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Improvement In Taste And Solubility Of Atenolol By Solid Dispersion System

Soniya Madaan*[1], Atul Kumar Gupta[2], Vipin Sardana[3]

1. B.S. Anangpuria College of Pharmacy, Alampur (Faridabad), India
2. Maharishi Markendeshwar College of Pharmacy, Mullana (Ambala) , India
3. G.V.M. College of Pharmacy, Sonepat, Haryana, India

Work Affiliation- Maharishi Markendeshwar College of Pharmacy, Mullana (Ambala)

The aim of this study was to mask the bitter taste of Atenolol along with solubility enhancement by solid dispersion system. Solid dispersions were prepared by the solvent evaporation method using β-cyclodextrin. The solid dispersion of atenolol with β-cyclodextrin was evaluated by Differential scanning colorimeter (DSC), Scanning electron microscopy (SEM). The taste masking property of solid dispersions in different ratio combination of Atenolol with β-cyclodextrin was evaluated on human volunteers. The influence of different ratio of carrier on solubility of drug was also evaluated. Solid dispersion at ratio 1:3 w/w completely masks the bitterness of Atenolol. The solubility and dissolution rate of Atenolol was significantly increased by solid dispersion as well as by their physical mixture.

Keyword: β-cyclodextrin; Physical Mixture; Solvent Evaporation; Taste Masking.

INTRODUCTION: The major problem in oral administration of bitter drugs are unacceptability by the patients mainly pediatric and geriatrics [1] and this can be overcome by masking the bitterness of drug either by decreasing its oral solubility on ingestion or decreasing the interaction of drug particles to taste buds [2]. There are various techniques available which are used for masking the taste of bitter drugs including coating, solid dispersion, ion exchange resin, entrapment method and masking of taste buds etc. Coating avoids the contact of drug particles with taste buds and taste is not apparent to the users [3]. Dispersion of one or more active ingredients in an inert carrier or matrix in solid

Corresponding Author's Contact information:
Soniya Madaan *
B.S. Anangpuria College of Pharmacy, Alampur (Faridabad), India
E-mail: Soniya.madan21@gmail.com

state is mainly utilizes in solid dispersion for masking the bitter taste of drug [4] which can be done either Melting method, Solvent method or melting solvent method [5]. Atenolol belongs to a group of beta blocker (selective β1 antagonist) used as antihypertensive, antianginal and antiarrythmic [6].Due to its bitter taste, slightly solubility in water, low bioavailability (50%) makes it suitable candidate for masking the bitterness and increase its solubility [7].Cyclodextrins are cyclic oligosaccharides containing at least six D-(+)-glucopyranose units attached by a (1,4) glucoside bonds. The three natural cyclodextrins, α, β, and γ contains 6, 7, or 8 glucose units, respectively and obtained from starch by means of enzymatic conversion. Cyclodextrins are widely used in numerous food products, cosmetics and other commercial products as solubilizing agents to increase water-solubility of lipophilic compounds. The main objective of the study was to investigate the possibility of improving the taste and solubility of atenolol by solid dispersion method.

MATERIALS AND METHODS

Reagents and Chemicals

Atenolol, β-Cyclodextrin were obtained as a gifted sample from Himalayan Laboratories Ponta Sahib (H.P.) India. All other materials of analytical grades were used.

Preparation of Physical mixtures

The physical mixture of Atenolol (pulverized and sieved, #100) with β-cyclodextrin in different ratios (Table i) were prepared by mixing with weighed amount of β-cyclodextrin in a modified rotary flask shaker at 30 rpm (inclined an angle of 50^0) for 2 hours.

Preparation of solid dispersions

Solid dispersion of Atenolol with β-cyclodextrin was prepared by solvent evaporation method. Accurately weighed amount of Atenolol (Table i) and β-cyclodextrin were dissolved in 5ml of ethanol and poured into the petridish. The solvent was evaporated in vacuum oven at 600mm Hg at 60°C±0.5°C for 30min. Dispersion was collected from petridish with help of spatula. The dried mass was pulverized and sieved through mesh #100 for evaluation.

