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Fast Disintegrating Tablets of Atenolol by Dry Granulation Method

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Atenolol was formulated as fast disintegrating tablet using three superdisintegrants, croscarmellose sodium (Ac-Di-Sol), crospovidone (Polyplasdone XL) and sodium starch glycolate (Explotab). Thirteen formulations were prepared and all had the same amount of ingredients except, the superdisintegrant level. All the superdisintegrants were used at different concentration levels to assess their efficiency and critical concentration level. Physical characteristics, *in vitro* release characteristics, moisture uptake and stability profile of various formulations were evaluated. Moisture uptake by formulations was studied to reveal any relationship between moisture uptake and disintegration and/or dissolution efficiency. Ac-Di-Sol proved to be the best among the three and showed satisfactory results at 3 kg/cm² hardness. Formulations were found stable in release profile after 30 d stability studies at room temperature.

Atenolol is a β_1 selective antagonist[1] without membrane stabilizing[1] or intrinsic sympathomimetic activities[2]. Acting selectively and competitively on β adrenoreceptors, this drug blocks the actions of catecholamines. Atenolol can be administered once daily as 50 to 100 mg orally in the treatment of hypertension and angina pectoris[1]. Geriatric patients may have difficulties in swallowing and chewing the tablets resulting in patient non-compliance and ineffective therapy. Tablets that rapidly disintegrate upon contact with saliva could be a solution to this problem[3]. Thus the present drug is chosen as a suitable candidate for the formulation of fast disintegrating dosage form. In the present investigation, an attempt was made to formulate atenolol as a fast disintegrating tablet using three superdisintegrants in different ratios.

MATERIALS AND METHODS

Atenolol and magnesium stearate were procured from Trident Pharmaceuticals Pvt Ltd., Hyderabad. Croscarmellose sodium (Ac-Di-Sol, FMC Corp.), crospovidone (Polyplasdone XL, GAF Corp.), sodium starch glycolate (Explotab, Edward Mendell Co.), dibasic calcium phosphate, dihydrate (Vikas Pharma, Mumbai) and mannitol (E.Merck (India) Ltd., Mumbai) were obtained from commercial sources. All other reagents were of analytical grade. Sorenson's buffer (pH 6.2) was prepared using potassium phosphate and sodium phosphate solutions[4].

Formulation of tablets:

Amount of each ingredient (mg) was added according to the Table 1. Required quantities of atenolol, mannitol, and dibasic calcium phosphate (DCP) were weighed and mixed in geometric progression. This blend was then forced into 12 mm die tablet press to form slugs, having hardness of about 4.5 to 5.0 kg/cm². These slugs were then milled and screened through 22/44 mesh. Granules retained on 44 mesh were assayed for drug content and an amount equivalent to 50 mg of atenolol for one tablet was weighed and blended with superdisintegrants and magnesium stearate as per the Table1. Six milligrams of magnesium stearate was added to each tablet in the lubrication step. Superdisintegrants and magnesium stearate were passed through 60 mesh, before being added during the lubrication step. Lubrication was done for 3 min in a plastic container. Lubricated granules were punched and evaluated. Characteristics of blend like bulk density[5], compressibility index[5] and angle of repose[5]

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TABLE 1: FORMULAE OF TABLETS

Formulation	Granulation step (mg/tablet)			Lubrication step (mg/tablet)		
	Atenolol	Mannitol	DCP*	Ac-Di-Sol	Explotab	Polyplasdone XL
Control	50	114	30	-	-	-
DAI	50	106	30	8	-	-
DAII	50	102	30	12	-	-
DAIII	50	98	30	16	-	-
DAIV	50	94	30	20	-	-
DEI	50	106	30	-	8	-
DEII	50	102	30	-	12	-
DEIII	50	98	30	-	16	-
DEIV	50	94	30	-	20	-
DPI	50	106	30	-	-	8
DPII	50	102	30	-	-	12
DPIII	50	98	30	-	-	16
DPIV	50	94	30	-	-	20

*DCP stands for dicalcium phosphate dihydrate.

were determined for each formulation.

The dimensional specifications were measured using screw gauge. Weight variation test was conducted as per specifications of IP[6]. Hardness test[7] was performed by using a Monsanto hardness tester. The friability test[6] was performed using a Roche friabilator. Disintegration time was determined as per procedure given in IP[6]. Sorenson's buffer pH 6.2 was used as a medium at 37±0.5°.

Drug content determination:

Powder equivalent to 50 mg of atenolol was dissolved in Sorenson's buffer pH 6.2. Sufficient dilutions were made to obtain 20 μg/ml solution. Absorbance of the resulting solution was measured at 225 nm using Shimadzu (UV 1601) spectrophotometer. From the absorbance values, amount of drug present in the given tablet was calculated. Procedure was repeated by using four more tablets from the same formulation and the average value of all five tablets was calculated.

***In vitro* dissolution profile:**

Dissolution studies were carried out by USP[8] paddle method at 37±0.5°, taking 650 ml of Sorenson's buffer pH 6.2 as dissolution medium. Speed of rotation of the paddle was set at 50 rpm. Samples were diluted to 20 μg/ml and absorbance was measured at 225 nm in a Shimadzu (UV 1601) spectrophotometer.

