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Research article

FORMULATION, OPTIMIZATION AND EVALUATION OF EUDRAGIT S- 100 COATED NAPROXEN MATRIX TABLETS FOR COLON TARGETED DRUG DELIVERY

N.M.Vageesh*, Dr.C.Kistayya[1], Dr.Rakesh Jat[1]

*JJT University, Jhunjhun, Rajasthan, India.
[1]St.Johns college of Pharmaceutical sciences, yerrakota, Yemmiganur, Andhra Pradesh, India.

ABSTRACT

The present work describes development for colon targeted drug delivery by combination approach i.e., a polysaccharide based system and pH based matrix systems for colonic delivery of naproxen for inflammatory bowel diseases. Matrix core tablets were prepared by using polysaccharides like guar gum, Chitosan and sodium alginate alone and its combinations. Drug release studies were performed in gastric pH (1.2) for first 2hr and in pH 6.8 for next 3 hrs and finally at pH 7.4 for up to 24 hrs. The Naproxen uncoated or core tablets shows maximum amount of drug release in pH 1.2 and pH 6.8 so in order to mimic the drug release in upper GIT enteric coating was done for optimized formulation . Formulation F1, F4 and F13 were selected for enteric coating with Eudragit S-100. The enteric coated formulations shows negligible amount of drug releases in the stomach and maximum amount of drug release in colonic environment. Among all formulations F13 had shown good drug release in colonic environment. Further physiochemical characterization, pre and post compression were also conducted, all the results obtained are in acceptable limit.

Keywords: Guar gum, Naproxen, Eudragit S-100, Chitosan, Sodium alginate.

INTRODUCTION

The oral route is considers being the most convenient for administration of drug to patients. Nearly 50% of drug delivery systems available in the market are oral drug delivery systems and these systems have more advantages due to patient acceptance and ease of administration[1,2]. Oral administration of conventional dosage forms normally dissolves in the stomach fluid or intestinal fluid and gets absorbed from Gastro intestinal tract (GIT)[3] . From over the last two decades, delivery of a drug to a specific organ or tissue i.e., spatial placement and controlling the rate of drug delivery to the specific sites i.e., temporal delivery are the two main aspects of the drug delivery system[4]. Mainly the colon specific drug delivery system has provided importance for drugs, which are especially absorbed from colon region by preventing the degradation in upper gastro intestinal tract. Drug release at this site will ensure maximum therapeutical benefits[5,6]. Delivery of drugs to the colon is useful in the treatment of several colon diseases such as inflammatory bowel diseases (ulcerative colitis and Chron's diseases), corticosteroids have traditionally formed the basis of treating Inflammatory Bowel Diseases with steroids, while often effective, is plagued by a number of serious effects, e.g. acne, moon face, hypertension, peptic ulcer, impaired glucose tolerance and mood disturbances. These undesired side effects can be overcome or moderately reduced in both sub chronic and chronic dosage regimens [7]. The colon specific drug delivery system should protect the drug from absorption in the stomach and small intestine, thus prevent a sudden onset of drug release upon entry into an aggressive

Corresponding Author
N.M.Vageesh
JJT University, Jhunjhun, Rajasthan.
Email : vageesh.swamy@gmail.com

ambience of the colon[8]. Different approaches are available for colon specific drug delivery which includes, a) coating with pH dependent systems, b) Design of timed release systems, c) formation of prodrug, d) pressure dependent system, e) use of carriers that are degraded exclusively by colonic bacteria[8-10]. Time dependent drug delivery system can be formulate by applying coats on the drug core which are capable of delaying the release through different mechanism. The pH approach has been shown to lack site specificity because of inter/intra subject variations and the similarity of the pH between the small intestine and colon. To overcome from these above said approaches, presently focused on combination of approach namely use of the carriers that are degraded exclusively by colonic bacteria and coating with pH dependent system was chosen in the present study to develop an colon targeted drug delivery. Some of the natural polysaccharides which have been already studied for their potential as colon specific carrier system are Chitosan, Pectin, Chondrion sulfate, Cyclodextran, Guar gum, Inulin, Amylase and Bean gum[11-14].

Naproxen is a member of the aryl acetic acid group of non steroidal anti-inflammatory Drugs. It has analgesic and antipyretic properties. The mechanism of action of naproxen was believed to be associated with the inhibition of cyclooxygenase (COX) activity. Inhibition of COX-1 is thought to be associated with gastrointestinal tract and renal toxicity, while inhibition of COX-2 provides anti-inflammatory activity[15-17]. The present investigation is focused at using the inexpensive, natural and biodegradable polymers like Guar gum (plant source), Chitosan (animal source) and Alginate (algae) [15] was used with varying different concentrations and finally formulation was enteric coated by using Eudragit S-100with different ratios. The pH dependent coating polymers of Methacrylic acid polymers, example Eudragit S-100 is used for coating because it solubilizes at pH 7, so that the coating layer was prevent the drug release in the stomach or small intestine and to slow down the drug release in the stomach or small intestine and finally to slow down the drug release in the target site i.e., colon [18,19].

MATERIALS AND METHODS:

Naproxen was obtained as a gift sample from Divis laboratories Hyderabad. Guar Gum, Chitosan, Sodium alginate, Eudragit S-100 were purchased from Sd Fine chemicals Mumbai. All other chemicals and reagents were analytical grade.

