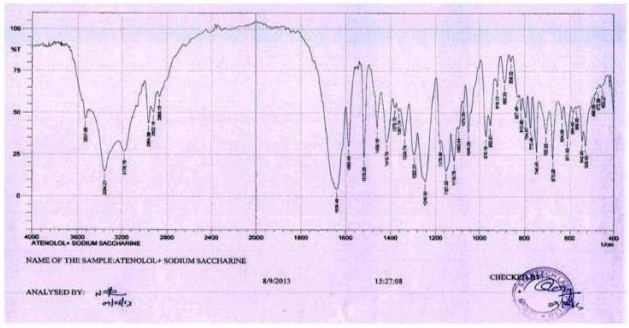


Figure 5: FT-IR Spectra of Atenolol & Sodium saccharine

Table 4: Post Compression Parameters of Atenolol sublingual tablets prepared by Direct Compression method

Formulations	Weight Variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)
F1	98.3±0.024	3.00±0.08	0.210±0.02	0.12±0.21
F2	96.5±0.027	3.01±0.08	0.213±0.02	0.15±0.22
F3	98.8±0.020	3.02±0.06	0.212±0.02	0.14±0.21
F4	97.7±0.022	3.00±0.07	0.212±0.01	0.19±0.22
F5	99.6±0.023	3.03±0.06	0.214±0.01	0.19±0.21
F6	99.5±0.021	3.02±0.05	0.213±0.03	0.10±0.23
F7	92.3±0.022	3.01±0.07	0.210±0.03	0.16±0.22
F8	93.4±0.021	3.03±0.08	0.212±0.04	0.14±0.23
F9	95.6±0.022	3.01±0.08	0.213±0.02	0.12±0.22
F10	92.3±0.021	3.00±0.07	0.212±0.02	0.21±0.22
F11	101.2±0.022	3.02±0.07	0.212±0.02	0.18±0.22
F12	99.9±0.024	3.01±0.08	0.213±0.02	0.11±0.22

All the values are expressed Mean ± S.D, N=3; Tablet friability was less than 0.21%, while hardness ranged from 3-3.03 kg/cm^2; Good uniformity in drug content was found among the various formulation batches; The drug content was more than 98% in all cases with less than 0.05% standard deviation. Thus, all the tablet formulations showed acceptable physical characteristics.

Drug-Excipients Interaction Studies

Pre-formulation studies are very important for the successful formulation of any dosage form. Differential Scanning Calorimetry (DSC), Fourier Transform Infrared (FT-IR) Spectroscopy studies were used for the evaluation of physicochemical compatibility and interactions, which helps in the prediction of interaction of the drug with polymers, binders and lubricants used in case of tablet formulations. Positive interactions sometimes have a beneficial effect as far as desired release parameters are concerned[10]. Therefore, in the present studies Atenolol, Polymers were used and analyzed for compatibility studies.

FT-IR studies

The FT-IR analysis was carried out to find out possible drug-polymer interaction. The FT-IR was performed on a Shimadzu electronic system. The samples were mixed required quantity of potassium bromide (KBr) sealed in an aluminum pan and heated at a constant rate 100^{0}C/minute, over a temperature range 25^0 to 400^{0}C.

Data Analysis

Different release kinetics is assumed to reflect different release kinetics mechanism. Therefore two kinetics models including zero order release equation (Eq.1), and first order equation (Eq. 2) were applied to process in vitro data to find the equation with the best fit.

$Q = K_1 t$..... (1)

$Q = 100 (1\text{-}e\text{-}K_2 t)$..... (2)

Where Q is the release percentage at time t. K_1, and K_2 are the rate constant of zero order, and first order respectively.

Table 5: Post Compression Parameters of Atenolol sublingual tablets prepared by Direct Compression method

Formulations	Drug Content Uniformity (%)	Disintegration Time (sec)	Wetting Time (Sec)
F1	99.92±0.02	29±0.05	34±0.07
F2	98.3±0.01	27±0.06	32±0.07
F3	100.01±0.02	23±0.05	31±0.07
F4	98.5±0.01	17±0.06	23±0.05
F5	98.9±0.01	27±0.07	31±0.07
F6	100.02±0.01	24±0.04	28±0.07
F7	98.6±0.01	19±0.04	23±0.05
F8	100.01±0.03	15±0.03	22±0.05
F9	99.2±0.02	20±0.02	24±0.07
F10	100.02±0.01	16±0.01	20±0.05
F11	99.78±0.02	12±0.08	17±0.05
F12	99.94±0.04	10±0.01	15±0.07

All the values are expressed Mean ± S.D, N=3

Evaluation of Tablet Formulations

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

Weight variation test

To study weight variation, 20 tablets of each formulation were weighed using an Electronic balance (Adventure OHAUS) and the test was performed according to the official method.

