

FORMULATION AND EVALUATION OF ATENOLOL ORODISPERSIBLE TABLETS BY PHASE TRANSITION TECHNOLOGY

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ABSTRACT

Oral delivery is currently the gold standard in the pharmaceutical industry. Orodispersible tablets a new form of NDDS is "a solid dosage form containing medicinal substance or active ingredient which disintegrate rapidly usually within a matter of seconds when placed upon the tongue". The aim of this study is to formulate and evaluate an ODT containing antihypertensive drug Atenolol by phase transition technology and to find the formula with least time of disintegration for phase transition technology. Xylitol and Perlitol SD 200 were used as sugar alcohols and maize starch as a diluents. The tablets were formulated by phase transition technology and evaluated for Hardness, friability, *In vitro* Disintegration time, weight variation, thickness, wetting time, Drug content. It was concluded that Xylitol, Perlitol SD 200 and Maize starch are the appropriate excipient and formulated in good proportions. The *in vitro* disintegration showed that formulation batch F6 & F8 showed least disintegration time.

Keywords: Phase transition technique, Xylitol Perlitol SD 200, Hardness, Disintegration time.

INTRODUCTION [1, 2, 3]

Oral delivery is currently the gold standard in the pharmaceutical industry. Despite of having popularity of solid oral dosage form such as TABLETS & CAPSULES important drawback of such dosage forms is 'Dysphasia' or difficulty in swallowing. This is seen to afflict nearly 35% of the general population. A new NDDS developed Orodispersible tablets. As per US FDA it is defined as 'a solid dosage form containing medicinal substance or active ingredient which disintegrate rapidly usually within a matter of seconds when placed upon the tongue.' Fast dissolving tablets are also known as mouth-dissolving tablets, melt-in mouth tablets, Orodispersible tablets, rapimelts, porous tablets, quick dissolving tablet, which disintegrate in the oral cavity.

There are various approaches by which ODT can be prepared Phase transition is one of them.

Phase transition process [4]

Kuno et al proposed a novel method to prepare ODTs with sufficient hardness by involving the phase transition of sugar alcohol. In this technique, ODT were produced by compressing powder containing erythritol (melting point: 122 °C) and xylitol (melting point: 93 - 95 °C), and then heating at about 93 °C for 15 min. After heating, the median pore size of the tablets was increased and tablet hardness was also increased. Heating process enhances the bonding among particles leading to sufficient hardness of tablets which was otherwise lacking owing to low/little compactibility.

Atenolol, a β 1-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 [5]. Administration of conventional tablets of atenolol has been reported to exhibit fluctuations in the plasma drug levels, resulting either in manifestation of side effects or reduction in drug concentration at the receptor sites [6,7]. An attempt was made in the present investigation to prepare ODTs of atenolol by employing phase transition technology.

MATERIALS AND METHODS

Atenolol was obtained from Shreya Pharmaceuticals Aurangabad. Xylitol, Perlitol SD and Maize starch, Magnesium stearate and talc was also obtained from Shreya Pharmaceuticals Aurangabad. All other materials used were of analytical grade. The experiment was done at the Government College of Pharmacy Aurangabad in the academic year 2012-2013.

Preformulation study was done.

1) Solubility

The atenolol is freely soluble in methanol, soluble in acetic acid, Propanol, slightly soluble in water, very slightly soluble in acetone, practically insoluble in acetonitrile, ethyl acetate and chloroform.

2) Loss on drying

Loss on drying is the loss in weight in % w/w resulting from water and volatile matter of any kind that can be driven off under specific conditions. The test is carried out on a well-mixed sample of substance.

3) Flow property study [8]

a) Angle of Repose

Angle of repose was determined using 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 (θ) was calculated using the formula:

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

b) Bulk density

Apparent bulk density (ρ_b) was determined by pouring the blend into a graduated cylinder. The bulk volume (V_b) and weight of the powder (M) was determined. The bulk density was calculated using the formula:

$$\rho_b = M / V_b$$

c) Tapped density

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (ρ_t) was calculated using the formula

$$\rho_t = M / V_t$$

d) Compressibility index

Compressibility index I is calculated as follows:

$$I = \frac{V_0 - V_t}{V_0} \times 100$$

Where V_0 is the bulk volume

V_t is the tapped volume.