Methods: Preparation of Naproxen matrix tablets

Step I: Naproxen matrix tablets were prepared by wet granulation method [20,21] using different polymers like guar gum, Chitosan and sodium alginate. All the powders were weighed and ground to fineness in a clean and dry mortar and pestle. Sufficient amount of isopropyl alcohol were added and same was mixed thoroughly to form a coherent mass. The coherent mass was then passed through sieve no 16. The wet granules were allowed to dry for 2-3 hrs in hot air oven at 40° C. The dried granules were resized using sieve no 20 and 40. 10 % of the fines collected below sieve no 40 were blended thoroughly with the granules of sieve no 20/40. This mixture was blended with talc and magnesium stearate in a blender. The blended mass was compressed to form a tablet using single station tablet punching machine using 12mm die punch. Formulations composition is given in table 1.

Step II: Enteric coated of the Naproxen matrix tables[22]

Among the formulation from F1 to F15, which shows maximum amount of drug release was selected for enteric coating i.e., F1, F4 and F13. The enteric coating of all selected matrix tablets containing Naproxen was performed by Dip coating method [23,24]. These selected formulations were enteric coated using 12.5% concentration w/w solution Eudragit S-100, in isopropyl alcohol and water containing PEG 400 as plasticizers in the concentration of 1.25% w/w [25-27] after coating, the tablets were immediately dried with dryer. The coating procedure was repeated till the coat weight increased to 5% of original weight of the tablet. The percentage mass increase of the tablet upon coating was inductive of coat thickness.

Characterization of granules[28,29]: The granules were evaluated for their flow properties, Angle of repose, Bulk Density, Tapped density, Compressibility index, and Hausners ratio.

Angle of repose: The angle of repose can be calculated by using funnel method. An accurately known weighed quantity of granules was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just in such a way that the tip of the funnel was just touches the apex of the heap of the granules. The granules are allowed to flow through the funnel freely onto the surface. The height and diameter of the granules were calculated using the following equation

$$\mathbf{Tan\ Ø = h/r}$$

Where, h= height of the cone, r = radius of the granules cone, Θ = Angle of repose.

Bulk Density:

An accurately weighed quantity of granules was transferred into a 50 ml measuring cylinder with use of the funnel. The unsettled apparent volume, to the nearest graduated unit occupied by the granules was measured. It was calculated by using the formula

$$\rho_b = m/V_0$$

Where, $\rho_{B=}$ Bulk Density, m = Mass of the blend,

V_o = untapped volume

Tapped Density: It is done by mechanically tapping a measuring cylinder containing a sample. Place a sample in a measuring cylinder, after observing the initial volume, the cylinder is tapped mechanically and volume readings are taken until little volume was changed in measuring cylinder is observed, it was calculated b using the formula,

$$\rho_t = m/V_t$$

Where, ρ_t= Tapped Density, m = Mass of the granules
V_t = Final Tapped Volume

Carr's or Compressibility Index:
It is a measure of tendency for arch formations and the ease with which the arches will fail .It is calculated by using the formula,

$$CI = \rho_t - \rho_t / \rho_t$$

Where, CI = Compressibility Index, ρ_t= Tapped density, ρ_{bulk} = Bulk Density

Hausener's ratio: it was defined as the ratio of (ρ_t/ ρ_{bulk}), tapped density to the bulk density, related to interparticle friction and as, such could be used to predict powder flow properties. . It is calculated by using the equation,

$$\text{Hausener's ratio} = \rho_t/\rho_b$$

Where, ρ_t = Tapped Density , ρ_b = Bulk density .

Drug Excipient studies (FTIR study)[30]: The Fourier transform infrared (FTIR) spectra of pure drug (Naproxen), Guar Gum, Chitosan, Sodium Alginate, Physical mixture of Naproxen- with other excipients were recorded using a FTIR spectrophotometer according to the KBr pellet technique. The smoothing of the spectra and the baseline correlation procedures were applied. The FTIR measurements were performed in the scanning range of 4000 – 400 cm^{-1} at ambient temperature.

Physiochemical Evaluation of Matrix tablets: [31,32]
The prepared tablets were evaluated for diameter, thickness, hardness, friability and drug content.
a) Diameter: Diameter of tablet was determined by Vernier calipers
b) Thickness: Thickness of each formulation was determined by using a Dial thickness apparatus mitutocyo 2046F Japan.
c) Hardness: Tablet Hardness was determined by using Monsanto hardness tester.
d) Friability: Compressed tablets from all formulations were subjected for friability test using friabilator. Ten tablets were weighed (W_0) and placed inside the Roche friabilator. The instrument was operated for 4mins at 25 rpm. The resulting tablets after 100 falls from a height of six inches were collected; weighed (W_t) and percentage loss was calculated using formula;

$$\text{Percentage friability} = \frac{W_o - W_t}{W_o} * 100$$

e) Weight variation: The individual weights of 20 tablets from each formulation were determined accurately to determine the weight variation. The sample mean and standard deviation of each batch of tablets were reported.
f) Determination of Drug content: Ten tablets were finely powdered; quantities of the powder equivalent to 100 mg of Naproxen were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml of pH 7.4 phosphate buffer. The flask was shaken in rotary shaker for 12 hr. The volume was made up with pH 7.4 phosphate buffer and mixed thoroughly. The solution was filtered, suitably diluted and content of naproxen was estimated using UV-visible spectrophotometer at 331 nm[33]. Each study was conducted in triplicate.

