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Research Article
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FORMULATION AND EVALUAION OF pH-RESPONSIVE MINI-TABLETS FOR ATENOLOL COLONIC DRUG DELIVERY SYSTEM

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ABSTRACT

In the present study a novel colon specific drug delivery system of an Anti-Hypertensive drug is Atenolol, for treatment of chronic cardiac diseases like Heart failure, sudden increases in blood pressure was developed. Mini tablets of Atenolol were prepared by wet granulation method using matrix forming natural polymers like pectin, Guar gum and Xanthum gum in combination with different proportions (F1-F13). The further effect of enteric coat on the mini tablets for colon specific drug release was investigated. The Atenolo optimized matrix formulation F7 shows drug release around 32.37±0.33% in 2 hrs. So it was further enteric coated with Eudragit S100 in cumulative ratio and formulated the formulations from F14-F17.Apart from F14 showed optimum drug release after 24 hrs. All formulations were subjected to Hardness test, Friability test, determination of uniform diameter and thickness, drug content for optimization and further evaluation. In vitro dissolution studies revealed that the drug release in upper part of GIT from matrix tablets of Atenolol can be prevented by enteric coating with pH sensitive polymer (Eudragit®S100), which releases the drug specifically in colonic region to achieve target delivery.

KEY WORDS

Atenolol; Pectin; Xanthan gum; Guar gum; Eudragit®S100, in vitro drug release; Colon-Specific Drug Delivery.

INTRODUCTION

The Colonic Drug Delivery Systems have recently gained importance for delivering a variety of drugs. Colonic drug delivery may be achieved by either oral or rectal administration. Rectal administrations of drugs for colon targeting always face high variability in the distribution of drug, when they are administered in form of dosage forms like enemas and suppositories, which are not always effective. Therefore, the oral route is the most preferred. Conventional oral formulations dissolve in the stomach or intestine and are absorbed from these regions. The major problem with the delivery of drugs by oral route to the colon is the absorption and degradation of the drug in the upper part of the gastrointestinal tract (GIT) which must be overcome for successful colonic drug delivery[1]. In conditions where localized delivery of the drugs is required in the colon or drugs which are prone to degradation in the environment of the upper GIT, colonic drug delivery may be valuable.

Drug release at this site will ensure maximum therapeutic benefits. Oral delivery of drugs to the colon is valuable in the treatment of chronic cardiac diseases, whereby high local concentration can be achieved while minimizing side effects that occur because of release of drugs in the upper GIT or help to avoid unnecessary systemic absorption of the drug. However, in this case it is desirable to localize the release of Atenolol to be effected in site of colon. Thus, Atenolo was used as a model drug in the present study[2].

MATERIALS AND METHODS

Atenolol, Guar gum, Pectin, Xanthan gum, Sodium starch glycollate, Micro crystalline cellulose, Magnesium stearate, and Eudragit®S100are collected from S.D. Fine chem. Ltd., Mumbai, India. Weighing balance (ATX224) Shimadzu, Japan. UV-Visible spectrophotometer (UV 3200) Labindia, Mumbai, India. Tablet Compressing machine (Rimek mini press-I) Karnavati, Mumbai, India. Dissolution tester (DS-8000) Labindia, Mumbai, India.

Preparation of Matrix mini-tablets by wet granulation method[3]: (F1-F17)

All the ingredients were accurately weighed as per formula and were dispensed in clean polythene cover. Atenolol, microcrystalline cellulose passed through sieve no 60. Magnesium Stearate and talc were passed through sieve no 40. All the above sifted ingredients were mixed in polythene cover thoroughly for about 30min. The mini tablets were prepared by compressing thoroughly the mixed materials using 4 mm round, flat and plain punches on table top pilot scale 10 station rotary tablets Rimek mini press-I (M/S Karnavati Engineering Ltd., Gujarat, India). Finally it produces 50 mg of Matrix mini tablet of Atenolol.