Table i): Composition of Batches Containing Atenolol and β-Cyclodextrin

Batches for Physical Mixture	Atenolol (mg)	β-cyclodextrin (mg)	Drug Carrier Ratio (w/w)	Batches for Solid dispersion
PM1	100	50	1:0.5	SD1
PM2	100	100	1:1	SD2
PM3	100	200	1:2	SD3
PM4	100	300	1:3	SD4
PM5	100	400	1:4	SD5
PM6	100	500	1:5	SD6

EVALUATION

Thermal analysis

Thermal analysis of pure materials, physical mixtures, and solid dispersion were determined by a differential scanning calorimeter (UniversalV4.1D TA).2 mg of drug, β-cyclodextrin, physical mixture and solid dispersion was sealed in an aluminium sample pan. The scanning rate was 10°C/min. and the scanning temperature range was between 40-300°C under a nitrogen purge at 60 ml/min.

Scanning Electron Microscopy

The images of the pure material, solid dispersion were analyzed by scanning electron microscopy (Joel 457 V, Japan). Samples were prepared by sprinkling the powder on an adhesive tape stuck to an aluminium stub. The stubs were then coated with gold under an argon atmosphere. The coated samples were then scanned and images were analyzed at 500 or 1000 axis.

Taste Evaluation

Taste evaluation was carried out by sensory test on a trained panel of healthy volunteers, with their prior consent [8].

- Selection of volunteers- A panel of 10 healthy volunteers selected randomly from age group of 20 to 30 and the consent form was filled and signed by the volunteers.
- Standard Stimuli- Pure active ingredient (Atenolol).
- Test Stimuli- Atenolol solid dispersion and physical mixture.
- Sample Delivery method- Each volunteer received all 6 formulations of one batch in 4 hr after morning breakfast in 1 day.
- Scale of measurement- Taste Evaluation starts immediately after administration and continued for upto 15 secs. The scale used a ranking system from +++ tasteless to -- Extremely bitter.

Phase solubility studies

Known excess amount of Atenolol with β-cyclodextrin in different ratios (physical mixture and solid dispersion separately) was added in 5ml of gastric fluid (0.1N HCL) and placed at 30rpm, $37^0 \pm 0.5^0$C overnight in water bath incubator shaker [9].The solution filtered through #0.22micron micro-syringe filters, diluted and studied by UV-VIS spectroscopic method (Shimadzu UV-2101PC, Japan).

In Vitro Dissolution Rate Study

In vitro dissolution studies of pure drug (Atenolol), physical mixture and complexes (with β-cyclodextrin) were carried out in 900 ml of 0.1 N HCl (pH 1.2), using USP 8-stage dissolution rate apparatus (USP XXI/XXII, TDT08L ELECTROLAB, Mumbai, INDIA). Using modified basket method. Samples equivalent to 150 mg of Atenolol was tied in muslin cloth and kept in basket and rotated at 50rpm [10].Samples at different time intervals were taken, filtered with #0.22micron micro-syringe filters and analyzed.

RESULT AND DISCUSSION

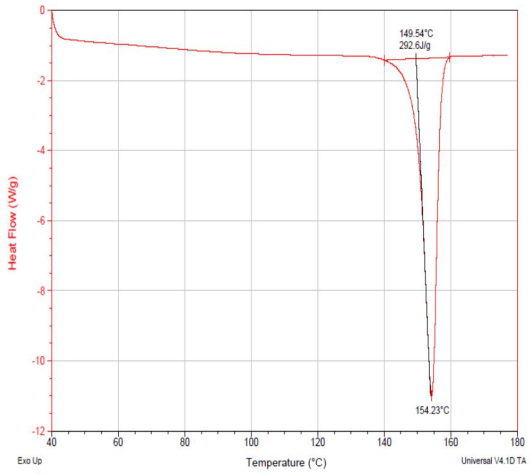

Figure 1: DSC of atenolol (pure drug)