Swelling index:[34]
Swelling index was determined by taking initial weight of the dried tablet (W_o). The tablet was immersed in pH 1.2 buffer for 2 hrs and in pH 7.4 buffer for 6 hrs following pH progression method in a beaker. The swollen tablets were withdrawn periodically after every 60 minutes from medium and reweighed (W_t) after removal of excess surface water by light blotting with filter paper. The swelling index was calculated from the formula:

$$SI = \frac{W_t - W_o}{W_o} * 100$$

Where SI is swelling index of tablet, W_t is the weight of tablet at appropriate intervals in buffer saline; W_o is absolutely dried weight of the tablet.
Swelling test were separately carried out in simulated gastric fluid (0.1N HCl, pH 1.2) for first 2 hrs and simulated colonic fluid (phosphate buffer ,pH 7.4) for 6 hrs.

***In-vitro* release studies:**
In-vitro release studies were performed using USP dissolution test apparatus (basket) type. The dissolution studies were performed in 900ml dissolution medium, which was stirred at 100 rpm , 37 ± 05 ° C following pH progression method i.e., pH 1.2 for 2 hrs, pH 6.8 for 3 hrs and pH 7.4 for remaining 19 hrs of the study. Aliquots of 5ml of sample withdrawn periodically and replaced with fresh medium and aliquots were analyzed UV-visible spectrophotometer at 231, 273 and 331 nm for pH 1.2, pH 6.8 and pH 7.4 for rest of samples [35,36]. The Experiment was conducted in triplicate till 24hrs.

Preparation of rat cecal content for dissolution studies[37]

The *in-vitro* drug release study was also performed in presence of rat cecal content medium to stimulate the human intestinal microflora. Male wistar rats weighing about 100–150gm maintained on a normal diet were used for the study. Using carbondioxide (Co_2), the

rats were asphyxiated. Caecal content were collected by dissection at the abdominal region and immediately transferred into phosphate buffer (pH 7.4) to prepare a final suspension at a concentration of 2% (w/v). Constant supply of Carbondioxide was maintained throughout the experiment to maintain anaerobic conditions of colon. The experimental were carried out on Animals, bearing CPCESA registration no. 1561/PO/RE/S/11/CPCSEA.

***In-Vitro* release study in the presence of rat cecal content[38]**

The *In-vitro* drug release studies in presence of rat cecal content were performed using USP dissolution test apparatus (basket) type. The dissolution studies were performed in 900ml dissolution medium, which was stirred at 100 rpm, 37 ± 05 ° C following pH progression method i.e., pH 1.2 for first 2 hrs, the matrix tablet was transferred to pH 6.8 phosphate buffer for 3 hrs. Further it was transferred in to 200 ml phosphate buffer pH 7.4 diluted with 2% (w/v) rat cecal medium for rest of studies (up to 24 hrs). As caecum is naturally anaerobic, the experiment was carried out with continuous CO_2 supply into the beaker. Aliquots 5ml of sample withdrawn periodically and replaced with 5 ml of 2 % rat cecal medium. The absorbance was measured at 231nm, 327 and 331 nm for pH1.2, pH 6.8 and pH 7.4 respectively. Drug release studies were also performed in presence of rat cacecal content to evaluate the effect of microbial degradation on drug release from the prepared tablets. The experimental procedure for dissolution studies in presence of rat cacecal content was same as described above but with a modification that 2% w/v rat caecal contents were added to phosphate buffer (pH 7.4) , simulating to colonic fluid.

Release kinetics:[39,39]

In-vitro release data were fitted into various kinetic models to explain the kinetics of drug release from matrix tablets. The kinetics models used were first order, zero order and Higuchi release. To explore the kinetic behavior, *in-vitro* release results were fitted into the following Koresmeyer-Peppas equation:

$$M_t / M_\infty = Kt^n$$

Where,

M_t / M_∞ is the fraction of drug released after time t, K is a kinetic constant and n is release exponent that characterize the drug transport.

Stability studies [40]

The enteric coated formulations like F1, F4, F13 were subjected for 3 month stability studies according to ICH guidelines by exposing the tablets in suitable packing mode and placing them to a temperature 40° C and relative humidity 75±5% in programmable environmental test chamber (CHM-10S, Remi Instrument Ltd, Mumbai, India). At the end of every month tablets were analyzed for any change in appearance, physical attributes, drug content, swelling studies and *in-vitro* release studies.

RESULTS AND DISCUSSION

The present study was carried out to developing oral colon targeted formulations for Naproxen for Treatment inflammatory bowel diseases (IBD) using polysaccharides like Guar gum, Chitosan and Sodium alginate. Further, it was aimed to identify most suitable polysaccharide, either alone or in combinations, for colonic delivery of Naproxen based on microbial degradation. For the formulation of a delivery system targeting colon, it is an essential prerequisite that the drug release should be minimal until the dosage forms reaches the colon. Hence, an attempt was made to formulate matrix tablets using different polysaccharides like Guar gum, Chitosan and Sodium alginate either alone or in combination based on bacterial degradation concept.