The value below 15% indicates a powder with usually give rise to good flow characteristics where as above 25% indicate poor flowability.

e) Haussner's ratio

Haussner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula

$$\text{Haussner's ratio} = \rho_t / \rho_b$$

ρ_t = tapped density

ρ_b = bulk density

Lower Haussner's ratio (<1.25) indicates better flow properties than higher ones (>1.25)

Drug excipient compatibility study

Drug excipient compatibility study was done by FTIR and DSC

1) Fourier Transform Infrared (FTIR) spectroscopy

Fourier Transform Infrared spectroscopy was conducted. The procedure consisted of placing a drug sample in FTIR sample holder. The drug sample was placed in the light path and scanned over the range of 4000-400 cm^{-1} on Shimadzu FTIR (IR Prestige-21) and spectrum was recorded.

2) Differential Scanning Calorimetric (DSC) analysis

Thermogram of Atenolol was recorded on a TA-60 WS Thermal Analyzer (Shimadzu) as shown. The samples were hermetically sealed in aluminum pans and heated at a constant rate of 20°C/min over temperature range of 40 to 300°C. Inert atmosphere was maintained by purging nitrogen gas at flow rate of 20 ml/min.

Formulation of Tablets

The tablets were prepared by Phase transition technology in which two sugar alcohols were used one is having High melting point (Perlitol SD), other is having low melting point (Xylitol). Appropriately weighed quantity of sugar alcohol mixed together then mix with diluent and another ingredient. The tablets was punch with round face 6mm punch these prepared tablets were then placed in oven at 93°C for 15 min. after heating kept it for 4 hr. at room temperature.

Evaluation of Tablets [9]

1) Weight variation

The weight variation test was carried out as per USP/NF

The test was carried out by weighing 20 tablets individually and calculating the average weight and comparing the individual tablet weight with the average weight of 20 tablets.

2) Hardness

Tablet hardness is defined as the force required to break a tablet in a diametric compression test. The hardness or crushing strength of a tablet was measured with the Monsanto hardness tester.

3) Thickness

The thickness of individual tablets was measured using vernier caliper, which permits accurate measurement and provides information of the variation between tablets.

4) Friability

The tablet friability was carried out using Roche friabilator. Preweighed sample of tablets was placed in the friabilator and subjected to 100 revolutions for 4 min. the tablets were dedusted and reweighed.

5) *In vitro* Disintegration time

The disintegration time for tablets was determined using the disintegration test apparatus as per the specifications in European pharmacopoeia stating the maximum limit for disintegration time of 3 min for orodispersible tablets. The test was carried out without using the disc.

5) Wetting time

To determine wetting time a piece of tissue paper folded twice was placed in a Petri plate of internal diameter 6.5 cm containing 6 ml of aqueous solution of Erythrosine. The tablet was then placed over the tissue paper and the time for complete wetting of tablet i.e. uniform distribution of dye over entire tablet was determined.

6) Drug content [10]

The amount of active ingredient in the dosage form is determined by the assay procedure. For this procedure 5 tablets were weighed individually and powdered. The quantity of powder equivalent to the drug dose i.e. about 40 mg was weighed and transferred to the 100 ml volumetric flask. To it 5ml of methanol was added and vortexed for some time to dissolve the drug moiety completely in 0.1 M HCl. Volume was made up to 100 ml with 0.1 M HCl to give the stock solution of 400µg/ml. The resultant solution was then filtered through filter paper. From above stock solution 250 µl was withdrawn and transferred to 10 ml volumetric flask. Volume was made up to 10 ml with 0.1 M HCl to give the dilution of 10µg/ml. The dilution was then analyzed at 224.5 nm using double beam UV-visible spectrophotometer.