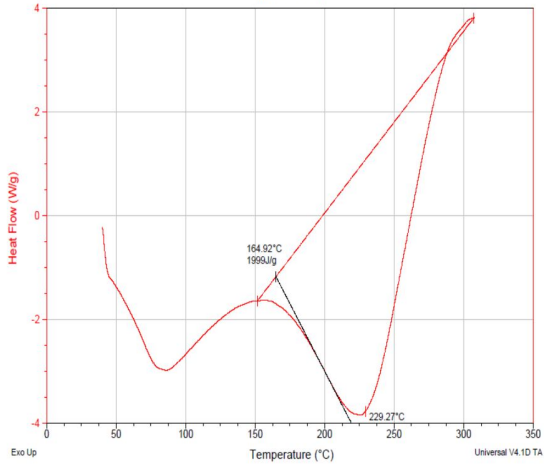

Figure 2: DSC of β-cyclodextrin

DSC curve of Atenolol (Figure 1) showed the sharp endothermic peak at 154.23°c correspond to melting point indicate their crystallinity and purity, broad endothermic peak of β-cyclodextrin (Figure 2) at 229.27°c indicate its hydrated behavior with crystallinity and purity. Atenolol β-cyclodextrin solid dispersion (Figure 3) at 1:3 ratio showed the drug peak so small which gave two possibilities [11] either amorphous precipitation of drug or better solubilization of atenolol in β-cyclodextrin.

The decrease or disappearance of the thermal features of the atenolol also indicates that it penetrate into β-cyclodextrin cavity replacing the water molecule [12].

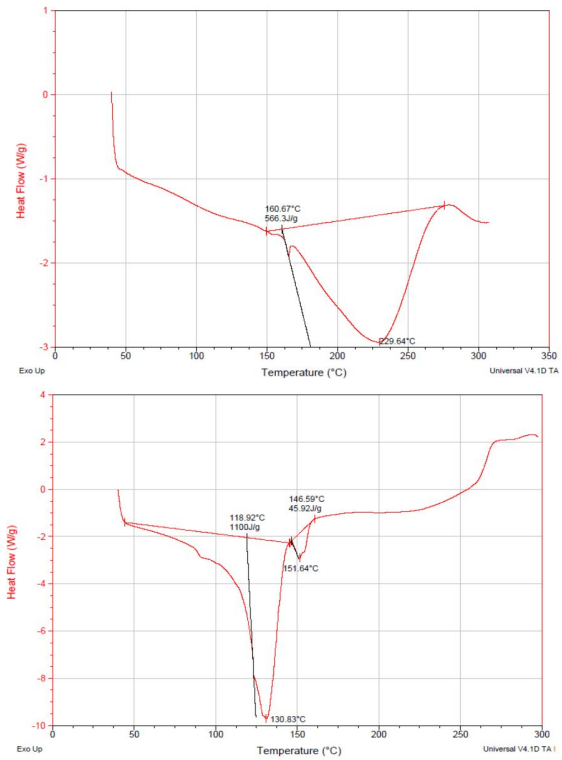

Figure 3: DSC of atenolol β-cyclodextrin SD
Figure 4: DSC of atenolol β-cyclodextrin PM

Figure 4 illustrate the DSC of physical mixture. In physical mixture peak of atenolol shift towards lower temperature indicate its amorphous precipitation but sharp peak indicate that its crystallinity not completely disappear. SEM of Atenolol (Figure 5) and β-cyclodextrin (Figure 6) showed crystalline particles of irregular size. In Solid dispersion of Atenolol and β-cyclodextrin (Figure 7), nature of Atenolol changed from crystalline to amorphous. It showed that it formed a complex with β-cyclodextrin and it was not observed as separate entity.