Characterization of granules: The granules were characterized with respect to Angle of repose, Bulk density, Tapped density, Carr's index, and Hausener ratio. The obtained results were tabulated in table no. 2. The Angle of repose of different formulation from F1 to F15 was found to be from 24.12±0.36 to 31.36±0.25 ^{0}C. The angle of repose was obtained not more than 31 ^{0}C, which indicates good flow behaviour. Similarly, bulk density and tap density of all the formulation batches from F1 to F15 were found to be from 0.356±0.001 to 0.656±0.012 g/ml. and from 0.302±0.014 to 0.587±0.015 g/ml, depicting good flow properties of the granules. The Compressibility index of all formulation batches was in the acceptable range from 10.35±0.36 to 12.35±0.24. The Hausners ratio of all formulation batches from F1 to F15 was found to be from 1.11±0.02 to 1.17±0.23. The Hausners ratio less than 1.17 indicates good flowability.

FTIR studies: The FTIR spectra of Naproxen and optimized formulation F13 are shown in fig.1 and fig.2. FTIR spectrum characteristics are shown in table 3. From the characteristics results it was concludes that there is no interaction between Drug and polymer.

Physicochemical Evaluation of Naproxen Matrix Tablets

The Naproxen matrix tablets of different formulations from F1 to F15 core matrix tablets and enteric coated were subjected to various evaluation tests of like Diameter, thickness, Hardness, Friability, weight variation and Drug content., the results are tabulated in table 3 and table 4 and Table 6. The Diameter of formulations F1 to F15 was found to be in the range of 12.12 ± 0.04 to 12.18 ± 0.05 mm. The thickness was found to be in the range of 5.1 ± 0.06 to 5.3 ± 0.01. Hardness of the matrix tablet from formulations F1 to F15 was found in the range of 6.4 ± 0.37 to 5.5 ± 0.25 Kg/cm$^{2.}$ Hardness of the tablet was

found in the acceptable range. Friability of the F1 to F15 formulations tablets shows that 0.72 ± 0.01 to 0.98 ± 0.07 % where the friability of the tablets is inacceptable range i.e. less than 1%. Weight variation F1 to F15 formulations showed 398.2 ± 1.20 to 404.5 ± 1.25 mg, which is less than 4% within an acceptable limit. The drug content of all the formulations from F1 to F15 shows in the range of 99.62 ± 1.5 .52 ± 0.09 %. Similarly for coated matrix tablet were weight variation 12.15 ± 0.02 to 12.62 ± 0.06 mm. thickness was found to be 5.7 ± 0.01 to 5.4 ± 0.08 mm. hardness of the tablet was found in the range of 6.5 ± 0.42 to 7.9 ± 0.54 Kg/cm^2. Friability for enteric coated tablets was found to be in the range of 0.56 ± 0.12 to 0.95 ± 0.17 %, which is less than 1%. Drug content uniformity for enteric coated formulations was found to be 97.01 ± 0.07 to 99.4 ± 0.09 %.

Swelling index: Swelling index describes the amount of water that is contained within Hydrogel at equilibrium and is a function of the network structure, hydrophilicity and ionization of the functional groups. Swelling study was performed for all batches for 8 hrs. While the plot of swelling index against time (hr) is depicted in fig 3. Similarly studies were conducted for coated tablets shown in fig.4. The swelling index for the formulations F1, F2 and F3 at pH 1.2 after 2 hrs was 45.2%, 52.2% and 30.2% respectively and at pH 7.4 after 6 hrs was 98.2%, 72.1% and 70.5% respectively. The order of decrease in swelling index at gastric pH was F2 > F1 > F3 and at intestinal/ colon pH was F1 > F2 > F3. This order would indicate that at initial acidic pH Chitosan based matrix tablets shows maximum swelling index followed by Guar gum and Sodium alginate. But in colonic pH Guar gum showed more swelling index followed by Chitosan and Sodium Alginate. There is an initial rapid uptake of water by drug matrices during first 6 hrs following which there is a leveling off the wet weights due to the increasing rate of erosion release. This proceeds until rate of erosion exceeds rate of water uptake with a resultant decrease in weight with time.