Figure: 01 Preparation of Matrix mini-tablets of Atenolol

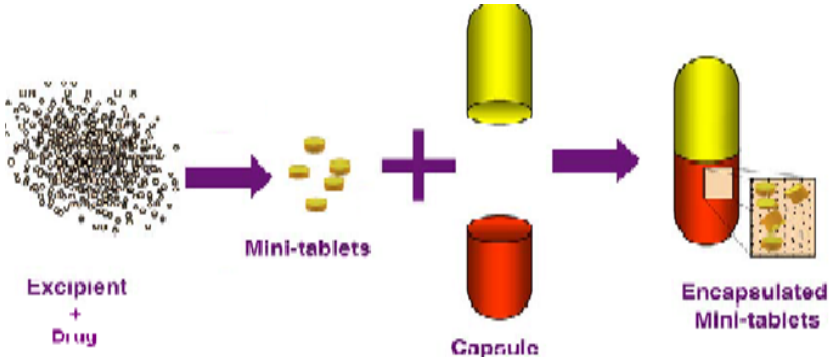


Table: 01 Composition formula for Atenolol Mini tablet without Eudragid S-100

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
API (mg)	5	5	5	5	5	5	5	5	5	5	5	5
Pectin (mg)	5	10	15	20	---	----	----	----	----	-----	-----	----
Xanthum.gum(mg)					5	10	15	20	----	----	-----	----
Guar gum(mg)	----	----	----	----	----	----	----	----	5	10	15	20
Talc (%)	1	1	1	1	1	1	1	1	1	1	1	1
Mg.stearate(%)	1	1	1	1	1	1	1	1	1	1	1	1
MCC (Q.S)	50	50	50	50	50	50	50	50	50	50	50	50
Total Wt (in mg)	50	50	50	50	50	50	50	50	50	50	50	50

Preparation of coating Solution[4]:

The outer coating layer was applied on the matrix tablets using dip coating method. An organic polymer solution consisting of EudragitS-100 in acetone was used for the coating. Castor oil was incorporated in the coating solution as a plasticizer (20% w/w based on the polymer). An Opacifier, titanium dioxide (0.05% w/w) and an antiadherant, talc (5% w/w) to prevent adhering of tablets during the coating process were also added to the coating solution. For preparing the capsule formulation 05 enteric coated mini-tablets equivalent to 25 mg of Atenolol were filled into size 1 HPMC capsule

Table: 02 Composition Atenolol mini tablets with Eudragid S-100

Ingredients	F13	F14	F15	F16	F17
API (mg)	5	5	5	5	5
Pectin (mg)	-	-	-	-	-
Xanthum.gum(mg)	15	15	15	15	15
Guar gum(mg)	-	-	-	-	-
Eudragid S100 (%)	1.5	3	4.5	6	7.5
Talc (%)	1	1	1	1	1
Mg.stearate(%)	1	1	1	1	1
MCC (Q.S)	54.25	53.5	52.75	52.0	51.25
Total Wt (in mg)	55	55	55	55	55

Drug Polymer Interaction by FTIR Analysis[5]

The drug and optimized formulation were characterized by IR Spectroscopy using a FT-IR 8400S (Shimadzu, Japan). The spectra were taken by KBr discs method in the range of 4000-500cm-1.

Evaluation of Pre-Compressional parameters[6]

The angle of repose (θ) of the granules was determined by using funnel method. Bulk density (BD) and tapped density (TD) were calculated by formula: BD = Bulk mass/Bulk volume; TD = Bulk density = Bulk mass/Bulk volume. Compressibility index and Hausner's ratio of the granules was determined by using the formula: CI (%) = [(TD-BD/BD)]×100 and HR = TD/BD, respectively. The experiments were performed in triplicate and average value with SD was noted.

Evaluation of Post-Compressional Parameters[7]

The mini-tablets were evaluated for post-compression for parameters to determine their physicochemical properties .The thickness of the tablet is measured by Digital vernier calipers. 20 tablets were selected at a random and average weight was calculated. Then individual tablets were weighed and the weight was compared with an average weight. Tablets were evaluated for hardness using Monsanto hardness tester and friability using Roche friabilator.

