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Co-Processed Super disintegrant Loaded Atenolol Beads Sublingual Tablet for Hypertension

G. Swapna[1,3*], K. Sesha Maheswaramma[2], and K. Bhaskar Reddy[3]

[1] Research Scholar, JNTUA, Anantapur - 515002, Andhra Pradesh, India.
[2]Department of Chemistry, Jawaharlal Nehru Technological University Anantapur College of Engineering, Pulivendula- 516-390, Andhra Pradesh, India.
[3] Centre For Pharmaceutical Nanotechnology, Department of Pharmaceutics, Sri Venkateswara College of Pharmacy, RVS Nagar, Tirupati Road, Chittoor – 517 127. Andhra Pradesh, India.

Abstract

Hypertension develops over many years and affects everyone eventually without having any signs and symptoms. It is considered as one of the primary medical issues and its successful treatment is of high significance. Last few years the remarkable advancement in the drug delivery system has been made. For this purpose current study focused on the formulation of atenolol sublingual tablet (ST) containing beads developed by co-processed superdisintegrants. Co-processed superdusintegrants were used to improvise the formulation and their processability and efficacy of the active drug. Atenolol is an antihypertensive drug combined with different superdisintegrants (croscarmellose sodium (CS), crospovidone (CP), and sodium starch glycolate (SSG)) at a different ratio to formulate beads, which again compressed into a tablet by direct compression technique. Formulated sublingual tablets were evaluated by different parameters for pre and post-compression studies. The post-compression parameters are weight variation test, hardness, thickness, friability, drug content, swelling index, pH, disintegration test, and in vitro dissolution studies at pH 6.8. Compatibility study between drug-disintegrants was investigated by FTIR and DSC studies. Formulation F6 which contains a Co-processed superdusintegrant produces short wetting, disintegration, and dissolution time. Formulation F6 has shown faster drug release 100% at 4 min.

Keywords Antihypertensive, Atenolol, Fast dissolving tablet, Beads, Disintegrants

1. Introduction

The oral route has grabbed a lot of attention of clinicians for drug delivery due to its ease of administration, safety, good patient compliance [1], and avoidance of pain like parenteral. Enzymatic degradation in GIT, irritation or pain for the stomach, and low absorption or poor bioavailability was observed for many drugs which are prohibited by the oral route. Drug delivery through the buccal route is considered as one of the better alternatives over the oral route. It shows a better and faster drug absorption site by avoiding hepatic first-pass metabolism and also improves the bioavailability of the drug [2,3]. The mucous membrane present in the buccal cavity is highly vascularized which helps many drugs for easy permeation and better absorption [4]. The buccal route is considered as one of the potential sites for drug administration due to the better absorption, improved bioavailability, rapid onset of action, and ease of accessibility.

Clinician prefers several types of dosage form for the treatment purpose such as tablets, capsules, suspensions, emulsions, syrups, aerosols, cream, paste, nano-drug delivery, films, beads, microspheres, etc. Last few decades the researchers focused on modern technology in the development of new dosage forms to enhance the quality of treatment. Oral solid dosage became more popular due to painless insertion, self-administration, accurate dosing, and avoid non-compliance [5]. Dysphagia is the main drawback associated with the patient, frequently using solid dosage form. Geriatric and

children who found difficulty in swallowing solid dosage form need a convenient drug delivery system [6]. Among different formulations administered through the buccal route, sublingual tablets became more popular and increased acceptance due to rapid disintegration and dissolution when placed under the tongue. The sublingual tablet doesn't require a skilled person to be administered and without water can be administered easily. Different types of drugs such as antiulcer, antihypertensive, antitussives, antiasthmatics, antihistamines, anticancer and pain removal drugs can be used as sublingual tablets [7].

Beta receptor blocking drugs is predominantly used for the treatment of cardiovascular disorder such as hypertension, cardiac arrhythmia, and heat treatment. These drugs possess one chiral center which helps in the binding of the β-adrenergic receptor. Drugs like atenolol having single chiral center shows (-) enantiomer help in binding to the β-adrenergic receptor [8]. Atenolol is a hydrophilic β-adrenergic receptor blocking agent widely used for the treatment of cardiac diseases such as hypertension, angina pectoris, arrhythmias, and myocardial infarction [9]. Atenolol shows activity towards the treatment of migraines. The absorption of atenolol through the oral route is rapid but incomplete and shows 50%-60% bioavailability [10]. Reports confirm that atenolol exhibits fluctuation in plasma drug concentration due to its incomplete absorption. To maintain a constant plasma drug concentration for a desired therapeutic response a suitable drug delivery system is required. In this current study, we have used a co-processed technique in which two or more disintegrants interacting at sub particle level to obtain a disintegrant having superior property as compare to individuals [11].