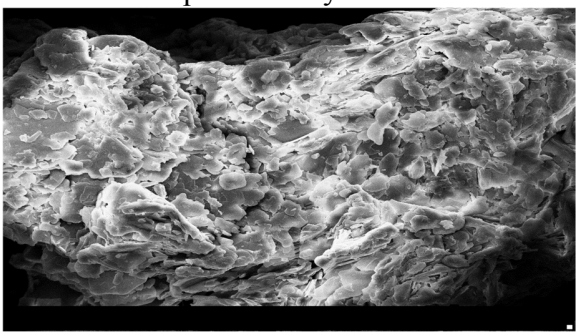

Figure 5: SEM of Atenolol

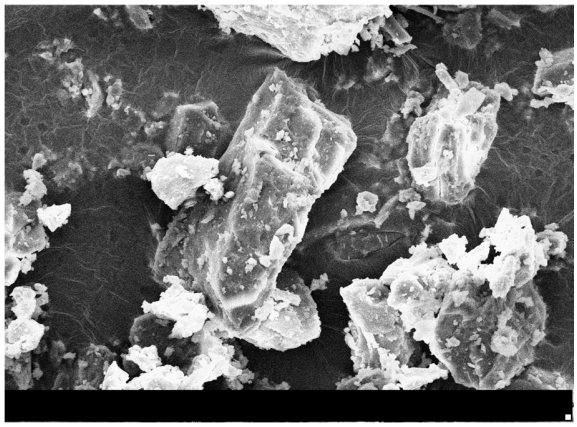

Figure. 6: SEM of β-cyclodextrin

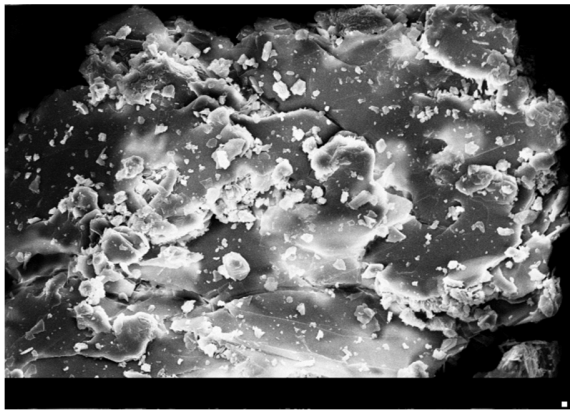

Figure 7: SEM of Atenolol β-cyclodextrin SD of 1:3 ratio

Taste Evaluation study

In taste evaluation (table ii) 100% volunteers reported that solid dispersion of β-cyclodextrin at 1:3 ratio was tasteless but 90% volunteers reported that it was palatable at 1:2 ratio.

Table ii): Scale values for taste evaluation of solid dispersion

RATIO	SOLID DISPERSION*
1:0.5	-
1:1	+
1:2	++
1:3	+++
1:4	+++
1:6	+++

*(--) Extremely Bitter, (-) Bitter, (+) Slightly bitter but not Palatable , (++) Palatable formulation, (+++) Completely taste masked (Tasteless)

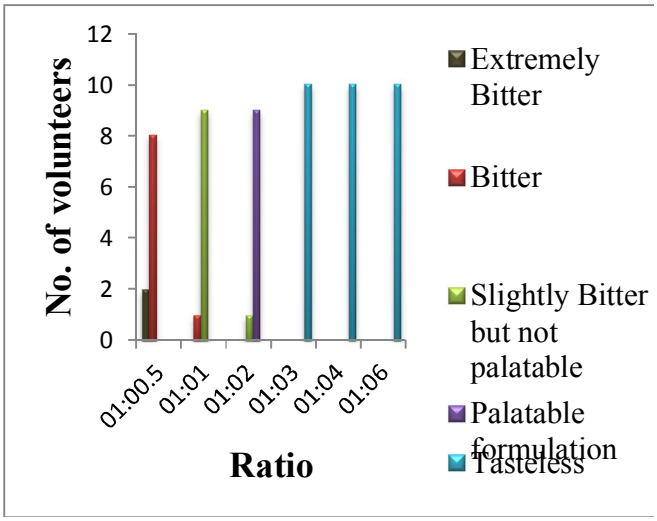

Figure. 8: Taste evaluation of solid dispersion by volunteer judgement

Phase solubility study

The solubility of atenolol in 0.1N Hcl at $37^0 \pm 0.5^0$C was found to be 5.85 µg/ml. The influence of β-cyclodextrin upon solubility of atenolol is presented in table iii) and it shows the solubility of atenolol increase was observed as increase the concentration of β-cyclodextrin.

Table 3: Solubility of Atenolol

Sample	**Solubility (µg/ml)**
Pure drug	5.85
Pure drug + Cyclodextrin 5%w/v	6.78
Pure drug + Cyclodextrin 10%w/v	7.07
Pure drug + Cyclodextrin 15%w/v	7.15
Pure drug + Cyclodextrin 20%w/v	7.17