7) *In vitro* dissolution test [11,12]

In vitro dissolution test was carried out for all factorial batches.

Dissolution profiles of Atenolol tablets were determined using the paddle, USP type 2 dissolution apparatus at 50 rpm. Dissolution was performed in 0.1 M HCl maintained at 37±0.2°C. 5 ml of samples were withdrawn at specified time intervals. The volume of dissolution medium was again adjusted to 900 ml with 5 ml of 0.1 M HCl each time the sample withdrawn. The samples were filtered through syringe filter (0.45 µ), samples were diluted as needed and analyzed at 224.5 nm using double beam UV-visible spectrophotometer.

RESULTS AND DISCUSSION

Preformulation studies were undertaken.

1) Organoleptic Properties

The drug substance is visually inspected to verify that it is a white or almost white, amorphous odorless powder and it complies with the IP, BP, and USP specification.

2) Melting Point

Melting point of Atenolol was found in the range of 159- 163°C as reported in literature, thus indicating purity of sample.

3) Solubility Analysis

Solubility profile of Atenolol indicated that the drug is freely soluble in ethanol; sparingly soluble in water; slightly soluble in dichloromethane and practically insoluble in ether which complies with the IP.

Table 1: Solubility Study of Atenolol

Solvent	Solubility(mg/ml)
Phosphate buffer, pH 6.8	22.5
0.1 N Acetate buffer, pH 4.6	28.6
0.1 N HCl, pH 1.2	33.52

4) Fourier Transform Infrared Spectrum

The FTIR spectrum of Atenolol/ 4-(2-Hydroxy-3-[(1-methyl ethyl) amino] propoxy) benzene acetamide 4000 cm^{-1} to 400 was recorded over a range of cm^{-1} . The spectrum obtained was concordant with the structure.

5) Differential Scanning Calorimetry

DSC thermogram of Atenolol showed endothermic peak of fusion, having peak maximum of 160.84°C. DSC thermogram is shown in Fig. 2

