International Standard Serial Number (ISSN): 2249-6807

International Journal of Institutional Pharmacy and Life Sciences 2(2): March-April 2012

INTERNATIONAL JOURNAL OF INSTITUTIONAL PHARMACY AND LIFE SCIENCES

Pharmaceutical Sciences **Research Article……!!!**

Received: 04-04-2012; Accepted: 20-04-2012

DESIGN AND IN VITRO EVALUATION OF ORODISPERSIBLE TABLETS OF ATENOLOL USING DIFFERENT SUPER DISINTEGRANTS

N.Raghavendra Naveen*[1], T.S.Nagaraja[1], R.Yogananda[1], Snehalatha[1], P.Divya[1], Farida Begum[2]

1. Post Graduate Department of Pharmaceutics, SJM College of Pharmacy, Jmit campus, Chitradurga, Karnataka-577502, India

2. Department of Pharmaceutics, Manipal College of Pharmaceutical Sciences, Manipal, Karnataka-576104, India

Keywords:

Mouth dissolving tablets, Atenolol, Crospovidone, Sodium starch glycolate

For Correspondence:

N.Raghavendra Naveen

Post Graduate Department of Pharmaceutics, SJM College of Pharmacy, Jmit campus, Chitradurga, Karnataka-577502, India

E-mail:

raghavendra.naveen@gmail.com

ABSTRACT

Atenolol is β1-selective adrenergic blocking agent and widely used in the treatment of hypertension and angina pectoris. Administration of conventional tablets of atenolol has been reported to exhibit fluctuation in the plasma drug levels, resulting either in manifestation of side effects or reduction in drug concentration at the receptor site. Therefore the present investigation was to design a formulation of mouth dissolving tablets of Atenolol by direct compression using combination of different superdisintegrates like sodium starch glycolate and crospovidone. The blend was examined for angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio. The prepared tablets were evaluated for weight variation, hardness, friability, disintegration time, wetting time and dissolution rate. Release profile of F-3 was found to have maximum release of 97.12 % at the end of 4 minutes. The drug release from all batches was found to be concentration dependent. It was concluded that superdisintegrants addition technique is a useful method for preparing mouth dissolving tablets by direct compression method.

INTRODUCTION

The tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness, and ease in manufacturing. However, geriatric and paediatric patients experience difficulty in swallowing conventional tablets, which leads to poor patient compliance. To overcome this weakness, scientists have developed innovative drug delivery systems known as orally disintegrating tablets (ODTs). These are novel types of tablets disintegrate/dissolve/disperse in saliva. Their characteristic advantages such as administration without water, anywhere, anytime lead to their suitability to geriatric and paediatric patients. They are also suitable for the mentally ill, the bedridden, and patients who do not have easy access to water. The benefits, in terms of patient compliance, rapid onset of action, increased bioavailability, and good stability make these tablets popular as a dosage form of choice in the current market [1,2]. The basic approach used in the development of the ODTs is the use of superdisintegrants. Another approach used in developing ODTs is maximizing pore structure of the tablets. Freeze-drying [3,4] and vacuum-drying [5,6] techniques have been tried by researchers to maximize the pore structure of tablet matrix. Atenolol, a β1-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 [7]. 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 site [8,9]. An attempt was made in the present investigation to prepare ODTs of atenolol using superdisintegrants at different concentrations.

MATERIALS AND METHODS

Materials

Atenolol obtained from Kopran Ltd. (Mumbai, India). Microcrystaline cellulose, Sodium starch glycolate, Crosspovidone were obtained as gift sample from Micro Labs (Bangalore, India). Magnesium stearate, Talc and Aspartame from Yarrow chemicals (Mumbai, India). All other materials used were of pharmaceutical grade.

METHOD PREPARATION OF MIXED BLEND OF DRUG AND EXCIPIENTS

All the materials were passed through sieve no. 60. Required quantity of each ingredient was taken for each specified formulation (Mentioned in Table no.1) and all the ingredients were subjected to grinding to a required degree of fineness (except magnesium stearate and talc). The powdered blend was evaluated for flow properties as follows and results were reported in Table no.2

Angle of repose [10]

Angle of repose was determined using fixed 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 (ɵ) was calculated using the formula.