In vitro dissolution test[8]

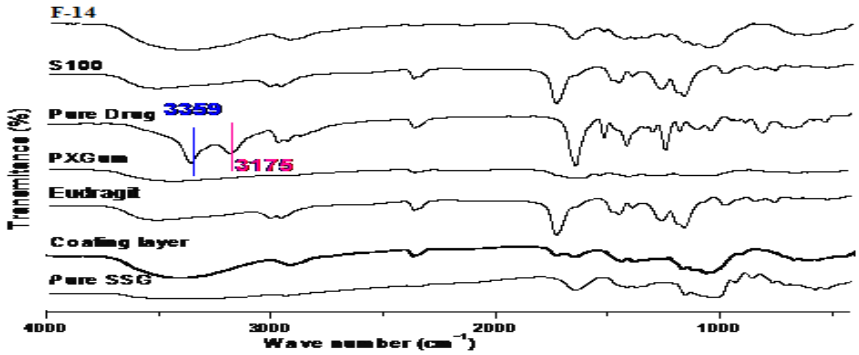
Dissolution studies were carried out by using USP-I dissolution test apparatus using basket method. For dissolution testing of core mini-tablets, five mini-tablets were immersed completely at a time, as they are equivalent to 25 mg of Atenolol and evaluated in pH 1.2, 7.4, and 6.8 dissolution media. For dissolution testing of enteric coated mini-tablets filled capsule formulations, one capsule filled with five mini-tablets were immersed completely at a time. To match the changes in pH along the GI tract, three dissolution media with pH 1.2, 7.4 and 6.8 were used sequentially. These three media represents

the stomach, proximal part of the small intestine and terminal ileum respectively. When performing studies, the pH 1.2 medium was first used for 2 h, and then replaced with the fresh pH 7.4 phosphate buffers. After 3-4 hr the medium was again replaced with fresh pH 6.8 dissolution medium and the test was subsequently continued in 900 ml up to 24hrs.

RESULTS & DISCUSSION

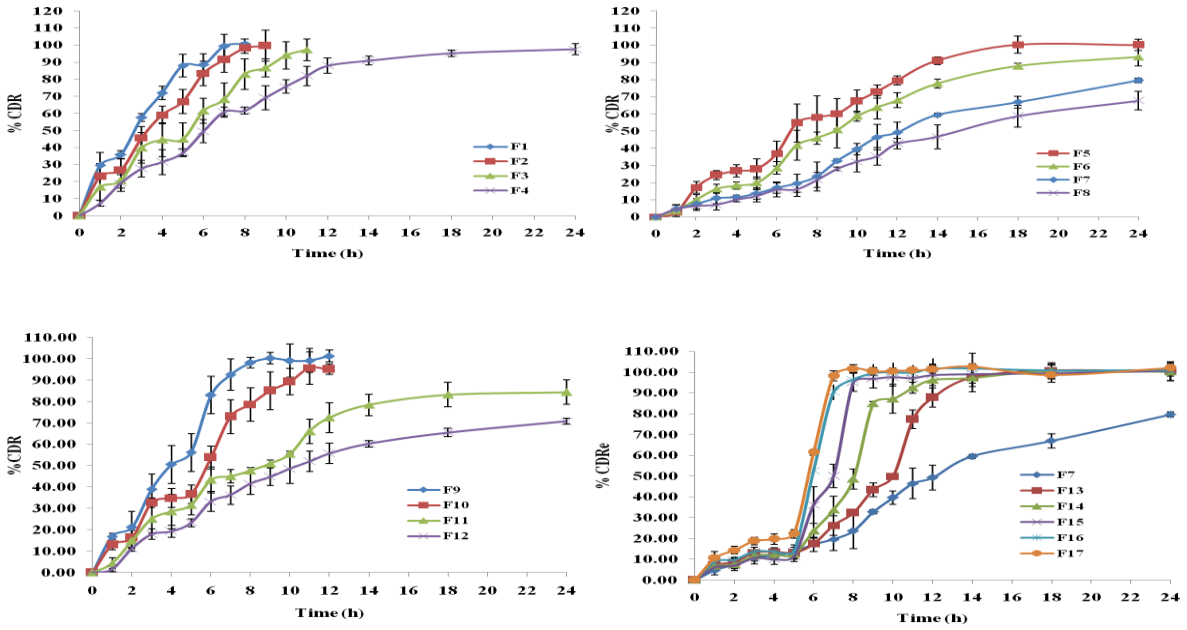
Formulation and Evaluation of PH-responsive Mini tablets is one of the approaches for ileo-colonic drug delivery system. Several attempts have been made for preparation of present study with variable concentration of natural polymers and rate retarding polymer i.e., EudragidS-100 as for adjusting release pattern according to marketed formulation and USP guidelines of Atenolol colonic drug delivery system. In which, formulations of Core mini-tablets were prepared by wet granulation method. From this, optimum formulation was selected (F7) then coated with enteric coating polymers such as Eudragit S100 in different concentrations and filled into an empty hydroxypropyl methylcellulose (HPMC) capsule. Fourier transforms infrared spectroscopy (FTIR) studies on the pure drug and their combinations with polymers were performed to assess compatibility. Fig. 1 demonstrates the FT-IR spectrum of pure Atenolo and Optimized formulation (F14).