The main objective of the present research work is to improve the bioavailability of atenolol at the receptor site by formulating atenolol beads as a sublingual tablet. Different types of superdisintegrants (croscarmellose sodium, crospovidone, and sodium starch glycolate) [12] are used at different ratios in a co-processed form to obtain the sublingual tablet.

2. MATERIALS AND METHODS

Atenolol was purchased from Sigma Aldrich, India. Croscarmellose sodium and sodium starch glycolate are obtained from Signet, Mumbai. Crospovidone was procured from a Nice laboratory, India. Similarly, microcrystalline cellulose, mannitol, camphor, aspartame, talc, magnesium stearate, and remaining excipients were of analytical research-grade and used as received from Divya Chemicals, India.

2.1. Preparation of co-processed superdisintegrants

The co-processing between the different superdisintegrants was prepared by the solvent evaporation method [13]. A mixture of croscarmellose sodium, crospovidone, and sodium starch glycolate have been taken at different ratio (Table 1) was added to 10 ml ethanol and stirred continuously till the ethanol evaporated completely. The obtained wet mass was dried followed by grinding with mortar and pestle and passed through sieve no. 44. Obtained granules were shifted to an airtight container for further use.

2.2. Preparation of atenolol loaded beads

Atenolol-containing beads (Formulation F1-F7) were prepared using 1% calcium chloride solution as a cross-linking agent by ionotropic gelation technique. Briefly, the required amount of superdisintegrants say croscarmellose sodium, crospovidone, and sodium starch glycolate individually and co-processed superdisintegrants at different ratios (Table 1) were used to prepare the solution independently. Further

atenolol was added to the previously prepared solution and ultra-sonicated for 5-10 min for debubbling. The resulting solution was added via a 21-gauge needle dropwise into 100 ml of 1% calcium chloride solutionand 10 ml of 10% w/v acetic acid, allow retaining the beads as such for 15-25 min to complete the reaction and harden the droplets [14]. The beads were rinsed thrice with distilled water and dried at 45^{o}C in a hot air oven for 6h and stored in a desiccator for further use.

2.3. Formulation of atenolol beads as sublingual tablets

Beads converted into tablets by direct compression method, using different disintegrants and combinations of co-processed disintegrants shown in formulation F1-F7 (Table 1) [15-18]. The weight amount of beads was taken accurately from individual formulations for tablet compression. The hydraulic press was used at a pressure of 15 psig using flat faced punch of 10 mm diameter for compression of tablet [19, 20]. The effect of atenolol sublingual tablets has been studied considering % of drug release.

Table 1. Formulation of atenolol beads as a sublingual tablet by direct compression method

Batch No.	Drug (mg)	CS (mg)	CP (mg)	SSG (mg)	Co-processed (mg)			Camphor (mg)	Lactose (mg)	MS (mg)	Aspartame (mg)	Total weight (mg)
					CS	CP	SSG					
F1	25	30	-	-				30	50	5	10	150
F2	25		30	-				30	50	5	10	150
F3	25			30				30	50	5	10	150
F4	25	-	-	-	10	10	10	30	50	5	10	150
F5	25	-	-	-	20	5	5	30	50	5	10	150
F6	25	-	-	-	12	12	6	30	50	5	10	150
F7	25	-	-	-	5	5	20	30	50	5	10	150

3. Evaluation of powder blend:

3.1. Bulk density

Bulk density is the ratio of the mass by the volume of an untapped powder sample. The bulk density is measured in g/ml. The bulk density depends upon both the density of the powder particles and the arrangement of the powder particles. The bulk density influences preparation, storage of the sample. The mathematical representation is given below.

Bulk density = weight of the powder/Bulk volume

3.2. Tapped density

In tapped density, the bulk powder is mechanically tapped in a graduated cylinder until the volume change is observed. Here the tapped density is calculated as mass divided by the final volume of the powder.

Tapped density = weight of the powder/tapped volume

3.3. The angle of repose

It gives an idea of the flowability of a powder or a bulk solid. There is some factor which responsible for the flowability of powders such as particle size, size distribution, shape, surface area, etc. Flowability of the powder depending on the different environments and can be changed easily. The angle of repose was calculated by the following formula.

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

Where,

θ = angle of repose

h = height of the formed cone

r = radius of the circular base on the formed cone.

