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FORMULATION AND EVALUATION OF PH INDEPENDENT TABLET ATENOLOL

V. Bhasker*, G. Snehankitha, M. Mounika, B. Raju, G. Pavan Kalyan, N. Suresh
Department of Pharmaceutics, Talla Padmavathi Pharmacy College,
Orus, Kareemabad, Warangal, Telangana, India

ABSTRACT

Atenolol was chosen as a drug candidate, which is widely prescribed drug especially in cardiovascular diseases. Introduced in 1976, Atenolol was developed as a replacement for Propanolol in the treatment of Hypertension. The chemical works by slowing down the heart and reducing its workload. Unlike Propanolol, Atenolol does not pass through the blood-brain barrier thus avoiding various central nervous system side effects. Atenolol is used for a number of conditions including: hypertension, angina, acute myocardial infarction, supraventricular tachycardia, ventricular tachycardia, and the symptoms of alcohol withdrawal. It is also used to treat the symptoms of Graves' disease until antithyroid medication can take effect.Due to its hydrophilic properties; the drug is less suitable in migraine prophylaxis compared to propranolol, because, for this indication, atenolol would have to reach the brain in high concentrations, which is not the case. The aim of this work is to investigate the possibility of obtaining a prolonged, relatively constant effective level of Atenolol. Sustained release formulation of Atenolol presents the formulator with significant challenges due to its less protein binding and less half life. Present study investigates the possibility for development of a direct compression sustained release tablet using Hydroxy propyl methyl cellulose and to develop a SR tablet dosage form of Atenolol by direct compression method. The half-life of Atenolol is also short (6 to 7hrs) which makes it suitable candidate for sustained release formulation, moreover it reducing side effects, decreasing frequency and improve patient compliance. Oral absorption of the antihypertensive agent Atenolol is confined to the Gastro intestinal tract, therefore rational controlled release formulations of this drug should ensure a complete release during transit from stomach to jejunum. Keeping these factors in view it is aimed to formulate and evaluate sustained release tablets , to provide a controlled and predictable release of Atenolol, which is an oral antihypertensive drug used in treatment of hypertension once daily administration. Due to increase in awareness of medical and pharmaceutical community, about the importance of safe and effective use of drug, much attention has-been paid to develop the controlled drug delivery system. The aim of this study were to sustain the release of drug from tablets by using of hydrophilic polymer for sustained release tablets, based on the results of an in vitro dissolution study by considering the cost of drug by reducing the drug dose and increasing its effectiveness and deliver drug at a near constant rate for approximately 8 hrs, independent of food intact and gastrointestinal pH.

Key Words: Atenolol sulfate, HPMC, Citric acid, Tartaric acid

***Corresponding Author:**
V. Bhasker,
Talla Padmavathi Pharmacy College,
Orus, Kareemabad,
Warangal,Telangana,India.

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INTRODUCTION

For many decades treatment of an acute disease or a chronic illness has been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms, including tablets, capsules, pills, suppositories, creams, ointments, liquids, aerosols, and injectables as drug carriers. This type of drug delivery system is known to provide a prompt release of drug or immediate release product. Such immediate release products result in relatively rapid drug absorption and onset of accompanying pharmacodynamic effects. However, after absorption of drug from the dosage form is complete, plasma

drug concentrations decline according to the drug's pharmacokinetics profile. Eventually, plasma drug concentrations fall below the minimum effective plasma concentration (MEC), resulting in loss of therapeutic activity. Before this point is reached another dose is usually given if a sustained therapeutic effect is desired. An alternative to administering another dose is to use a dosage form that will provide sustained drug release, and therefore, maintain plasma drug concentrations, beyond what is typically seen using immediate release dosage forms. In recent years, various modified release and/ or the time for drug release.[1,2,3]