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

Bulk density [10, 11]

Bulk density was determined by pouring the blend into a graduated cylinder. The bulk volume (Vb) and weight of the blend (M) was determined. The bulk density was calculated by using the below mentioned formula,

$$\text{Bulk density} = \frac{\text{Weight of the blend}}{\text{Volume of blend (Vb)}}$$

Tapped density [10, 12]

The measuring cylinder containing a known mass of blend was tapped for a fixed number of times. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density was calculated using the following formula,

$$\text{Tapped density} = \frac{\text{Weight of the blend}}{\text{Volume occupied in the cylinder (Vt)}}$$

Compressibility index [13]

The simplest way for measurement of free flow of powder is compressibility , a indication of the ease with which a material can be induced to flow is given by compressibility index (I) which is calculated as follows,

$$I = \frac{Vb - Vt}{Vb}$$

Here, Vb is bulk volume and Vt is tapped volume.

The value between 13-19% indicates a powder with usually good flow characteristics, whereas above 21% indicate poor flowability.

Hausner's Ratio [13]

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

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Lower Hausner's ratio (<1.25) indicates better flow properties and vice versa.

Compression of tablets by using direct compression technique

Finally magnesium stearate and talc were added to the prepared blend. The mixed blend of drug and excipients was compressed into tablets weighing 200 mg using flat faced punches of 8 mm diameter in a rotary tablet press (Rimek mini press- 1, Model RSB-4, Karnavati Engineering, Ahmedabad). A minimum of 50 tablets were prepared for each batch.

EVALUATION OF ATENOLOL MOUTH DISSOLVING TABLETS

Evaluation was done on tablets of all formulations batches considering following parameters and results were reported in Table no.3

1) Weight variation test [14]

Twenty tablets were selected randomly and average weight was determined. Then individual tablets were weighed and was compared with average weight. If the variation is within the I.P limits, the tablets pass the weight variation test.

2) Tablet hardness [14]

The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm^2. 3 tablets were chosen randomly and tested for hardness. The average hardness of 3 determinations was recorded.

3) Wetting time [14]

The wetting time of the tablets can be measured using a simple procedure. Five circular tissue papers of 10 cm diameter were placed in a petridish with a 10 cm diameter. 10 ml of water was poured on the tissue paper placed in the petridish. A table is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time.

4) Tablet friability [14]

Five tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. Then tablets were removed from the friabilator, dusted off the fines, weighed and the weight was recorded.

Percentage friability was calculated by using the formula:

$$\frac{\text{Initial weight - Final weight X100}}{\text{Initial weight}}$$

5) *In-Vitro* Disintegration time [14]

The test was carried out on 6 tablets using tablet disintegration tester ED – 20, Electrolab. Distilled water at 37ºC ± 2ºC was used as a disintegration media and the time in second taken for complete disintegration of tablet with no mass remaining in apparatus was measured in seconds.

6) Dissolution studies [15]

In Vitro dissolution studies for all the prepared tablets and the marketed available tablets was carried out using USP paddle method at 50 rpm in 900 ml of 0.1 N HCl (pH 1.2) as dissolution media, maintained at 37 ± 0.5º. 5 ml of samples, were withdrawn from the dissolution medium at the specified regular intervals, filtered through whatmann filter paper and release of the drug was determined spectrophotometrically at 224.2 nm. An equal volume of pre warmed (37ºC) fresh medium was replaced into the dissolution medium after each sampling, to maintain the constant volume of the dissolution medium throughout the test. Then the cumulative percentage of drug release was calculated and represented graphically (Figure-1).

Table- 1: Composition of mouth dissolving Tablets of Atenolol

	F1	F2	F3	F4	F5	F6
Atenolol	25	25	25	25	25	25
SSG	10	10	10	15	15	15
Crosspovidone	2	4	6	2	4	6
Aerosil	2	2	2	2	2	2
Lactose	30	30	30	30	30	30
Aspartame	3	3	3	3	3	3
Mg.stearate	1	1	1	1	1	1
MCC	127	125	123	122	120	118
Total weight	200	200	200	200	200	200

Table-2: Evaluation of the Powder Blend

	Angle of repose (θ)*	Bulk density (g/ml)*	Tapped density(g/ml)*	Carr`s index (%)	Hausner's ratio.*
F1	26.65 ±0.329	0.3978±0.015	0.4625± 0.019	14.44± 1.92	1.1626±0.082
F2	28.32 ±0.201	0.4002±0.013	0.4669 ±0.017	14.28± 1.77	1.1666±0.025
F3	25.36± 0.098	0.3997±0.009	0.4612± 0.019	13.33± 1.93	1.1538±0.038
F4	27.43± 0.187	0.4043±0.016	0.4751± 0.016	14.81± 1.87	1.6664±0.026
F5	28.50± 0.067	0.4073±0.011	0.4807± 0.010	12.13± 1.82	1.1802±0.023
F6	22.54± 0.265	0.4157±0.006	0.4923± 0.016	15.15± 1.93	1.1842±0.033