3.4. Carr's index

It is one of the most important parameters to characterize the nature of powders and granules.

Carr's index (%) = (Tapped density - Bulk density/ Tapped density) x 100

3.5. Hausner's ratio

It is an important character to determine the flow property of powder. This can be calculated by the following formula.

Hausner's ratio = Tapped density / Bulk density

Values less than 1.25 indicate good flow and greater than 1.25 indicate poor flow.

3.6. Drug compatibility study

3.6.1. FTIR study

The powders were characterized by Fourier-transform infrared spectroscopy (FTIR) using IR-Affinity-1 (Shimadzu, Japan). FTIR analysis has been carried out for atenolol, different disintegrants, and their combinations to ascertain the compatibility of the drug.

3.6.2. DSC study

Drug and superdisintegrants are used to determine the possible interaction between them using the DSC analysis technique as a thermal analyzer (SDT.Q600, USA). Drug and superdisintegrant and their

compositions have been taken individually and heated in a sealed aluminum pan at a rate of 100/min from 0 to 300 ° under nitrogen flow. Nitrogen flow rate maintained 50ml/min.

4. Post compression parameters of compressed atenolol ODTs

4.1. Weight variation

Twenty tablets were selected randomly from each formulation. Individually weighed tablet and then collectively, the average weight of the tablets was calculated, then weight variation was calculated.

4.2. Hardness

The hardness of the tablets was determined using a Monsanto hardness tester. Hardness is one of the important factors having a significant role in transportation. The hardness of ten tablets was measured using a Pfizer hardness tester. It is expressed in kg/cm2.

4.3. Thickness

The thickness and diameter of the prepared tablets were evaluated with the help of vernier calipers and screw gauges.

4.4. Friability

The tablets were tested for friability testing using Roche friabilator. For this test, twenty tablets from each formulation have been selected. All tablets were weighed properly and subjected to the friabilator plastic chamber, revolving at 25 rpm for 4 min, and the tablets were then dusted and reweighed. The friability was then calculated using the formula.

$$\% \text{ loss} = \frac{\text{Initial wt. of tablets - Final wt. of tablets}}{\text{Initial wt. of tablets}} \times 100$$

4.5. Drug content

Twenty tablets were crushed into powder, the quantity of powder equivalent to an average weight of formulation was weighed and taken in a volumetric flask dissolved in 15 ml of methanol, the solution is filtered through Whatman filter paper, from this 1 ml of solution is withdrawn and after suitable dilution analyzed by UV spectrophotometer at 224nm.

4.6. Water absorption ratio

To determine the water absorption capacity of the formulated tablet was carried out by taking 6ml of water in a petri dish. A folded tissue paper was placed inside the petri dish. Pre-weighted tablet from each formulation individually places on to the tissue paper in the petri dish. After wetting, the final weight was determined and the water absorption ratio is calculated [21]

4.7. Surface pH

Surface pH studies were carried out to find out any side effects or any irritation. This has to be due to the alkaline or acidic pH which could irritate buccal mucosa.

4.8. Tablet disintegration study

Tablet disintegration study was conducted by taking 6 tablets at a time under aqueous buffer pH 6.8. The temperature was maintained at 37 ± 0.5°C. The time taken by the tablet to disintegrate completely was noted for each formulation [21].

4.9. *In vitro* drug release

The USP type II dissolution apparatus was used to find out the % of drug release at regular intervals of time from the buccal cavity. The dissolution medium consists of 900 ml of phosphate buffer pH 6.8. The temperature was maintained at 37 ± 0.5°C, at a revolution per minute 50 rpm. Dissolution was carried out and at regular intervals of time 5 ml of sample is pipetted and the same amount of fresh buffer medium replaced in the basket. The collected samples were analyzed under UV Spectrophotometer at 224nm with suitable dilution. Phosphate buffer pH 6.8 chosen as a blank for the detection of absorbance [22, 23]

4.10. Stability study

Stability study is an important parameter that provides information regarding the lifespan of a drug. The stability study for the sublingual tablet has been performed for three months as per the ICH (international conference of harmonization) guideline. The best formulation of atenolol sublingual tablets was stored in ambient conditions at 40°C ± 2°C / 75% ± 5% RH in stability chamber. The samples were analyzed periodically for up to three months and evaluated for various stability parameters namely physical appearance, drug content, disintegration time, and in-vitro drug release. All the operations were done in triplicate.