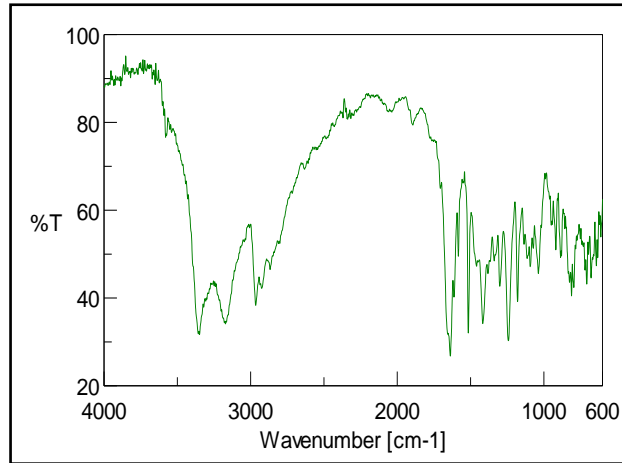


Fig. 1: FTIR spectrum of Atenolol

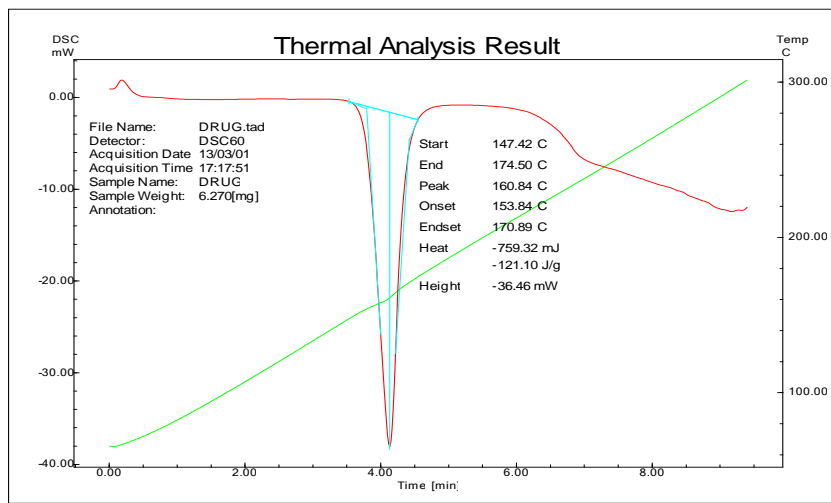


Fig. 2: DSC Thermogram of Atenolol

On the basis of melting point, UV spectrum, IR spectrum and DSC thermogram, the procured sample of Atenolol was found to be of acceptable purity and quality.

Drug and Excipients Compatibility Studies

The possible interaction between the drug and the sugar alcohol was studied by DSC and FTIR spectroscopy.

1) Differential Scanning Calorimetry

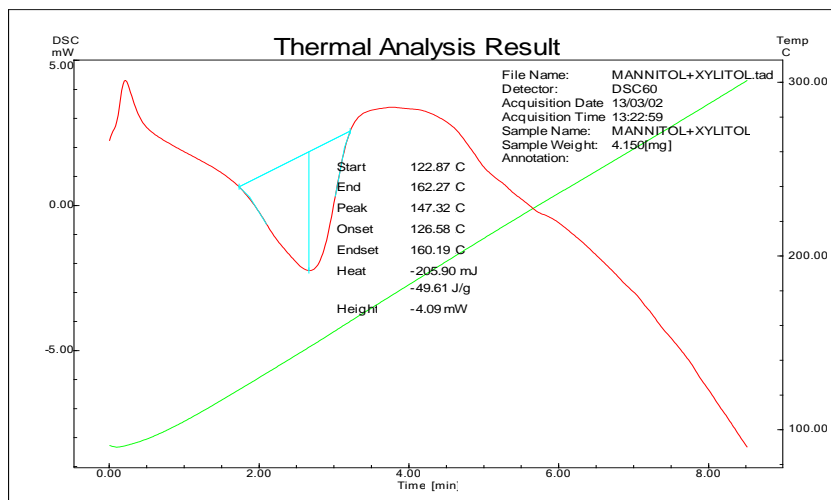


Fig. 3: DSC Thermogram of Xylitol+Perlitol SD

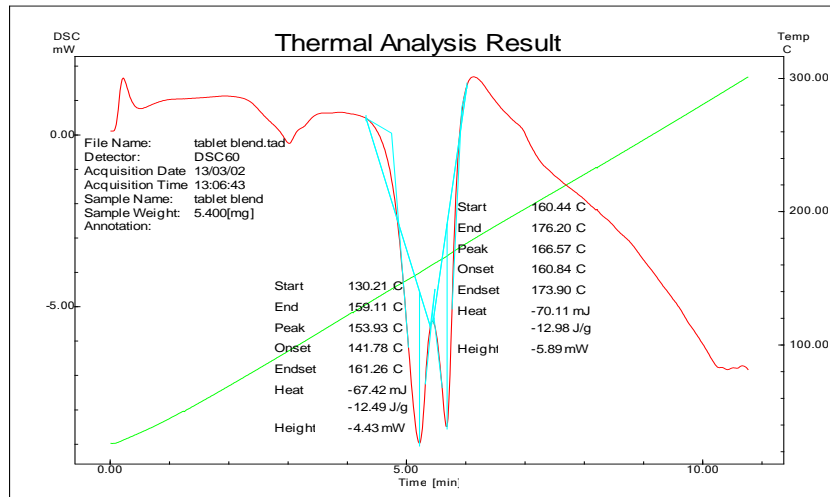


Fig. 4: DSC Thermogram of Atenolol + Sugar alcohol

2) Fourier Transform Infrared (FTIR) spectroscopy

In a physical mixture of drug and sugar alcohol, there was neither masking of single characteristic peak nor existence of additional

peak in FTIR when compared to the FTIR spectrum of pure Atenolol, so it can be concluded that drug and polymer are compatible with each other. FTIR spectrum for the physical mixture is shown in Fig.5

