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Original Article

Formulation and *in-vitro* evaluation of pH responsive mini-tablets for nadolol colonic drug delivery system

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ABSTRACT

In the present examination a novel colon explicit medication conveyance arrangement of an Anti-Hypertensive medication is Nadolol, for treatment of constant cardiovascular diseasess like Heart attack, abrupt increments in pulse was created. Smaller than usual tablets of Nadolol were set up by wet granulation method utilizing lattice shaping regular polymers like gelatin, Guar gum and Xanthum gum in blend with various extents (F1-F13). The further impact of enteric coat on the small scale tablets for colon explicit medication release was researched. The Nadolol improved lattice definition F7 shows medication discharge around 32.37±0.33% in 2 hrs. So it was further enteric covered with Eudragit S100 in total proportion and defined the definitions from F14-F17.Apart from F14 indicated ideal medication discharge after 24 hrs. All details were exposed to Hardness test, Friability test, assurance of uniform measurement and thickness, sedate substance for streamlining and further assessment. In vitro disintegration studies uncovered that the medication discharge in upper piece of GIT from grid tablets of Nadolol can be averted by enteric covering with pH touchy polymer (Eudragit®S100), which discharges the medication explicitly in colonic area to accomplish target conveyance.

Keywords: *Nadolol; Pectin; Xanthan gum; Guar gum; Eudragit®S100, in vitro drug release; Colon-Specific Drug Delivery*

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INTRODUCTION

The Colonic Drug Delivery Systems have as of late picked up significance for conveying an assortment of medications. Colonic medication conveyance might be accomplished by either oral or rectal organization. Rectal organizations of medications for colon focusing on consistently face high changeability in the dissemination of medication, when they are managed in type of measurements structures like bowel purges and suppositories, which are not constantly viable. Accordingly, the oral course is the most liked. Traditional oral definitions break up in the stomach or digestive system and are consumed from these districts. The serious issue with the conveyance of medications by oral course to the colon is the assimilation and debasement of the medication in the upper piece of the gastrointestinal tract (GIT) which must be defeated for effective colonic medication delivery[1]. In conditions where limited conveyance of the medications is required in the colon or medications which are inclined to corruption in the earth of the upper GIT, colonic medication conveyance might be significant.

Medication discharge at this site will guarantee greatest helpful advantages. Oral conveyance of medications to the colon is important in the treatment of interminable heart maladies, whereby high neighborhood fixation can be accomplished while limiting reactions that happen in light of arrival of medications in the upper GIT or help to maintain a strategic distance from pointless foundational retention of the medication. In any case, for this situation it is alluring to limit the arrival of Nadolol to be affected in site of colon. Along these lines, Nadolol was utilized as a model medication in the present study[2].

MATERIALS AND METHODS

Nadolol, 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.

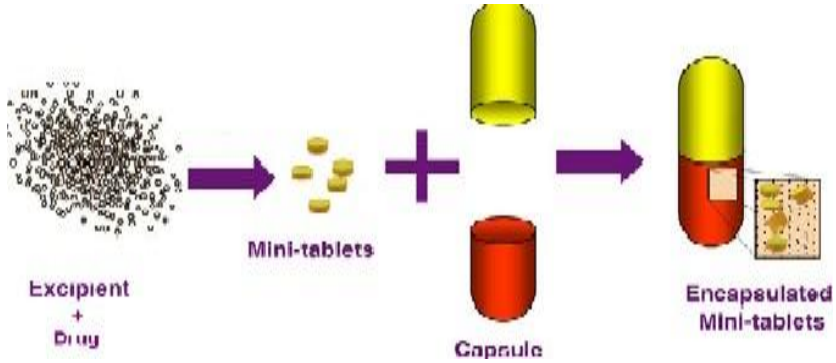


Figure: 01 Preparation of Matrix mini-tablets of Nadolol

Table: 01 Composition formula for Nadolol Mini tablet without Eudragit 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 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. Nadolol, 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 Nadolol.**Preparation of coating Solution[4]:**

The external covering layer was connected on the network tablets utilizing plunge covering technique. A natural polymer arrangement comprising of Eudragit S-100 in acetone was utilized for the covering. Castor oil was fused in the covering arrangement as a plasticizer (20% w/w dependent on the polymer). An Opacifier, titanium dioxide (0.05% w/w) and an antiadherant, powder (5% w/w) to avert following of tablets during the covering procedure were additionally added to the covering arrangement. For setting up the container detailing 05 enteric covered smaller than usual tablets comparable to 25 mg of Nadolol were filled into size 1 HPMC case.