5. RESULTS AND DISCUSSION

5.1. Pre-formulation study for all formulations

Bulk density and tapped density mainly depend on the unit volume include the space between particles. Filling technique of the material by which the volume between the particles could be minimized. The effect of degree of compression played an important role in bulk density value. It also depends on the nature of the compound and its size. The size of the final dosage could be easily identified by this technique. The flow property of the final product is easily identified. The result of the pre-compression of a study is reported in Table 2. The bulk density of the formulations is in the range of 0.31 to 0.39 gm/ml, tapped density in between the range of 0.37 to 0.43 gm/ml, angle of repose observes as 24.01 to 28.21, carr's index found to be 4.63 to20 and Hauser's ratio value in the range of 1.04 to 1.25. Results concluded that powders for the different formulations show excellent flow properties.

Table 2. Pre-formulation study for atenolol formulations (F1- F7)

Pre-Compression Parameters	F1	F2	F3	F4	F5	F6	F7
Bulk density	0.391±0.0	0.373±0.0	0.312±0.7	0.391±1.0	0.362±0.0	0.348±1.0	0.31±0.21

	3	4		3	2	3	
Tapped density	0.41±0.31	0.43±1.01	0.39±0.25	0.413±1.08	0.398±0.09	0.391±0.81	0.379±0.88
Angle of repose	26.21±0.6	24.01±0.04	26.8±0.08	27.32±0.01	26.09±0.5	25.01±0.03	28.21±0.07
Carr's index	4.63±2.81	13.25±0.91	20±1.01	5.32±1.73	9.04±1.28	10.99±0.03	18.20±0.08
Hausner's ratio	1.04±0.03	1.15±0.07	1.25±0.01	1.05±0.09	1.09±0.07	1.12±0.03	1.22±0.07

FTIR study

The safety, physical appearance, and therapeutic efficacy of the active drug are very important factors to study before the final formulation. In a formulation, between the several excipients drug could interact and finally increase or decrease its efficacy. So compatibility study played a significant role. The drug, superdisintegrants, and their mixtures were taken and their compatibility was performed. The FTIR spectrum of individual superdisintegrants, drug (atenolol) and drug superdisintegrants combination has shown in Fig. 1. The obtained result reveals that individual superdisintegrants and atenolol shows different spectra. Whenever the drug superdisintegrants combination has been taken into the consideration, it is observed that there is no shifting or change in the spectra of atenolol. The FTIR spectra confirm that there is no interaction between drug and superdisintegrants. superdisintegrants are considered to be an important excipient for the formulation of atenolol sublingual tablets and compatible with the active drug.

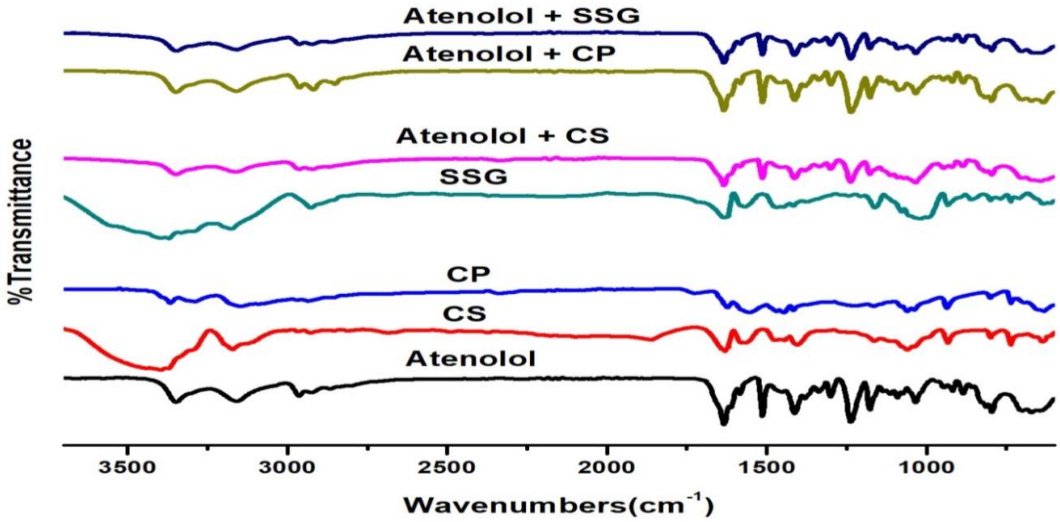

Figure 1. FTIR Spectra of pure atenolol, CS, CP, SSG, and their compositions

DSC study

DSC techniques were used to study the compatibility of the active drug such as atenolol, different superdisintegrants, and their compositions. DSC curve of the pure drugs was compared with 1:1 ratio physical mixtures with superdisintegrants. Thermal spectra of exothermic/endothermic peak of drug and superdisintegrants compare with their physical mixture. Moreover, slight changes in the peak

shape, height, and width could be the indication of incompatibility. DSC curve of pure atenolol, superdisintegrants, and their mixtures has been represented in Fig. 2 indicating that the drug and the superdisintegrants are compatible with each other.