Friability test

For each formulation, the friability of 10 tablets was determined using the Roche friabilator (Remi equipment Pvt. Ltd., Mumbai, India). 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 pre weighed 10 tablets was placed in Roche friabilator, which was then operated for 100 revolutions for 4 minutes. The tablets were then de dusted and reweighed. The results are depicted in Table 4.

Hardness

For each formulation, the hardness of 6 tablets was determined using calibrated 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/cm^2. Then constant force was applied by rotating the knob until the tablet fractured. The value at this point was noted in kg/cm^2. The results are shown in Table No: 04.

Thickness

For each formulation the thickness of 6 tablets was determined by using vernier caliper (Pico India) and results were depicted in Table No: 04.

Drug content

20 randomly selected tablets from each formulation (F1-F12) were finely powdered and powder equivalent to 25 mg of Atenolol was accurately weighed and transferred to 100 ml volumetric flask containing 50 ml pH 6.8 phosphate buffer. The flask was shaken to mix the contents thoroughly and the volume was made up to the mark with phosphate buffer pH 6.8. 1ml of the filtrate was suitably diluted and Atenolol was estimated by using double beam UV-Visible spectrophotometer at 225 nm. This was repeated thrice and the results are depicted in Table No: 05.

Wetting time

The wetting time was measured by the tablet was placed at the centre of two layers of absorbent paper fitted in to a dish. After the paper was thoroughly wetted with distilled water, excess water was completely drained out of the dish. The time required for the water to diffuse from the wetted absorbent paper throughout the entire tablet was then recorded using a stopwatch. The results are depicted in Table No: 05.

Disintegration Time

Disintegration time for sublingual tablets was determined using Electro lab tablet disintegration apparatus with phosphate buffer of pH 6.8 as a medium. The volume of medium was 900 ml and temperature was 37± 0.5^0C. The time in seconds taken with no palatable mass remaining in the apparatus was measured. The results are presented in Table No: 05.

In-vitro drug release study

In-vitro drug release rate of ATL sublingual tablets was carried out using Dissolution testing apparatus (Electro lab, India). The dissolution test was carried out using 900 ml of 6.8 pH phosphate buffer, at 37±0.5°C and stirred at 50 rpm. 5 ml of aliquots were withdrawn at different time intervals (5, 10, 15 and 30 min) and an equivalent volume of medium (pre warmed at 37°C) was added to maintain constant volume. Withdrawn samples were analyzed spectrophotometrically at 225 nm using an Elico double beam UV-Visible Spectrophotometer.

RESULTS AND DISCUSSION

Atenolol sublingual tablets were prepared by direct compression method. Three different groups of formulation with variation of tablet excipients and super-disintegrant variations were prepared with each group containing four different formulations. All batches of the tablets were preliminarily evaluated for various physical parameters such as hardness, friability, drug content, disintegration time and dissolution which were reported in Table No: 04. All above properties and value were near to boundary of standard limit. All the tablets maintained hardness in the range of 3.00 to 3.03 kg/cm^2. The loss in total weight of the tablets due to friability was in the range of 0.10 to 0.21%. The drug content in different formulations was highly uniform and in range of 98 to 100.02%. Formulation F12 was quickly disintegrated compared to other formulations and the optimized formulation F12 is compared with pure drug Atenolol. From the in-vitro dissolution studies, it was observed that formulation F12 showed 99% dissolution efficacy in 15 min. The drug release patterns for different formulations were shown in Graph 2. The tablet Formulations containing CP of F12 showed less disintegration time and maximum drug release and is compared with pure drug Atenolol. The release pattern was shown in Graph No: 3. Hence the formulation F12 is selected as an optimized Atenolol sublingual tablet for subjecting into emergency conditions for the treatment of anginal pain and hypertension diseases. The drug-excipient interactions was carried out by FT-IR examination and results found that no interaction between drug and excipients. The FT-IR graph of pure drug Atenolol and in combination of drug with cross povidone, LHPC, Sodium saccharine results are shown in Figure 2 to 5. The in-vitro drug release data of all Atenolol sublingual tablets were subjected to goodness of fit test by linear regression analysis according to zero order equation, first order equation, Higuchi's equation and Korsmeyer-Peppas equation to ascertain the mechanism of drug release. Hence the drug release followed the first order release kinetics with diffusion mechanism.

CONCLUSION

The drug release from all the formulations mentioned above followed first order kinetics. It was also concluded that the drug release was greatly influenced by the nature of the super disintegrants incorporated in the formulations. Finally to achieve a fast release formulation of Atenolol sublingual tablets by using a different polymers (super disintegrations). Formulation containing Atenolol, cross povidone, LHPC and MCC having ratios (1:1:5) was found to satisfy the desired criteria when used in the quantity given for formulation F12. From the study, it can be concluded that direct compression method showed better disintegration and drug release. The prepared tablets disintegrate within few seconds without need of water, thereby enhancing the absorption leading to its increased bioavailability.

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