* mean ± S.D., n=3 (all the values are the average of three determinations)

Table-3: Evaluation of Mouth dissolving tablets of Atenolol

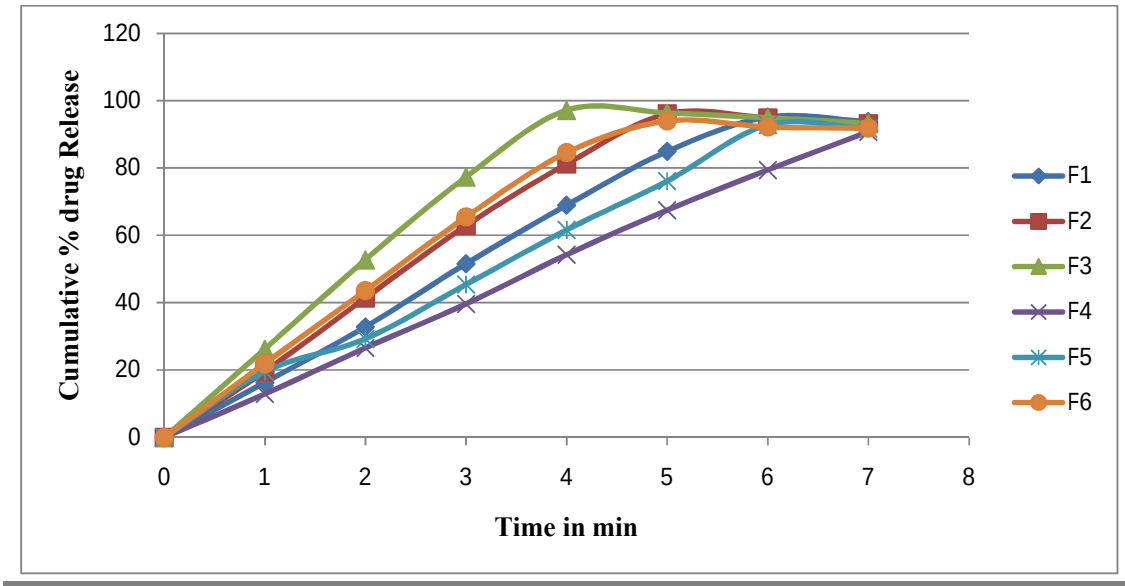
	F1	F2	F3	F4	F5	F6
Weight variation(%)*	201.95±0.44	201.3±0.74	202.1±1.82	201.5±1.63	201.1±1.19	200.3±1.12
Hardness (kg/cm^2)	3.5	3.8	3.6	3.2	3.1	3.4
Friability (%)	0.4024	0.4016	0.3879	0.5014	0.6024	0.4164
Wetting time (sec)*	113±1.18	81± 1.52	17± 1.10	120± 1.39	107± 1.42	59± 0.28
Disintegration time(sec)*	33± 0.43	26± 1.14	11± 1.49	49 ± 1.31	38± 1.05	22±1.32

* mean ± S.D., n=3 (all the values are the average of three determinations)

Table-4: In-vitro drug release of prepared atenolol mouth dissolving tablets.

Time in minutes	F1	F2	F3	F4	F5	F6
1	16.28	19.62	26.23	12.87	19.52	21.97
2	32.81	41.38	52.74	26.56	29.28	43.61
3	51.57	62.89	77.31	39.63	45.39	65.48
4	**68.93**	**81.19**	**97.12**	**54.24**	**61.60**	**84.57**
5	84.92	96.09	96.34	67.46	76.09	93.98
6	95.08	94.89	94.87	79.38	92.78	92.22
7	93.78	93.17	93.28	90.72	91.63	91.83

Fig. 1: Cumulative % drug Release Vs Time in min from prepared batches F-1, F-2, F3, F-4, F-5 & F-6 of mouth dissolving tablets of atenolol