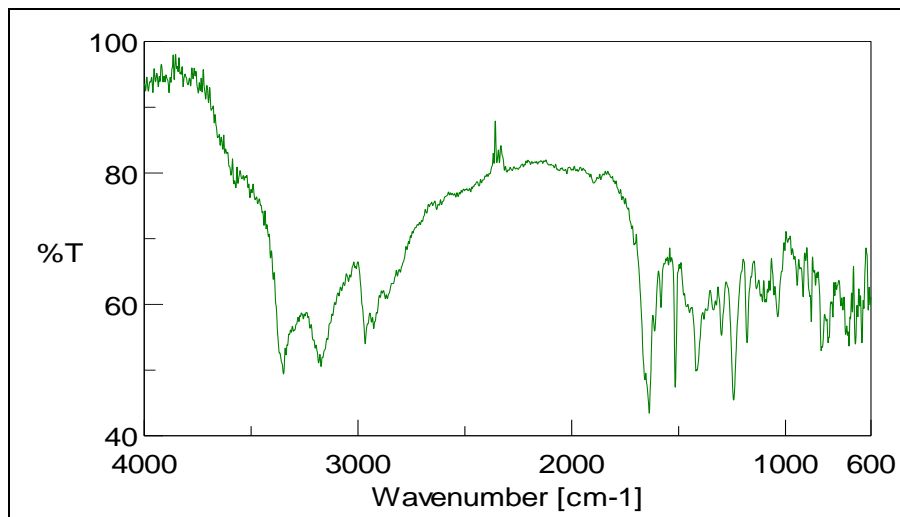


Fig. 5: FTIR spectrum of Atenolol + sugar alcohol

From FTIR spectroscopy and DSC thermogram results, it can be concluded that the drug and polymer were compatible with each other.

Table 2: Evaluation of flow properties of blends

Formulation batches	Evaluation of parameters					
	Angle of repose(°)	Bulk density	Tapped density	Compressibility index (%)	Hausner's ratio	Flowability
F1	24	0.44466	0.513	13.24	1.15	Good
F2	25	0.44460	0.488	8.893	1.09	Good
F2	19	0.4554	0.526	13.457	1.157	Good
F4	20	0.4545	0.50	11.06	1.125	Good
F5	21	0.4445	0.513	11.36	1.126	Good
F6	23	0.4343	0.540	17.78	1.21	Good
F7	24	0.44466	0.5	13.04	1.188	Good
F8	21	0.4466	0.527	15.41	1.125	Good
F9	23	0.4446	0.50	11.06	1.21	Good

Evaluation of flow properties of blends

1) Weight Variation Test

All the tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of $\pm 10\%$.

2) Hardness

The hardness for all formulation batches was found between 3 to 3.5 Kg/cm² for factorial design batches i.e. F1 to F9. The hardness of the prepared tablet varied insignificantly which have satisfactory strength to withstand the mechanical shocks.

3) Thickness

Thickness for all formulation batches i.e. F1 to F9 was found to be between 2.43 to 2.54 mm.

4) Friability

The % friability values found to be between 0.2589 to 0.6912% for factorial design batches. The friability of all the formulation was found to be less than 1.0%. The results reveal that as the amount of Xylitol increases, the percent friability decreases. The factorial batch F7 found to be less friable.

5) Drug Content

Drug content for all factorial design batches i.e. F1 to F9 showed in the range of 93.78% to 103.61%. The results indicated that in all the formulations the drug content was uniform.

6) Wetting Time

Wetting time for factorial design batches i.e. F1 to F9 showed wide variation in the range of 35 to 56 seconds. It was evident that wetting

time increased with increase in concentration of Xylitol with increase in concentration of Perlitol SD 200.