After 20th century investigation of new drug has been retained due to investigation cost of new drug. Therefore, pharmaceutical industries and academic laboratories have been focused on establishment of novel drug delivery system / or modified release dosage form rather investigation and development of new drug[2]. The basic rationale of a sustained drug delivery system is to optimize the Biopharmaceutic, Pharmacokinetic and Pharmacodynamic properties of a drug in such a way that its utility is maximized through reduction in side effects and cure or control of condition in the shortest possible time by using smallest quantity of drug, administered by the most suitable route.[4] The novel system of drug delivery offer a means of improving the therapeutic effectiveness of incorporated drugs by providing sustained, controlled delivery and / or targeting the drug to desired site. The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration.[5, 6] There is a continuously growing interest in the pharmaceutical industry for sustained release oral drug delivery systems. There is also a high interest for design a dosage formulation that allows high drug loading, particularly for actives with high water solubility.[7]

Modified Release Dosage Form and Drug Delivery[3, 8]

Drug products designed to reduce the frequency of dosing by modifying the rate of drug absorption have been available for many years. Early modified release products were often intramuscular/subcutaneous injection of suspensions of insoluble drug complexes, e.g. Procaine penicillin, protamine zinc insulin, insulin zinc suspension or injections of the drug in oil, e.g. Fluphenazine decanoate. Advance in technology have resulted in novel modified release dosage form. In contrast to conventional (immediate release) forms, modified release products provide either delayed release or extended release of drug. Extended release products are designed to release their medication in a controlled manner, at a predetermined rate, duration, and location to achieve and maintain optimum therapeutic blood levels of drug.

RESULTS AND DISCUSSION

Table 1: Instruments / Equipments

S. No.	Name of the Instrument / Equipment	Make
1	Single stroke tablet compression machine	Model-CMS, Cadmach
3	Friabilator USP EF-2	Electro Lab
4	Hardness tester	Pfizer
5	Digital vernier scale	Mitutoyo, Japan
6	Bulk Density apparatus	Veego
7	Mettler Balance	model-AE-160, Mettler, Switzerland.
8	pH meter	Digisun electronics
10	Disintegration tester USP	Electro Lab
11	FT-IR	model-FTIR-SHIMADZU
12	KBr-Dye	Model-15.011, PERKIN-LMER.

Table 2: Instruments / Equipments

S. No	Drug/Exciepents	Source
1	Atenolol	Arthi drugs, Mumbai
2	HPMC	Fmc.USA
3	Citric acid	ISP USA
4	Tartaric acid	Signet Mumbai
5	Dicalcium phosphate	Signet Mumbai
6	Magnesium stearate	Signet Mumbai

13	Dissolution apparatus	Model-TDT-06 USP(XXI) sisco
14	UV spectrophotometer	Model-UV-1371

Standard curve of atenolol by u.v spectrophotometer:

100 mg of atenolol is dissolved in 100 ml of phosphate buffer of pH 6.8 and. From this stock solution 10 ml was further diluted to 100 ml of with buffer. From this stock solutions allocates of 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5 and 5 ml of stock solutions were pipetted out and made up to 10 ml volume with buffers. The absorbencies of above solutions were measured at 275 nm by using U.V. Spectrometer. The standard graph was potted.

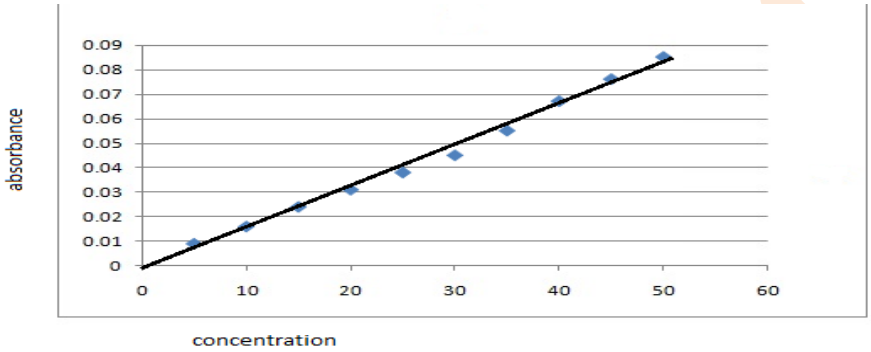

Fig. 1: Standard plot of Atenolol

Direct compression:

50 mg of the drug and the excipients were passed through sieve #60, lubricants were added by geometrical dilution followed by through mixing for 20 min. The prepared mass was compressed by using 13 mm flat faced punches in a controlled environment to get the average weight of 220 mg tablets. 7 formulations were prepared by using different concentrations of disintegrants. The compressed formulations were shown in the following table.