In vitro dissolution study

All soid dispersions of atenolol with β-cyclodextrin at different ratio (1:0.5, 1:1, 1:2, 1:3, 1:4, 1:6) were compared and there was no significant difference was found in the release profile of atenolol in all ratio. On the basis of taste masking property of solid dispersion of β-cyclodextrin , 1:3 ratio was selected for drug release study of solid dispersion and their physical mixture. The dissolution curve of atenolol and their solid dispersion were presented in Figure 9. The release rate profiles were plotted as the percentage of atenolol dissolved from the solid dispersion and physical mixture and pure atenolol versus time. It was evident that the rate of dissolution of pure atenolol was slow, 99% was dissolved in 1.30 hr. Comparing with that of pure atenolol, the dissolution rate of atenolol from its physical mixture, solid dispersion was appeared faster. The drug dissolves within 2 minutes and approximate 99% atenolol was dissolved within 5 minutes. This behavior might be attributed to the higher energetic amorphous state and solid dispersion formation. β-cyclodextrin increase the aqueous solubility of many poorly soluble drugs may be due to formation of complexes with their polar molecules or functional groups. The resulting complex hides most of the hydrophobic functionality in the interior cavity of the β-cyclodextrin while the hydrophilic hydroxyl groups on the external surface remain exposed to the environment. The net effect is that water soluble β-cyclodextrin Atenolol complex was formed [13]. Corresponding physical mixture also demonstrated higher dissolution rate. The improvement of dissolution rate obtained with physical mixture could be attributed to both improved drug wettability and formation of readily soluble complexes in the dissolution medium. During mixing of drug with hydrophilic carrier results in greater wetting, increase available for dissolution by reducing interfacial tension between drug and dissolution media. During dissolution, it was noted that drug carrier system sink immediately whereas pure drug keeps floating on the surface for a longer time interval.

In solid dispersion results the uniform distribution of drug in carrier in a highly dispersed state. Thus when such a system comes in contact with an aqueous dissolution medium, the hydrophilic

carrier dissolves and results in precipitation of the embedded drug into fine particles, which increase the dissolution surface available.

The Q5, Q10, Q20 values (i.e. percent of dissolved atenolol at 5, 10, 20 min) were showed in table iv) Improvement of the dissolution rate of atenolol was obtained by both physical mixture and formation of solid dispersion. The effect of physical mixture on the dissolution rate was less than that of solid dispersion. Rapid and excellent dissolution behaviour was obtained by forming solid dispersion with β-cyclodextrin.

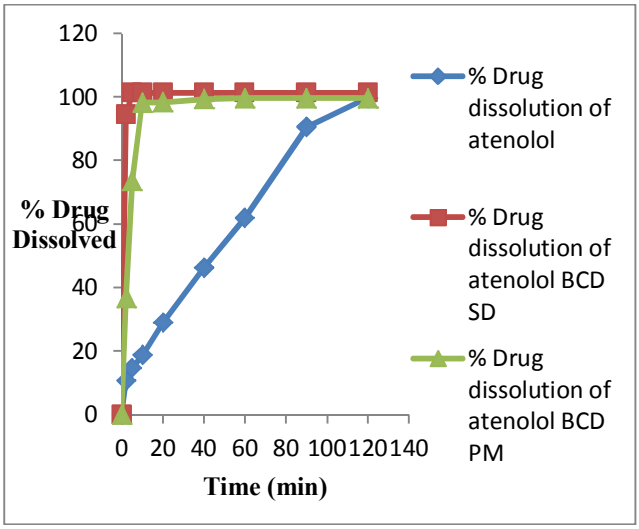

Figure 9: Dissolution study of physical mixture and solid dispersion

Table iv): The percent of drug dissolved atenolol from various samples at 5 min (Q5), 10 min (Q10) and 20 min(Q20)

Sample	Q5	Q10	Q20
Atenolol	14.749	18.75	28.958
1:3 Atenolol:BCD SD	101.2	101.2	101.2
1:3Atenolol: BCD PM	73.5	98.2	98.4

CONCLUSION

This study clearly shows that solid dispersion of β-cyclodextrin mask the taste of atenolol and also improves their dissolution rates. Mechanisam involved may be due to the molecules or functional groups that cause unpleasant tastes or odors can be hidden from the sensory receptors by encapsulating them within the β-cyclodextrin cavity. The resulting complexes have no or little taste or odor and are much more acceptable to the patient **and** these complex molecules are strongly hydrated on their outer surface, therefore they do not get attached to the taste bud receptor on the tongue in the mouth cavity. Formulation of solid dispersion further improves the dissolution rate compared with physical mixture. No interaction was found between atenolol and carrier. The crystallinity of drug was also reduced. Solid dispersion of atenolol β-cyclodextrin (1:3) showed the maximum dissolution efficiency among all the solid dispersion and physical mixture. Based on the results solid dosage form of atenolol with β-cyclodextrin with efficient taste masking and high dissolution could be manufactured.

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