Figure: 02 FT-IR spectrum of Optimized formulation of F-14 with Excipients



The angle of repose for the granules of core mini-tablets was found to be 22.62 ± 0.11 º. The values for both loose bulk density and tapped bulk density were found to be 0.40 ± 0.01 and 0.48 ± 0.04 gm/cc respectively. The value of compressibility index for the blend was found to be 15.56 ± 0.95 %. The value for Hausner's ratio was found as 1.18 ± 0.03. These results indicate that the granules were of good flow properties. So above the optimized formulation (F14) were produced suitable conditions to avoid processing variables. The weight variation, hardness, friability, thickness and content uniformity of all formulations were found to be within acceptable limits as per official specifications. Weight of the optimized mini-coated tablet formulation (F14) was 55.10±0.87mg, hardness was 5.95±0.08kg/cm2 and thickness was 5.13±0.08. The percentage friability of the formulation was ranged from 0.57±0.05 to 0.78±0.04 which is less than 1% of their weight. Values of the hardness test and percent friability indicated good handling properties of the prepared mini tablets. The drug content (assay) uniformity in the mini tablets was ranged from 99.67±0.05 to 100.45±0.07%. In vitro drug release study was done by buffer change method to mimic the GI environment and the drug release study was continued for 24 hours for all formulations (F1-F12) in order to check the variability of the drug release pattern(Fig: 03).

Figure: 03 Dissolution profile of Atenolol mini Tablets (F1-F17)



The tablet formulations were subjected to in vitro drug release rate studies in Stomach gastric fluid (pH 1.2) for 2 hrs and in mixture of Stomach and Small Intestinal fluid (pH 7.4) for next 3-4 hrs in order to investigate the capability of the formulation to withstand the physiological environment of the stomach and small intestine. The Atenolo matrix tablets optimized formulation F7 shows desired drug release 78.11±0.26% after 24 hrs as it is composed of suitable amount of Xanthan gum (15mg), but it releases around 12.37±0.33% of drug in 2 hrs. So it was further enteric coated with EudragitS-100 with cumulative concentrations and formulated as F13-F17. From the above formulations, F14 only prevents the drug release in upper part of GIT and shows 99.09±0.16% of drug release after 24 hrs as compared than other formulations.

CONCLUSION

From the above research outcomes it can be concluded that Xanthum gum has the potentiality for colon specific drug delivery of Atenolo than the other natural polymers such as Pectin and Guar gum. Eudragit S100 can be used to protect the drug release in the hostile environment of upper GIT when Atenolol administered as mini-tablet dosage form. The bioavailability of Atenolol at the colonic site found to be improved through colonic delivery.

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