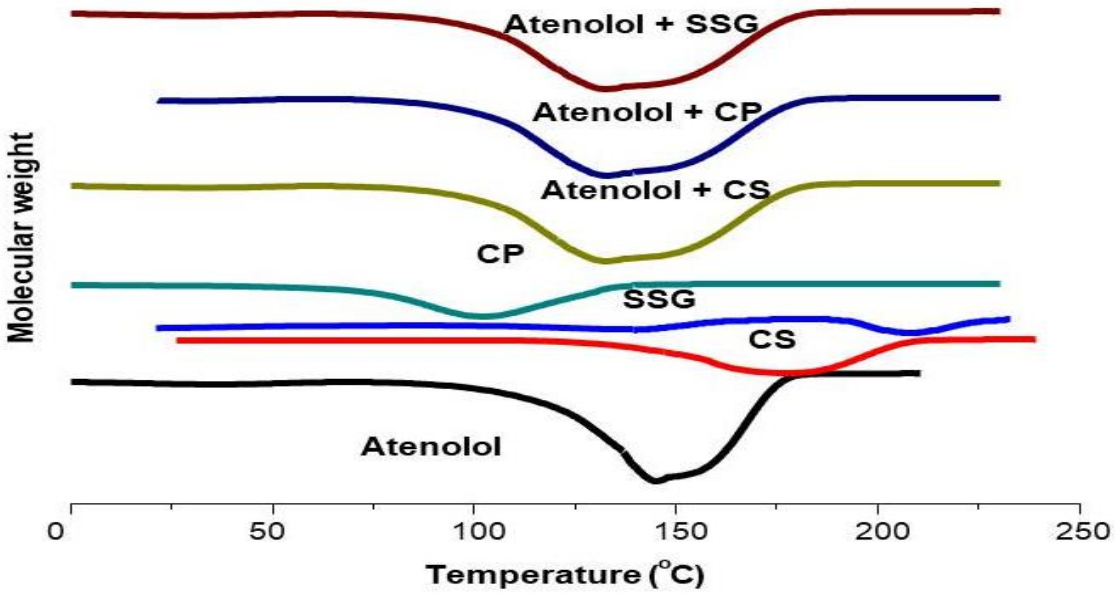

Figure 2. DSC Spectra of pure atenolol, CS, CP, SSG, and their compositions

SEM analysis

A digital image has been taken immediately after the preparation of atenolol-containing beads shown in Fig. 3. The morphology analysis of the obtained atenolol beads was carried out by SEM analysis shown in Fig. 4. The SEM images of best formulation F6 were captured at two different magnifications (lower magnification-75x and higher magnification-5000x) to obtain a complete surface morphology. Lower magnification of SEM analysis confirms that beads were quasi-spherical in shape with rough surface morphology also noticed at higher magnification. In higher magnification, SEM images reveal that crystal structure has been developed on the surface could help to disintegrate the beads easily.