7) Disintegration

All tablets disintegrated without disc in the IP test especially when used at optimum concentrations of Xylitol. The disintegration time profile is shown in Fig. 7

The factorial batches F1 and F3 showed less disintegration time as compared to other batches. This disintegration of the ODTs were due to penetration of water into the tablets, which leads to the erosion of Sugar alcohol. As concentration of Xylitol increased disintegration time was also increased.

8) Dissolution study

Drug Release Study in Simulated Gastric Fluid (0.1 N HCl, pH 1.2)

The percent drug release after 15 minutes (Q_{15}) for all factorial design batches i.e. F1 to F9 showed in the range of 80.11 to 90.51%.

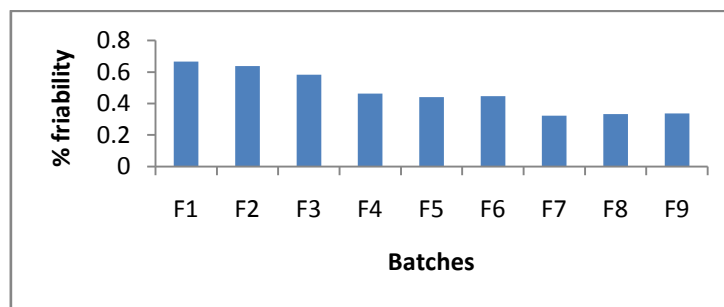


Fig. 6: Comparative friability profile

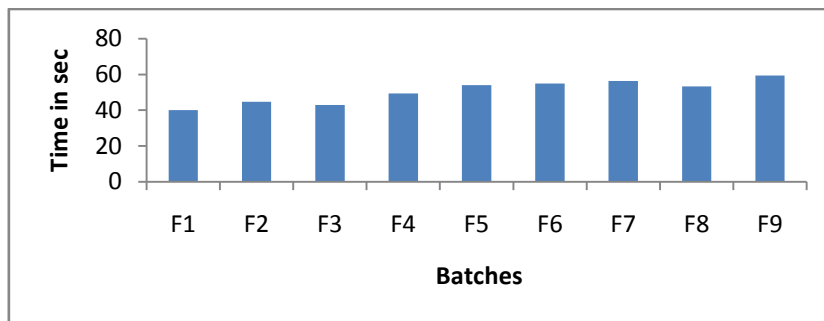


Fig. 7: Comparative disintegration time profile

Table 3: Dissolution Profile of Factorial Batches in Simulated Gastric Fluid

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	12.28	15.96	15.55	7.17	18.69	18.59	14.19	14.80	15.83
10	36.02	30.36	35.83	14.02	36.02	34.93	31.27	28.25	30.80
15	88.25	86.33	88.99	80.11	90.51	89.34	81.30	89.15	87.06
20	94.59	91.62	91.09	85.82	95.54	91.41	90.98	92.46	97.51
25	103.05	99.83	95.67	96.60	100.51	97.66	100.37	96.50	95.27
30	93.01	99.20	96.86	96.16	96.46	99.33	99.60	94.45	95.90