Moisture uptake by formulations:

Ten tablets from each formulation were kept in a desiccator, over calcium chloride at 37° for 24 h. The tablets were then weighed and exposed to 75% RH, at room temperature for two weeks. Required humidity was achieved by keeping saturated sodium chloride solution at the bottom of the desiccator for three days[9]. One tablet as a control (without superdisintegrnts) was kept to assess the moisture uptake due to other excipients. Tablets were weighed and the % increase in weight was recorded.

Stability studies:

Tablets were packed in tightly closed plastic containers and stored at room temperature for 1 mo. The product was analyzed after 30 d storage and drug release profile was found out using Sorenson's buffer pH 6.2 as dissolution medium. Samples were withdrawn at 2 min and 10 min intervals and compared with release obtained immediately after compression.

RESULTS AND DISCUSSION

The present investigation was undertaken to fabricate and evaluate fast disintegrating tablets of atenolol by dry granulation method by comparing with control tablets. Superdisintegrants at different concentration levels (4, 6, 8 and 10% w/w) were used to assist disintegration.

Bulk densities of various formulations varied between 0.34 to 0.38 g/ml. The angle of repose values varied from 15° to 17°. The compressibility values varied from 13.3 to 14.6 %. From these values, it was evident that these blends had excellent flow properties.

Physical parameters conformed to the requirements. Weight variation was found within the specifications of IP. Average weight of one tablet of all thirteen formulations was found in the range of 190-205 mg. Hardness of all the tablet formulations was observed in the range of 3.0-3.2 kg/cm^2. Thickness and diameter of all thirteen formulations were found in the range of 3.48-3.83 mm and 9.76-10 mm, respectively. Friability of all formulations was found in the range of 0.718-0.914%. Drug content of all formulations was found in the range of 97-102%.

Disintegration time of different formulations is shown in fig. 1. All formulations had disintegration time of less than 70 s. Among the three superdisintegrants used, Ac-Di-Sol showed the highest efficiency. Formulations containing 10% w/w Ac-Di-Sol (DAIV) showed the least disintegration time of 30±2 s. Comparing Explotab and Polyplasdone XL, it was observed that at lower concentrations (up to 6% w/w), Explotab is more efficient than Polyplasdone XL, whereas at higher concentrations (6-10% w/w), Polyplasdone XL is more efficient than Explotab. For Explotab, minimum disintegration time was 52±2 s, at 8% w/w concentration and for Polyplasdone XL minimum disintegration time was 42±3 s at 10% w/w concentration.

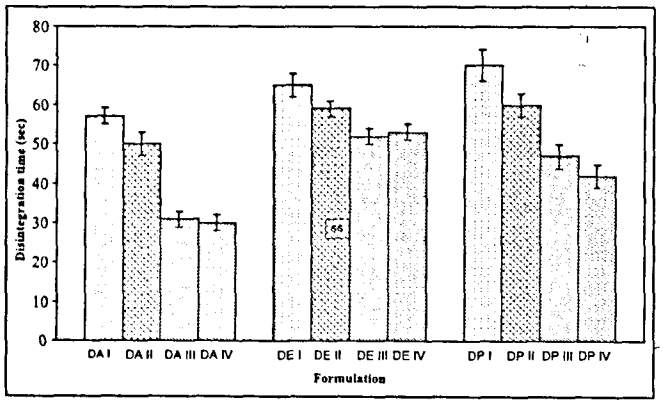

Fig. 1: Disintegration time of various formulations*.

***Average value of 6 tablets.**

The concentration of superdisintegrant also affected the disintegration time. In case of Ac-Di-Sol and Explotab formulations, concentrations higher than 8% w/w showed no effect or increase in disintegration time. In case of Polyplasdone XL formulations, this steady state was reached at 10% w/w or higher. So it may be assumed that 8% w/w concentration is optimum for Ac-Di-Sol and Explotab, whereas 10% w/w concentration is optimum for Polyplasdone XL. Such a behavior of superdisintegrants at higher concentrations may be due to the blockade of capillary pores, which prevents the entry of fluid into the tablet.

In vitro dissolution studies of various formulations at different time intervals are reported in fig. 2. Ac-Di-Sol formulations showed maximum dissolution rates with more than 95% of drug release in 10 min. Polyplasdone XL tablets released more than 85% of the drug in 10 min and Explotab formulations released more than 75% of the drug in 10 min. This shows that the effectiveness of superdisintegrants was