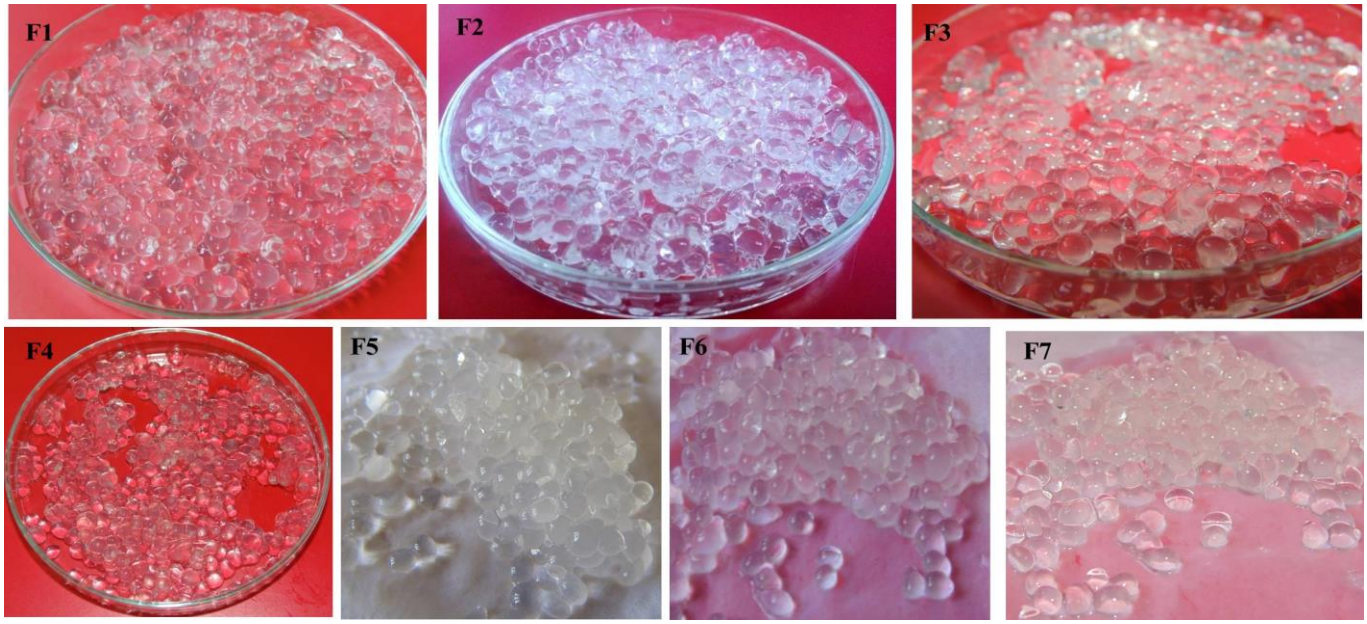

Figure 3. Images were taken immediately after the formulation of beads formulation F1 to F7

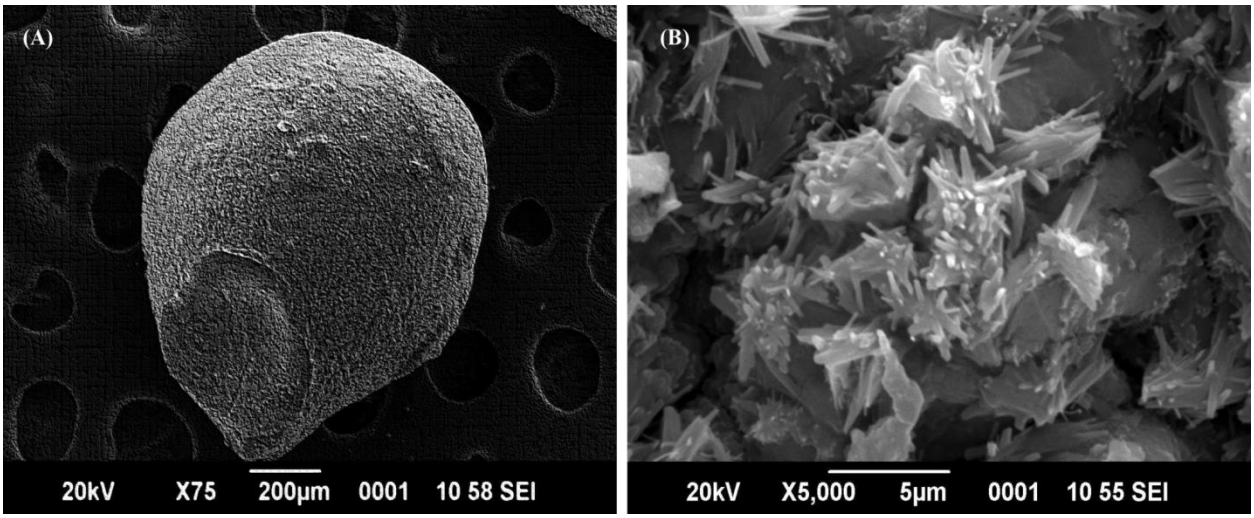

Figure 4. SEM images of atenolol beads at different magnifications (A-lower magnification and B-higher magnification) for formulation F6