Table: 02 Composition Nadolol mini tablets with Eudragit 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)	-	-	-	-	-
Eudragit 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 Nadolol 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

Detailing and Evaluation of PH-responsive Mini tablets is one of the methodologies for ileo-colonic medication conveyance framework. A few endeavors have been made for readiness of present examination with variable centralization of characteristic polymers and rate impeding polymer i.e.,EudragitS-100 concerning changing discharge example as indicated by showcased plan and USP rules of Nadolol colonic medication conveyance framework. In which, definitions of Core smaller than expected tablets were set up by wet granulation technique. From this, ideal definition was chosen (F7) at that point covered with enteric covering polymers, for example, Eudragit S100 in various fixations and filled into a void hydroxypropyl methylcellulose (HPMC) case. Fourier changes infrared spectroscopy (FTIR) thinks about on the unadulterated medication and their mixes with polymers were performed to survey similarity. Fig. 1 shows the FT-IR range of unadulterated Nadolol and Optimized definition (F14).

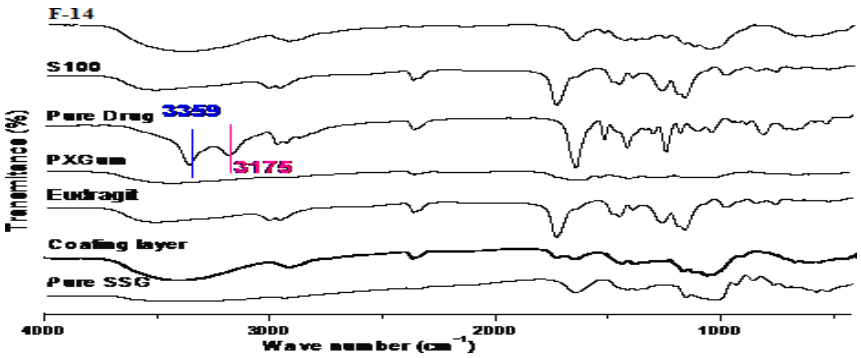
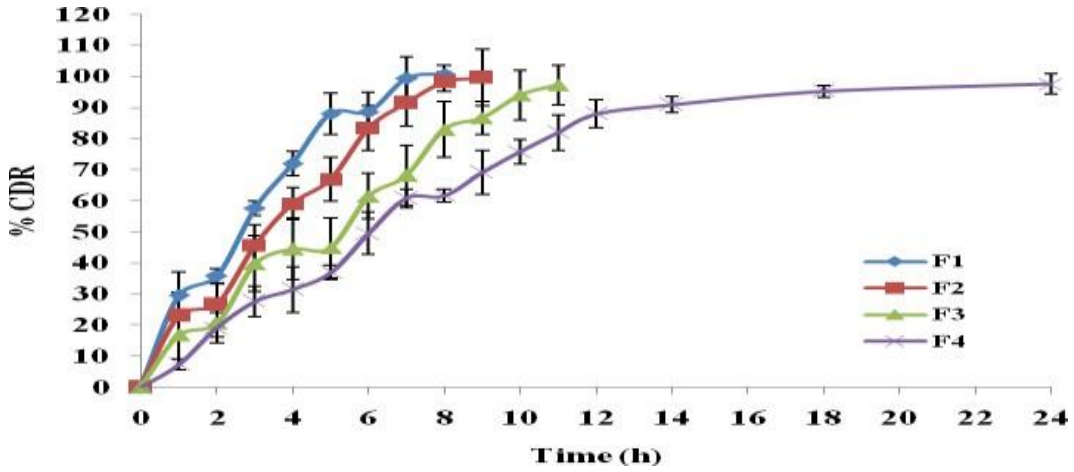


Figure: 02 FT-IR spectrum of Optimized formulation of F-14 with Excipients

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).