RESULTS AND DISCUSSION

Six formulations of Atenolol were prepared with combination of different concentrations of superdisintegrants like crospovidone, sodium starch glycolate. For each formulation, blend of drug and excipients were prepared and evaluated for various parameters as explained earlier. The formulated blends were evaluated and the results are shown in the table 2. The angle of repose was in the range of 22.54±0.265 to 28.50±0.067 indicating good flow property. The bulk density and tapped density was in the range of 0.3978±0.015 to 0.4157±0.006 gm/cc and 0.4612±0.019 to 0.4923±0.016 gm/cc. The compressibility index and Hauser's ratio was in the range of 12.13± 1.82 to 15.15 ±1.93% and 1.1538±0.038 to 1.1842±0.033 indicating good flow property. The powder blend was compressed using direct compression technique. The compressed tablets were evaluated for physical properties and the results are tabulated in table 3. The hardness was in the range of 3.1 to 3.8 kg/cm^2. Uniformity of weight was found to be in the range of 200.3 ± 1.12 to 202.1±1.82 mg. The friability of all the formulation was within 1%, and was in the range of 0.4016 to 0.6024 % indicating a good mechanical resistance of tablets. The wetting time for all the formulated tablets was in the range of 17 ± 1.10 to 120 ± 1.39 sec. The disintegration time of all the formulated tablets was found to be in the range of 11 ± 1.49 to 49 ± 1.31 sec. All the formulations in-vitro drug release results were mentioned in the Table no.4. The results revealed that the increase in proportion of superdisintegrants was associated with change in the overall cumulative drug release rate. Release profile of F-3 was found to have maximum release of 97.12 % at the end of 4 minutes. The drug release from all batches was found to be concentration dependent.

CONCLUSION

In the present work efforts have been made to prepare and evaluate fast dissolving tablets of atenolol with combination of different concentrations of superdisintegrants like sodium starch glycolate and crospovidone by direct compression technique. The results revealed that the increased proportion of various superdisintegrants were associated with change in the overall cumulative drug release rate. Release profile of F-3 was found to have maximum release of 97.12 % at the end of 4 minutes. The drug release from all batches was found to be concentration dependent. The mouth dissolving tablets (MDT) found to have excellent physical characters. The superdisintegrants were also found to be compatible with the other excipients of the formulation as well as with drug, which is evident from the drug release. Hence the formulation of F-3 fulfills the objective of the present study.

ACKNOWLEDGEMENTS

The authors are thankful to Dr.Shivamurthy Murugha Sharanaru, President, SJM Vidya Peetha for providing all necessary facilities through the Principal, SJM college of Pharmacy.

REFERENCES

1. R. Chang, X .Guo, B. Burnside, R.Couch, A review of fast dissolving tablets, *Pharm Tech*. (2000) 52-58.
2. Y.Bi, H. Sunada, Y. Yonezawa, K. Iida, Preparation and evaluation of a compressed tablet rapidly disintegrating in oral cavity, *ChemPharmBull*. 44 (1996) 2121-2127.
3. S. Corveleyn, J. P. Remon, Formulation and production of rapidly disintegrating tablets by lyophilization using hydrochlorthiazide as a model drug, *Int J Pharm*. 152 (1997) 215-225.
4. J. P. Remon, Freeze-dried rapidly disintegrating tablets, US patent 6 010 719, 2000.
5. H. Heinemann, W. Rothe, Preparation of poroustablets, US patent 3 885 026, May 20, 1975.
6. A. Knistch, Production of porous tablets, US patent 4 134 843, January 16, 1979.
7. D. M. Roden, Antiarrhythmic Drugs, In: Goodman and Gilman's Pharmacology Basis of Therapeutics, 10th ed., McGraw Hill Publishing Division, New York 2006, pp. 949-950.
8. S. R. Vaithiyalingam, S. V. Sastry, R. H. Dehon, I. K.Reddy, M. A. Khan, Long-term stability characterization of a controlled release gastrointestinal therapeutic system coated with a cellulose acetate pseudo latex, Pharmazie.56 (2001) 66Y69.
9. S. V. Sastry, Atenolol gastrointestinal therapeutic system: optimization of formulation variables using response surface methodology, J Control Release. 45 (1997) 121Y130.
10. United States of Pharmacopeia-National Formulary, USP 30 – NF 25.MD: The Unit States Pharmacopeial Convention Rockville.2007, 1, 644, 242, 645, 731 and 634.
11. Liberman, H.A., Lachman, L., Schwartz, J.B.,Pharmaceutical dosage forms: Tablets volume- 2. Marcel dekker, New York 2005, p.165-7. 15.
12. Gun, C.J., Powder Flow and Compaction, CBS publication, New Delhi 1986, p. 211-33.
13. Sinko, P.J., Martin's Physical pharmacy and pharmaceutical sciences, Lippincott Williams and Wilkins, New York 2006, p.557.
14. Siji, R.R., Shanmuganathan, S., Sekharan, T.R., SenthilKumar, S.R., Thanga, T., International Journal of Chem Tech Research.2009, 1,4, 1251-6.
15. Pharmacopoeia of India, Ministry of Health and Family Welfare, Govt. of India Controller of Publications, New Delhi 1996, P.735.