The swelling index for the formulations F4, F5 and F6 at pH 1.2 after 2 hrs was 37.6%, 41.50% and 34.6% respectively and at pH 7.4 after 6 hrs was 82.2%, 91.4% and 74.2% respectively. The order of decrease in swelling index at gastric pH as well as at intestinal/ colon pH was F5 > F4 > F6. This order would indicate that as guar gum concentration increases there will be increase in swelling index. From the results of swelling index indicates that Chitosan content formulations swells more in pH 1.2 (gastric fluids), but swelling decreases in pH 6.8 and pH 7.4 (Colonic fluid). The results would expect because the amine group of Chitosan is protonated in acidic medium causing substantial swelling, while in case of combination of Guar gum and Chitosan combinations for the formulations F7, F8, F9 at pH 1.2 after 2 hrs was 48.7%, 46.2% and 44.2% respectively and at pH 7.4 after 6 hrs was 66.4%, 91.5% and 78.2% respectively. The order of decrease in swelling index at gastric pH was F7 > F8 > F9 and at intestinal/ colon pH was F8 > F9 > F7. Chitosan with Sodium alginate F10, F11, F12 at pH 1.2 after 2 hrs was 41.2%, 35.5% and 45.4% respectively and at pH 7.4 after 6 hrs was 71.5%, 80.5% and 75.2% respectively. The order of decrease in swelling index at gastric pH was F12 > F10 > F11 and at intestinal/ colon pH was F11 > F12 > F10. In the case of combination of three polymers, the swelling index for the formulations F13, F14 and F15 at pH 1.2 after 2 hrs was 42.5%, 37.4% and 41.5% respectively and at pH 7.4 after 6 hrs was 78.2%, 73.5% and 74.2% respectively. The order of decrease in swelling index at gastric pH was F13 > F15 > F14 and at intestinal/ colon pH was F13 > F15 > F14.
Similarly in case of enteric coated formulations like F1, F4, and F13. Were guar gum alone and combination of Guar gum, Chitosan and Sodium alginate. Swelling index of enteric coated formulations showed maximum swelling in pH 7.4. Swelling study was performed for all batches for 8 hrs. While the plot of swelling index against time (hr) is depicted in fig 4. F1 at pH 1.2 after 2 hrs was 12.2% and at pH 7.4 after 6 hrs was 70.5%. But in colonic pH guar gum showed more swelling index followed by sodium alginate and Chitosan. There is no initial uptake of water by drug matrices during first 2 hrs in gastric environment and slowly increases swelling of tablets still 6 hrs which there is a leveling off the wet weights due to the increasing rate of erosion release. This proceeds until rate of erosion exceeds rate of water uptake with a resultant decrease in weight with time. Similarly in case of F13 combination of three polymers was more swollen compared with other.

In-vitro release studies: FormulationF1 – F3 using mono polymer shows at the end of 2hrs were 12.32, 45.25 and 20.15 % respectively, where as in pH 6.8 (SIF) at the end of 5 hrs 35.65, 74.36 and 50.64% respectively, similarly in the pH 7.4 (SCF) F1 shows 92.45 % at the end of 20th hr, F2 shows 94.36 with in 10th hr and F3 shows 95.16% within 16th hrs.

Combination of two polymers Guar gum and Chitosan blend (F4, F5, F6): Amount of drug released from formulations F4, F5, F6 at pH 1.2 after 2 hrs was 12.65, 15.36 and 17.12 respectively, where as in pH 6.8 (SIF) at the end of 5 hrs 28.13, 24.23 and 32.16 respectively similarly in the pH 7.4 (SCF) F4 shows 90.12% at the end of 24th hr, F5 shows 80.13 with in 24th hr and F6 shows 92.31% within 18th hrs. The order of decrease in drug release at gastric pH was F3 > F2 > F1 at intestinal fluid F3 > F2 > F1 similarly in case of colonic pH also in same order F2 > F3 > F1. This order would indicates that as proportion of sodium alginate increases there will be increase in percentage drug release in gastric environment also increases in colonic environment. But whereas in case

of F4 (Guar gum) formulation three cases release is retarded and maximum amount of release is in colonic pH.

Guar gum and Chitosan blend (F7, F8, F9) : from formulations F7, F8, F9 at pH 1.2 after 2 hrs was 15.23, 20.12 and 24.93% respectively, where as in pH 6.8 (SIF) at the end of 5 hrs 30.12, 32.15 and 35.12% respectively similarly in the pH 7.4 (SCF) 82.12, 74.23 and 68.95 at the end of 24th hr, the order of decrease in drug release at gastric pH was F7 > F8 > F9 at intestinal fluid F7 > F8 > F9 similarly in case of colonic pH also in same order F9 > F8 > F7. This order would indicates that as proportion of Chitosan increases there will be increase in percentage drug release in gastric environment also increases in intestinal environment. But whereas in case of F7 (Guar gum 150mg) show more amount of drug release in colonic environment i.e., about 82.12 %.

Chitosan and Sodium alginate blend (F10,F11,F12) : Amount of drug released from formulations F10, F11, F12 at pH 1.2 after 2 hrs was 35.32, 25.12 and 18.45% respectively, where as in pH 6.8 (SIF) at the enf of 5 hrs 45.96, 32.15 and 35.12% respectively simillarly in the pH 7.4 (SCF) 71.15, 66.36 and 73.15 % at the end of 24th hr, the order of decrease in drug release at gastric pH was F12 > F11 > F10 at intestnal fluid F11 > F12 > F10 similarrly in case of colonic pH in same order F11 > F10 > F12. This order wold indicates that as proportion of Chitosan and sodium alginated blend shows that as the increases ther will be decrease in perecentage drug release in gastric environment also increases in intestinal environment. But whereas in case of F12 (Chitosan : Sodium alginate (50 : 150mg) shows more amount of drug release in colonic environment i.e., about 73.15 %.