5.2. Post compression study of atenolol sublingual tablets

Atenolol sublingual tablets (Formulation F1-F7) were evaluated for their physicochemical properties that play a vital role in the drug release pattern. A comparison of physicochemical properties of all the formulations is listed in Table 3. The weight variation was found to be within the limit of ± 7%. The average weight for all formulations was found to be in the range of 147 to 151 mg. The measurement of thickness has been carried out by vernier caliper. Thickness is an important parameter that helps in the ease of swallowing of tablets. Obtained results concluded that uniform thickness has been observed for all formulations and found within the range of 2.18 to 3.11mm. The formulated tablets passed through the hardness and friability tests as per the standard limits, the hardness ranging from 3.39 to 4.01, and

the percentage of friability obtained below 1%. The friability and hardness of the tablet are directly implicated in the strength of the tablet. Similarly, drug content%, water absorption ratio, surface pH, and disintegration time for all the formulation are lie in the range between 97 to 99.71%, 89 to 98%, 5.75 to 6.84, and 5 to 7 respectively. Obtained results confirm that evaluation parameters are within the limit as per Indian pharmacopeia for all the formulations.

Table 3. Post-compression parameters for atenolol sublingual tablets formulation (f1-f7)

Formulation	Tablet Weight variation (mg)	Tablet Hardness (kg/cm^2)	Tablet Thickness (mm)	Tablet Friability (%)	Drug content (%)	Water absorption ratio (%)	Surface pH	Disintegration Time in (min)
F1	147.21±1.01	3.71±0.18	2.77±1.06	0.29±0.11	98.81±0.17	91.71	5.75±0.01	6
F2	150.36±1.1	3.39±0.03	3.08±0.13	0.76±0.19	99.03±0.19	93.11	5.88±0.07	5.4
F3	149.17±1.03	3.91±0.07	2.18±0.37	0.46±0.93	98.71±0.02	89.95	6.84±0.11	7
F4	151.07±0.98	3.81±1.08	2.75±0.89	0.61±0.16	98.18±0.96	93.13	6.79±0.03	5.6
F5	151.74±0.02	3.93±1.02	3.04±0.63	0.72±0.05	99.16±0.81	97.91	6.58±0.17	5
F6	150.13±1.9	3.96±0.93	3.69± 0.18	0.58±0.73	99.71±0.01	98.16	6.81±0.03	4.5
F7	150.61±2.03	4.01±0.16	3.11±0.31	0.66±0.73	97.17±0.13	90.05	6.79±0.06	5.5

Results are expressed as of mean ±SD (n=3)

***In vitro* drug release**

The dissolution was carried out triplicate by utilizing the diffusion medium Phosphate buffer with the pH 6.8. The percentage of complete drug release for all formulations of atenolol sublingual tablets found within 12 min of the application shows in Fig. 5. Camphor in the formulation played an important role such as antioxidant, antiseptic, cooling agent, and skin penetrant whereas aspartame was used as a sweetening agent. Formulation F1 to F7 shows complete drug release ranged from 99.01% to 100.17% at the end of 4 to12 min respectively. Faster drug release in an immediate disintegration manner was observed in the formulation F4 to F7 which contain superdisintegrants in co-processed form. But in the case of individual superdisintegrants, it consumes more time to disintegrate and produce a complete release of drug as compared to co-processed superdisintegrants. The reason for maximum release within less time may be due to the nature of superdisintegrants and their combination at different ratios in a co-processed form. Co-processing of superdisintegrants is a very simple and novel technique, which leads to the formation of superdisintegrants with the superior property as compared to a physical mixture of the individual compounds. In our current research, we observed that individual superdisintegrants disintegrating the atenolol sublingual tablets within 12 min but with the improved property of co-processed superdisintegrants at different compositions took lesser time to disintegrate the atenolol sublingual tablets. Dissolution result reveals that formulation F1 to F7 made by individual superdisintegrants such as croscarmellose sodium, crospovidone, and sodium starch glycolate shows drug release 99.18% at 8 min, 99.97% at 9 min, and 99.01% at 12 min respectively. Formulation F4 to F7 contains co-processed superdisintegrants at different compositions shows drug release 100.08% at 7 min, 99.86% at 6 min, 100.17% at 4 min, and 99.93% at 7 min respectively. All formulations which

contain co-processed superdisintegrants disintegrate atenolol sublingual tablets at a much lesser time as compare to individual superdisintegrants. Among all formulations, formulation F6 which contains an equal amount of croscarmellose sodium, crospovidone, and a lesser amount of sodium starch glycolate considered as the best formulation among others due to the less disintegration time and complete release of atenolol drug at 4 min shown in Fig. 5.