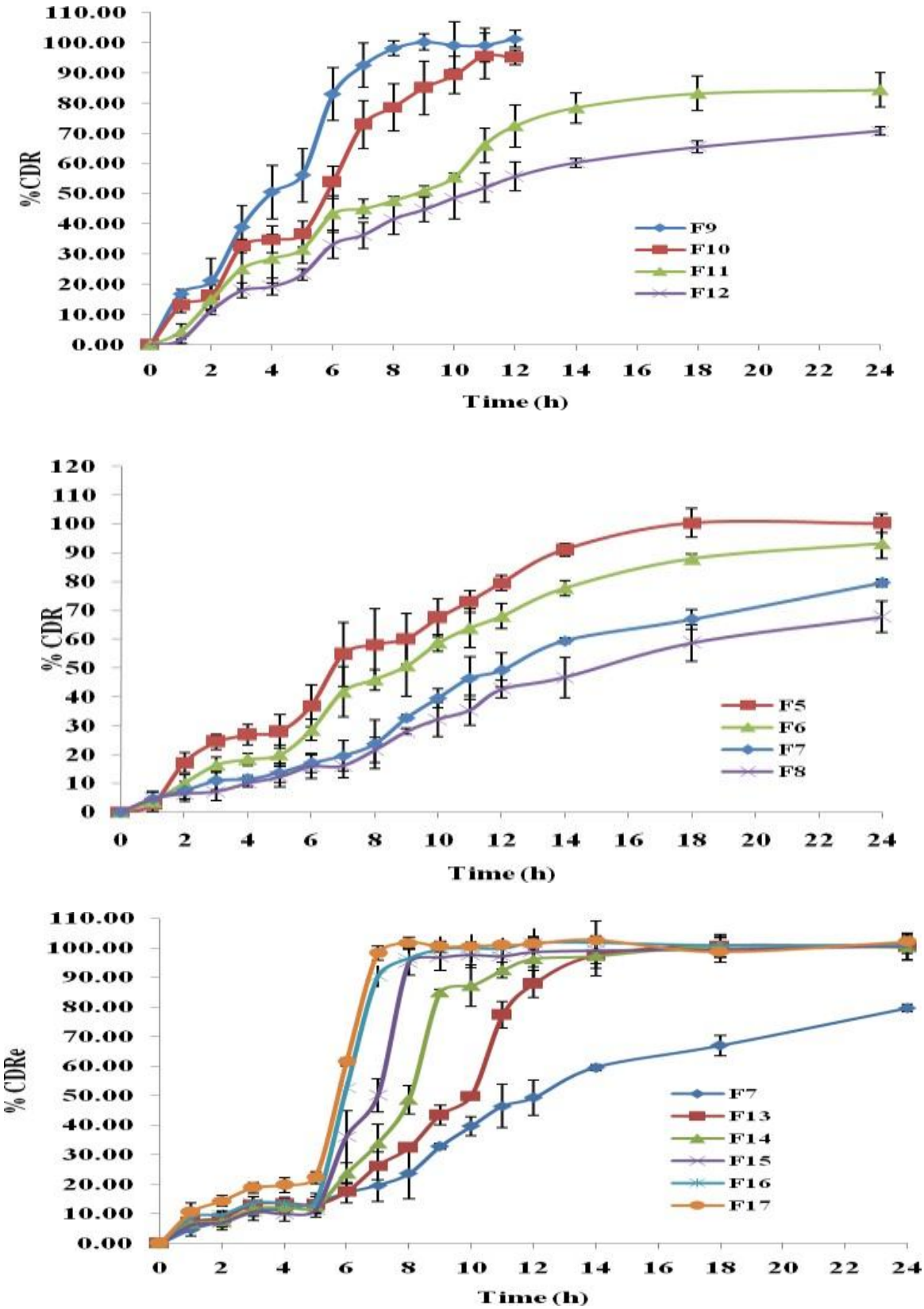


Figure: 03 Dissolution profile of Nadolol mini Tablets (F1-F17)

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 Nadolol 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 Nadolol 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 Nadolol administered as mini-tablet dosage form. The bioavailability of Nadolol at the colonic site found to be improved through colonic delivery.

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