Effect of combination of Three polymers blend F13,F14,F15: Dissolution studies for F13, F14, F15 at pH 1.2 after 2 hrs was 16.12, 23.15 and 19.45% respectively, where as in pH 6.8 (SIF) at the end of 5 hrs 26.78, 32.15 and 29.45% respectively simillarly in the pH 7.4 (SCF) 94.65, 76.45 and 83.17% at the end of 24th hr, the order of decrease in drug release at gastric pH was F13 > F15 > F14 at intestnal fluid F13 > F14 > F15 similarrly in case of colonic pH in same order F14 > F15 > F13. This order wold indicates by the combination of three polymers shows retard and sustain effect compare to mono polymer and bi polymers (F1,F2, F3, F4, F5, F6, F7, F8, F9, F10, F11 and F12). F13 (Guar gum : Chitosan : Sodium alginate) (100:50:50 mg) shows more amount of drug release in colonic environment i.e., about 94.65 %.

In-vitro release studies for Enteric coated formulations: The amount of drug released from the mono polymer formulations F1 at pH 1.2 after 2 hrs was 1.25%, whereas at pH 6.8 after 5 hrs was 28.36 %, Similarly at the end 24 hrs 90.15 % . Combination of Bi-polymer F4 at pH 1.2 after 2 hrs was 1.78% and at pH 7.4. At the end of 24 hrs was 82.12 %. Similarly in case of three polymers containing formulations F13 at pH 1.2 after 2 hrs was 1.02% and at pH 7.4 at the end of 24 hrs was 96.25%. Shows in fig 3.In the present study, polysaccharides along with enteric coated with Eudragit S-100 was studied with an aim to achieve drug release in colon region. The release studies indicate that combinations of polymers are suitable rather than a single polymer for modulating drug release profile.

Glycosidase and polysaccharides are colonic enzymes identified to cause hydrolysis of di- and tri–oligosaccharides and polysaccharides, respectively. Both these enzymes are in human colon produced by anaerobic bacteria. Rat cecum is believed to have the same microbial content as that of the human and rats being easily available are the common species used during microbial degradation studies. Microbial load in the colon is $10^{11} – 10^{12}$ CFU/ml and 2% w/v rat cecal contents is believed to mimic the desired microbial load in the dissolution fluid. On the basis of drug release data, formulations F1, F4 and F13 were selected for carry out dissolution studies in the presence of rat cecal contents. In-vitro drug release is modulating by the microbial degradation of the polymer matrix. A significantly ($P<0.05$) higher amount drug release in the presence of rat cecal contents (simulated colonic fluid) was observed. Inclusion of rat cacecal contents to the dissolution fluid, mimicking colonic environment, release glycosides which act upon polysaccharides like Guar gum, Chitosan and Sodium alginate causing complete drug release due to degradation.

Release Kinetics: The dissolution data for core tablets was treated with Zero, first, Higuchis and Koresmeyer peppas for analyzing the kinetics and mechanism of drug release. All formulations showed first order release including in the presence of 2% rat cecal contents. The mechanism of drug release was analyzed by plotting drug release data according to koresmeyer peppas equation. The ‘n’ value (diffusion exponent) indicates the mechanism of drug release. For a tablet system, the drug release is considered to be by anomalous (non fickian) transport. ‘n’ value of 0.89 indicates of zero order release and n>0.89 indicates a super case II transport. Expect for F8, F9, F11 and F14, the ‘n” values are in the range of 0.894 – 1.289, indicating a super case- II transport. This value indicated that drug release from the prepared matrix system was due to both diffusion and polymeric chain relaxation. Similarly in case of enteric coated tablets also, ‘n’ value is in the range of 1.901 – 1.964 results are shown in table 7. The ‘n’ values in the range of 0.801 - 0.889 which describes that the drug release was following anomalous transport mechanism.

Fig 1: FT-IR spectra of Pure drug Naproxen

Fig 2: FTIR spectra of optimized formulation F13.

Fig 3: Plot of swelling index against time of prepared matrix tablets (F1-F15) at pH 1.2 for 2 hrs and at pH 7.4 for next 6 hrs

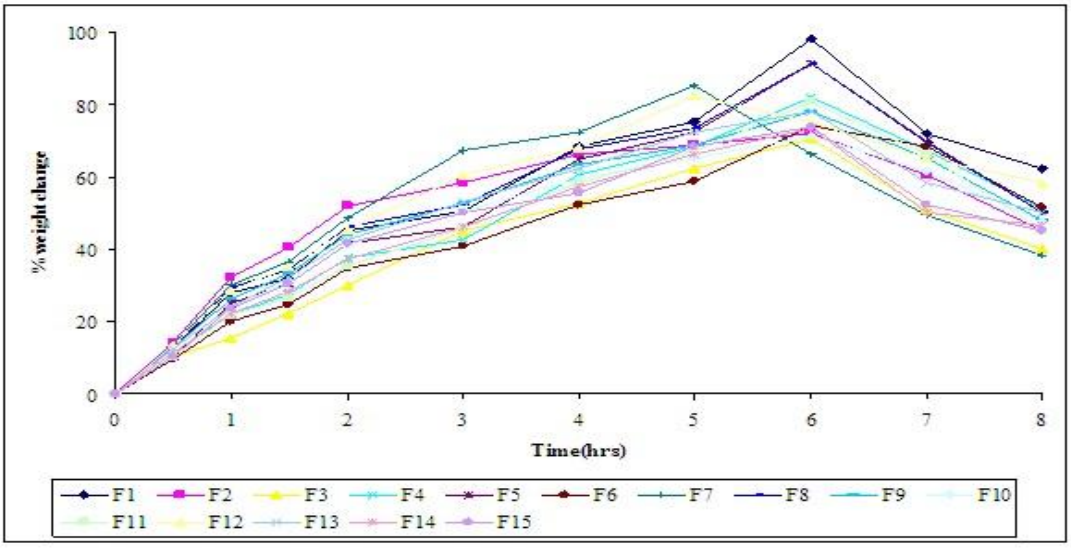

Fig 4: Swelling Index for Enteric Coated formulations F-1, F-4, F-13.