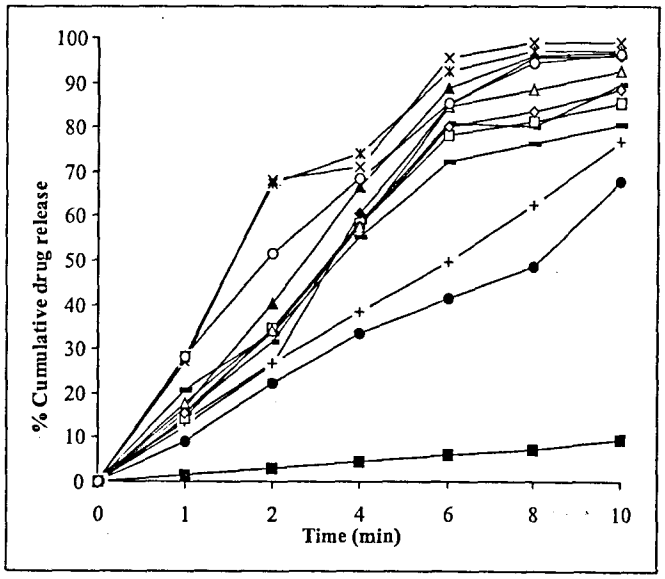

Fig. 2: Cumulative percent release of atenolol in Sorenson's buffer pH 6.2*.

Series 1- control (■) , series 2- DAI (◆), series 3- DAII (▲), series 4- DAIII (×), series 5- DAIV (✳), series 6- DEI (●), series 7- DEII (+), series 8- DEIII (-), series 9- DEIV (—), series 10- DPI (□), series 11- DPII (◇), series 12- DPIII (△) and series 13-DPIV (○).*Average value of 6 tablets.

TABLE 2: MOISTURE UPTAKE BY VARIOUS FORMULATIONS

Time (d)	% Increase in weight* of the formulations									
	Ac-Di-Sol			Explotab			Polyplasdone XL			
	DAI	DAII	DAIII	DEI	DEII	DEIII	DPI	DPII	DPIII	Control
1	3.52	3.88	4.24	4.78	4.75	5.01	2.92	3.13	3.51	1.86
2	4.92	4.89	4.84	5.35	5.51	5.62	3.41	3.68	4.11	1.98
3	5.14	5.55	5.63	5.83	5.92	6.11	3.72	3.91	4.24	2.15
4	5.35	5.84	6.08	6.11	6.34	6.42	4.12	4.30	4.38	2.22
5	5.64	6.11	6.64	6.58	6.68	6.69	4.51	4.51	4.56	2.28
6	5.78	6.20	6.87	6.75	6.84	6.92	4.68	4.67	4.72	2.31
7	5.84	6.23	7.08	6.86	6.91	7.11	4.73	4.70	4.76	2.34
15	7.13	7.88	8.17	8.08	8.14	8.41	5.21	5.48	5.92	2.88

*Average value of 6 tablets.

in the order of Ac-Di-Sol>Polyplasdone XL>Explotab. The concentration of superdisintegrants in the formulation also affected the dissolution rates. In case of Ac-Di-Sol and Explotab formulations, upto 8% w/w concentration, there was steady increase in dissolution rate with concentration. At higher concentrations, both showed decrease in dissolution rate. 8% w/w concentration is optimum for Ac-Di-Sol and Explotab. In case of Polyplasdone XL 10% w/w is optimum level because, up to 10% w/w concentration level it shows linear increase in dissolution rate. Decrease in dissolution rate with increase in concentration may be due to the blockade of pores resulting in interior of tablets inaccessible to water.

TABLE 3: CUMULATIVE RELEASE PROFILE OF ATENOLOL DURING STABILITY STUDY

Formulation	%Cumulative drug release*			
	At 2 min time interval		At 10 min time interval	
	0 Weeks	After 1 month	0 Weeks	After 1 month
Control	3.28	3.30	9.32	9.29
DAI	28.43	28.14	95.78	95.68
DAII	39.67	38.92	96.13	95.31
DAIII	68.48	68.25	99.12	98.86
DEI	20.73	20.46	66.78	66.46
DEII	27.16	26.84	77.25	76.94
DEIII	32.24	31.23	89.18	89.08
DPI	33.29	32.62	84.68	83.79
DPII	33.98	32.65	88.92	88.25
DPIII	34.15	33.78	93.46	92.98

*Average value of 6 tablets.

Moisture uptake of different formulations is reported in Table 2. Results were compared with control tablets. Since all excipients were the same in all formulations, any difference in moisture uptake may be due to difference in type or concentration of superdisintegrant added. From the observations, it is evident that water uptake of superdisintegrant follows the order Explotab>Ac-Di-Sol>Polyplasdone XL.

With the same superdisintegrant, there was a linear increase in water uptake with increase in concentration of superdisintegrant. This was in contrast to dissolution rates, which decrease with increase in concentration. At higher concentrations blockade of pores decreased the dissolution rates, but the outer layer of the tablet may still have the ability to pick and absorb the moisture. This may contribute to the unexpected moisture uptake behavior of the tablets. Release profiles from tablets kept at room temperature for 30 d are shown in Table 3. The tablets were stable for 30 d at room temperature.

From the present study, it may be concluded that the fast disintegrating atenolol tablets can be prepared by dry granulation method using superdisintegrants. Ac-Di-Sol was found to be the best among the three superdisintegrants. At 8% w/w concentration level it showed the least disintegration time of 31±2 s and the highest release of more than 98% of the drug in 10 min.

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