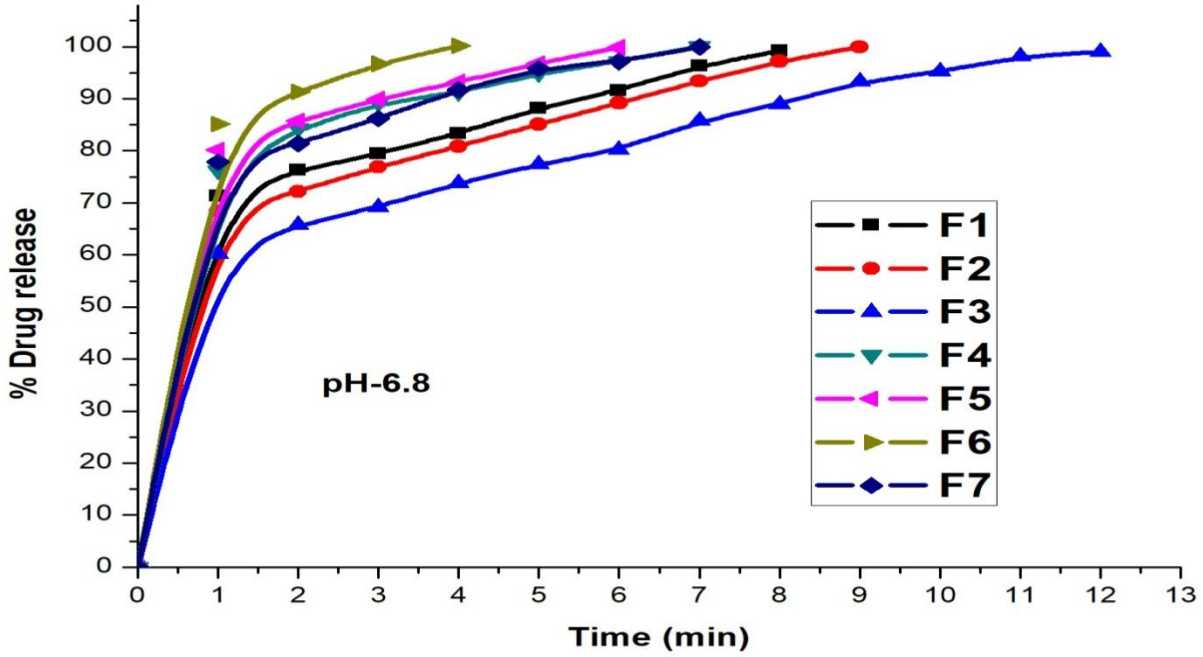

Figure 5. In vitro drug release of atenolol sublingual tablets (Formulations F1-F7)

Stability study

The best formulation of atenolol sublingual tablets was subjected for stability studies and observes that color, shape, and morphological appearance no significant changes observed after mixing with excipients. Obtained results confirm that physically sublingual tablets are stable.

The stability of the formulations at accelerated conditions was determined and shows satisfactory results in drug content %, disintegration time, and *in-vitro* drug release %. Differences were considered statistically very negligible and the data were presented in Table 4.

Table 4. Stabilitystudies of best formulation of atenolol sublingual tablet

Parameters	Drug	1st month	2nd month	3rd month
Physical appearance drug & excipients	Atenolol	NSC	NSC	NSC
Drug content %	Atenolol (F6)	98%	97%	96.3%
Disintegration time	Atenolol (F6)	4.9 min	5.2 min	5 min
In-vitro drug release %	Atenolol (F6)	98.85%	97.91%	96.53%

All values are expressed as mean ± standard deviation, (n=3), NSC: No Significant Changes

6. Conclusions

The current research focused on the development of atenolol sublingual tablets by incorporating different types of superdisintegrants at different compositions. Individual superdisintegrants and co-processed superdisintegrants are used for the formulation of fast dissolving sublingual beads. FTIR and DSC study confirms that atenolol is compatible with superdisintegrants. Obtained beads are compressed to formulate atenolol sublingual tablets. Obtained results for all the formulations confirm that evaluation parameters are within the limit as per Indian pharmacopoeia. From the water absorption ratio and disintegration time, it was confirmed that co-processed superdisintegrants has shown better result as compare to individual superdisintegrants. Similarly from the dissolution study, it concluded that sublingual tablets formulated by co-processed superdisintegrants (Formulation F4 to F7) show better results as compare to individual Superdisintegrants (Formulation F1 to F3). Formulation F6 is considered the best formulation among all formulations due to the quick disintegration time and 100% drug release at 4 min. Co-processing of superdisintegrants is a very simple and novel technique, which converts superdisintegrants with superior property to formulate a successful atenolol sublingual tablet.

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Conflicts of interest:

The authors declare that there is no conflict of interest.

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