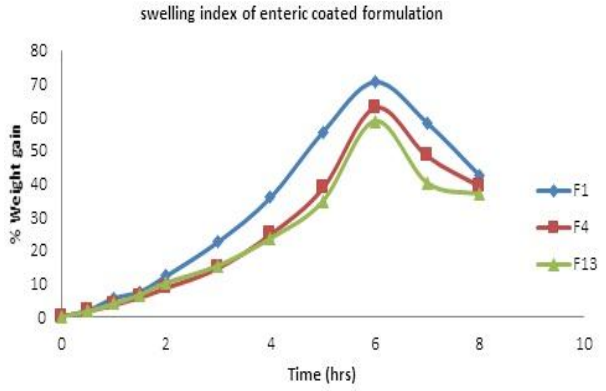

Fig 5: In-vitro release studies of enteric coated formulations-F-1, F-4 and F-13

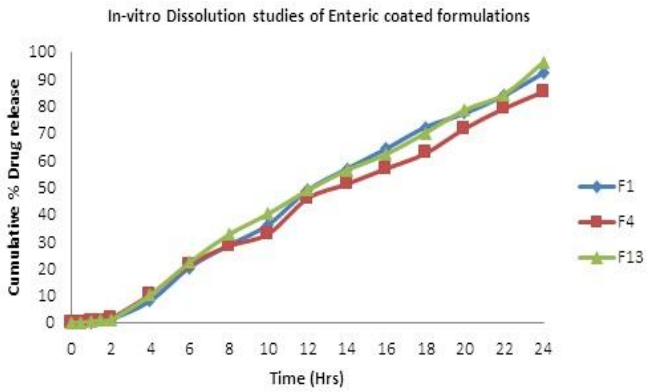

Table 1: Composition of Naproxen tablets (Drug -200mg and polymers in various concentrations) F1 – F15. Drug: Polymer (1:1)

Formulation code	Guar gum (mg)	Chitosan (mg)	Sodium alginate (mg)
F1	200	-	-
F2	-	200	-
F3	-	-	200
F4	150	-	50
F5	100	-	100
F6	50	-	150
F7	150	50	-
F8	100	100	-
F9	50	150	-
F10	-	150	50
F11	-	100	100
F12	-	50	150
F13	100	50	50
F14	50	100	50
F15	50	50	100

Table 2: Characterization of Naproxen granules

Formulation	Angle of repose (^{0}C)	Tapped Density (g/ml)	Bulk Density (g/ml)	Compressibility Index	Hausener's Ratio
F1	30.20±0.12	0.542±0.012	0.485±0.012	10.51±0.11	1.11±0.02
F2	27.01±0.85	0.415±0.018	0.365±0.011	12.04±0.12	1.13±0.04
F3	31.36±0.25	0.656±0.012	0.587±0.015	10.51±0.14	1.11±0.03
F4	26.41±0.51	0.356±0.015	0.312±0.012	12.35±0.24	1.14±0.02
F5	25.36±0.32	0.465±0.010	0.412±0.021	11.39±0.21	1.12±0.10
F6	31.31±1.78	0.356±0.001	0.302±0.014	15.16±0.36	1.17±0.23
F7	24.12±0.36	0.465±0.012	0.415±0.017	10.75±0.28	1.12±0.14
F8	25.36±0.14	0.398±0.010	0.356±0.011	10.55±0.15	1.11±0.54
F9	26.12±0.65	0.432±0.012	0.385±0.021	10.87±0.36	1.12±0.41
F10	24.52±0.31	0.458±0.015	0.402±0.012	12.22±0.47	1.15±0.22
F11	24.23±0.25	0.552±0.014	0.487±0.014	11.77±0.21	1.13±0.36
F12	27.89±0.32	0.458±0.081	0.402±0.011	12.22±0.12	1.13±0.84
F13	25.36±0.12	0.502±0.012	0.45±0.012	10.35±0.36	1.11±0.45
F14	27.36±0.36	0.478±0.011	0.421±0.017	11.92±0.41	1.13±0.67
F15	26.31±0.24	0.452±0.01	0.398±0.018	11.94±0.12	1.13±0.29

Table 3: FTIR spectra of Naproxen and optimized formulation (F13).