Table 3: Formulation of the Atenolol

Ingredietns (mg)	**F-1**	**F-2**	**F-3**	**F-4**	**F-5**	**F-6**	**F-7**
Atenolol	50	50	50	50	50	50	50
Citric acid	-	12.5	25	37.5	-	-	-
Tartaric acid	-	-	-	-	12.5	25	37.5
HPMC	75	75	68.75	62.5	75	68.75	62.5
Dicalcium phosphate	93	80.5	74.25	68	80.5	74.25	68
Magnesium stearate	2	2	2	2	2	2	2
Total	**220**	**220**	**220**	**220**	**220**	**220**	**220**

Table 4: Evaluation of the physical parameters of pH independent formulation of Atenolol

Formulation Code	***Physical Appearance***	***Weight Variation***	***Hardness kg/sqcm***	***Thickness mm***	***Friability***	***Content Uniformity***
F-1	Round, No spots,	Passes	2.932	4.52	0.82	99.18
F-2	Round, No spots	Passes	3.211	4.7	0.71	99.78
F-3	Round, No spots	Passes	3.537	4.55	0.79	98.12

F-4	Round no spots	Passes	3.12	4.56	0.87	99.19
F-5	Round no spots	Passes	3.35	4.872	0.82	98.00
F-6	Round no spots	Passes	3.52	5.015	0.80	99.18
F-7	Round no spots	Passes	3.38	4.83	0.82	98.25

Table 5: Drug release profile of pH independent formulation pH 1.2 & 6.8

TIME	F1		F2		F3		F4		F5		F6		F7	
	1.2	6.8	1.2	6.8	1.2	6.8	1.2	6.8	1.2	6.8	1.2	6.8	1.2	6.8
5 min	2%	3%	3%	2%	3%	2%	5%	3%	5%	6%	6%	5%	4%	3%
10 min	5%	6%	8%	4%	5%	4%	8%	6%	8%	10%	8%	8%	8%	6%
15 min	7%	7%	9%	8%	7%	6%	12%	10%	15%	10%	12%	10%	15%	10%
30 min	13%	13%	12%	10%	10%	12%	16%	12%	18%	15%	15%	15%	18%	18%
1 hr	21%	18%	19%	17%	18%	15%	20%	18%	20%	18%	22%	18%	20%	20%
2 hr	39%	30%	38%	25%	23%	28%	38%	13%	38%	22%	40%	25%	35%	35%
3 hr	44%	41%	42%	42%	35%	30%	48%	38%	50%	38%	59%	38%	40%	42%
4 hr	58%	54%	60%	56%	42%	38%	68%	48%	62%	42%	65%	45%	58%	58%
5 hr	62%	60%	80%	58%	50%	52%	78%	68%	80%	50%	78%	58%	68%	62%
6 hr	65%	63%	98%	62%	65%	60%	80%	60%	98%	82%	99%	62%	80%	75%
7 hr	71%	69%	99%	76%	68%	62%	92%	65%	98%	96%	100%	82%	85%	78%
8 hr	78%	78%	100%	78%	82%	76%	98%	75%	98%	97%	100%	96%	97%	80%
9 hr	82%	78%	100%	78%	85%	80%	100%	78%	98%	98%	100%	98%	98%	82%

Fig. 2: pH independent F5 formulation of Atenolol release in 0.1N HCL

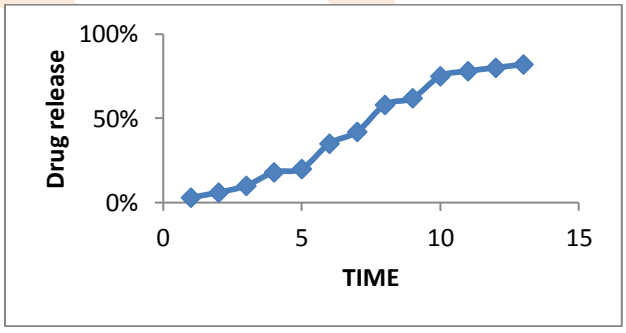

Fig. 3: pH independent F5 formulation of Atenolol release phosphate buffer pH 6.8