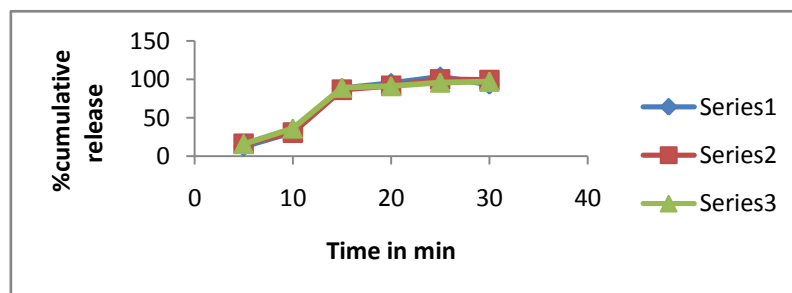


Fig. 8: Comparative Dissolution Profile for Batches F1-F3 in 0.1 N HCl

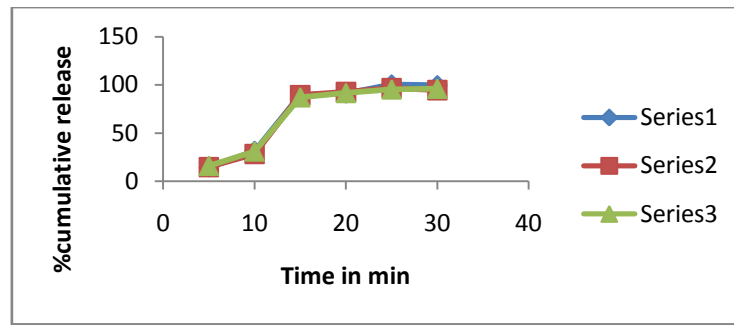


Fig. 9: Comparative Dissolution Profile for Batches F4-F6 in 0.1 N HCl

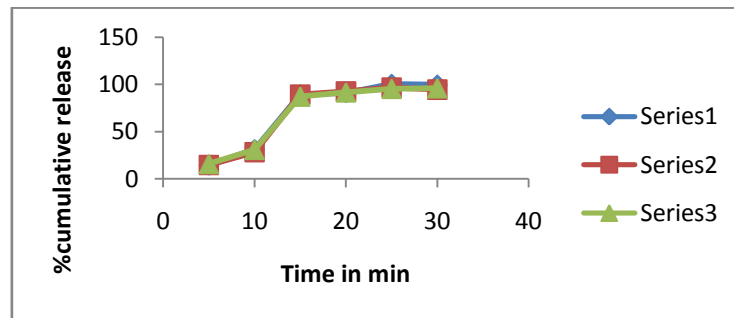


Fig. 10: Comparative Dissolution Profile for Batches F7-F9 in 0.1 N HCl

Table 4: Evaluation of Factorial batches

Batch code	Evaluation parameters						
	**Weight variation (mg±S.D)	Hardness (kg/cm ²)	**Thickness (mm±S.D)	Drug content (%)	In vitro *DT(Sec)	Wetting *time (Sec)	% Friability
F1	80±3	2-2.5	2.45±0.25	99.78	40±12	34±1.57	0.666
F2	80±3	2.5-3	2.47±0.23	98.94	44±1.26	41.66±1.45	0.636
F3	80±3	2.5-3	2.45±0.19	96.05	43±1.39	38±1.46	0.583
F4	80±3	3	2.46±0.22	95.99	49±1.52	45±1.64	0.463
F5	80±3	2.5-3	2.48±0.25	100.01	54±1.49	46.33±1.75	0.449
F6	80±3	3-3.5	2.43±0.21	99.88	55±1.33	47.66±1.26	0.446
F7	80±3	3-3.5	2.54±0.23	100.03	56.33±1.44	47.66±1.48	0.323
F8	80±3	3-3.5	2.49±0.20	95.05	53±1.13	50.33±1.64	0.338
F9	80±3	3-3.5	2.47±0.21	93.07	59±1.45	54±1.23	0.336

CONCLUSION

In the present study orally disintegrating tablet of Atenolol was prepared by Phase Transition technique. The physical characteristics of the blend of all the formulations were satisfactory. All the formulations were evaluated for physical characteristics, disintegration, *in-vitro* dissolution studies. The prepared tablets were found to be within the official limits with respect of weight variation, hardness and friability. The *in-vitro* disintegration and dissolution studies were performed for the F1-F9 formulations. Among these two formulations **F6** and **F8** showed the least disintegration time and maximum cumulative percentage drug release after 15 minutes. But formulation batch **F6** was found to be with good disintegration time and also requires less amount of Xylitol as compared to batch F8. Therefore batch **F6** was most robust formulation and considered to be optimum batch.

All prepared tablets met the compendial limits in terms of physicochemical parameters and thus pearlitol SD-200 and Xylitol were the appropriate excipients and formulated in good proportions.

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