Functional groups present		Standard peak region	Standard Drug	Procured drug	Optimized formulation
(-COOH) stretching	O-H	3500-2400	3175	3327.939	2954.583
	C = O	1730-1700	1728	1718.790	1655.512
	C – O	1320-1210	1229	1299.932	1290.947
Aromatic ring	**C** = C – C	1615-1580	1604	1591.976	1580.803
Ethyl	Aryl–O	1270-1230	1260	1248.231	1290.947
	Alkyl –O	1150-1050	1092	1044.872	1061.469

Table 4: Physico-chemical properties of core matrix tablets

Formulation	Diameter (mm)*	Thickness (mm)*	Hardness (Kg/cm^2)*	Friability (%)*	Weight variation (mg)*	Drug content (%)*
F 1	12.12±0.04	5.2± 0.01	5.5± 0.47	0.96± 0.02	402.5± 1.22	98.01± 0.04
F 2	12.14±0.06	5.3± 0.01	6.2± 0.32	0.72± 0.05	401.2± 1.74	97.52± 0.09
F 3	12.12± 0.06	5.4± 0.03	5.5± 0.42	0.91± 0.04	400.2± 1.37	98.90± 0.07
F 4	12.16± 0.07	5.1 3± 0.02	6.1± 0.35	0.86± 0.07	398.5± 1.50	98.53± 0.07
F 5	12.18± 0.05	5.2± 0.01	5.9± 0.54	0.79± 0.04	401.8± 1.19	98.45± 0.01
F 6	12.14± 0.01	5.1± 0.04	5.7± 0.47	0.72± 0.07	403.5± 1.25	99.62± 1.5
F 7	12.12± 0.06	5.3± 0.05	6.4± 0.32	0.91± 0.08	398.2± 1.20	99.57± 0.09
F 8	12.13± 0.04	5.1± 0.06	6.1± 0.34	0.96± 0.04	404.5± 1.57	98.09± 0.07
F 9	12.12± 0.06	5.2± 0.04	5.5± 0.32	0.75± 0.06	402.8± 1.48	99.02± 0.03
F 10	12.14± 0.04	5.1± 0.06	6.4± 0.37	0.98± 0.07	398.5± 1.80	98.07± 0.09
F 11	12.16± 0.02	5.3± 0.01	6.1± 0.35	0.72± 0.01	399.4± 1.75	99.48± 0.78
F 12	12.13± 0.06	5.2± 0.01	5.5± 0.25	0.74± 0.07	402.5± 1.56	98.46± 0.07
F 13	12.12± 0.06	5.1± 0.04	5.8± 0.42	0.78± 0.01	403.1± 1.67	98.51± 0.06
F 14	12.15± 0.05	5.2± 0.06	6.4± 0.35	0.79± 0.09	398.5± 1.45	99.30± 0.08
F15	12.14± 0.02	5.1± 0.08	5.7± 0.35	0.84± 0.03	400.1± 1.43	99.26± 0.07

Table 5: Release kinetic of Core matrix tablets

Formulation code	Zero order (r^2)	First order (r^2)	Higuchis (r^2)	Koresmeyer Peppas(r^2)	Koresmeyer Peppas (n)
F 1	0.986	0.937	0.968	0.913	1.121
F 2	0.925	0.978	0.984	0.522	0.983
F 3	0.947	0.976	0.960	0.880	1.289
F 4	0.977	0.978	0.9680	0.948	1.181
F 5	0.979	0.992	0.971	0.925	1.083
F 6	0.991	0.971	0.964	0.884	1.105
F 7	0.973	0.988	0.985	0.890	0.978
F 8	0.937	0.990	0.990	0.827	0.889
F 9	0.897	0.964	0.983	0.763	0.812
F 10	0.825	0.927	0.949	0.890	0.978
F 11	0.926	0.978	0.986	0.768	0.801
F 12	0.912	0.975	0.985	0.828	0.894
F 13	0.992	0.887	0.964	0.899	1.027
F 14	0.959	0.987	0.987	0.784	0.825
F 15	0.976	0.987	0.984	0.847	0.918

Table 6: Physico-chemical properties of coated matrix tablets

Formulation code	Diameter (mm)*	Thickness (mm)*	Hardness (Kg/cm^2)*	Friability (%)*	Weight variation (mg)*	% Drug content uniformity*
F 1	12.32 ±0.04	5.6± 0.01	6 .9± 0.47	0.85±0.02	422.5± 1.25	97.09± 0.02
F 4	12.32± 0.03	5.6± 0.02	7.9± 0.54	0.92± 0.09	421.8± 1.18	98.8± 1.20
F13	12.34± 0.05	5.3± 0.08	7.7± 0.35	0.56± 0.09	420.1± 1.45	98.4± 0.07

Table 7: Release kinetics data of enteric coated formulation Naproxen matrix tablets

Formulation code	Zero order (r^2)	First order (r^2)	Higuchiseq (r^2)	KorsmeyerPeppas (r^2)	(n)
F1	0.944	0.920	0.930	0.944	1.914
F4	0.996	0.946	0.936	0.921	1.901
F13	0.995	0.836	0.937	0.927	1.964

CONCLUSION

The present investigation was carried out to develop colon targeted drug delivery of naproxen using guar gum, Chitosan and Sodium alginate for inflammatory bowel diseases. Matrix tablets of naproxen using polysaccharides alone and its combination were failed to retard the drug release in the physiological and colonic environment. In the view of this result, alternatively colon targeted delivery were developed by enteric coating with Eudragit S-100 by dip coating method. in this view, results showed that combination of single polymer is not suitable either Guar gum or Chitosan or Sodium alginate, to release maximum amount of drug release in colon so combination of polymers like Guar gum; Chitosan: Sodium alginate (100:50:50) and enteric coated with Eudragit S- 100 tablets i.e. formulation F13 is mostly like to provide target delivery of Naproxen to the colon.

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