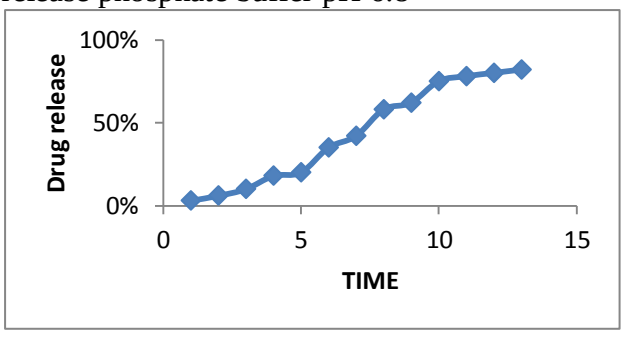

Fig. 4: pH independent F6 formulation of Atenolol release in 0.1N HCL

Fig. 5: pH independent F6 formulation of Atenolol release phosphate buffer pH 6.8

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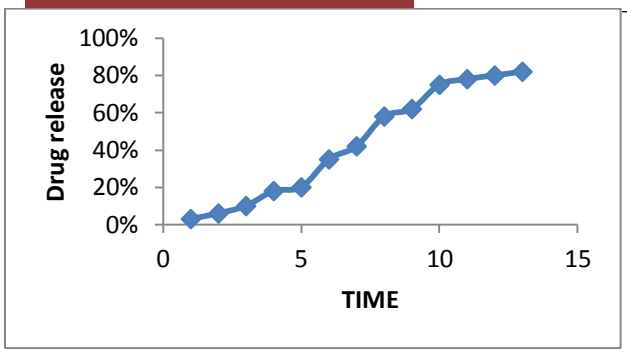

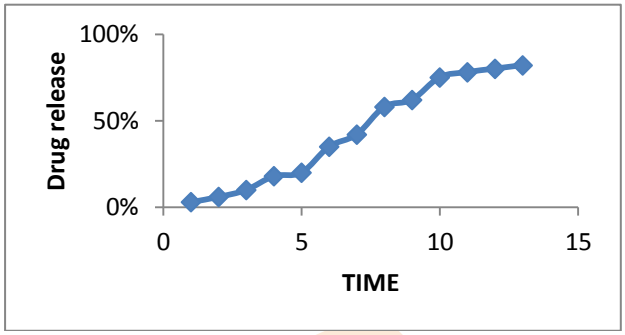

CONCLUSION

In present work attempts have been made to formulate sustained release tablet of pH independent formulation containg atenolol, by using hydrophilic polymer, which is preferably used as an antihypertensive agent. Tablets were prepared using polymer with HPMC in different concentration by direct compression technique. Atenolol meets all the ideal characteristics to formulate in the form of controlled release drug delivery system. Under preformulation study, the organoleptic properties were complied with the USP specification. Physical properties such as bulk density and tapped density were sutabul for compression. Solution properties, i.e. pH of the solution and solubility were evaluated; results were complied with the pharmacopoeial specification. The compatibility evaluations were performed by FTIR spectroscopy analysis. The studies imply that the drug and polymer are compatible with each other. There were no interaction found between polymer, excipients and drugs. The final formulations were evaluated on the basis of pharmacopoeial specification. Shape of the tablets was circular. The physical parameters thickness, hardness, friability and weight variation is carried out.

Addition of citric acid to HPMC based matrix tablets failed to achieve pH independent release of Atenolol, whereas formulations,F5 and F6 containing 5.6 and 11.2% of tartaric acid in tablet formulations, respectively, improved the drug release in phosphate buffer (pH 6.8) sufficiently and were considered as the best tablet formulations. It seems that lower pKa of tartaric acid results in a pH-independent drug release profile. The solubility of organic acid as well as the type of matrix former should also be considered as two other important aspects in achievement of appropriate results.

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