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Original Research Article

Formulation and Evaluation of pH-Responsive Mini-Tablets for Ileo-Colonic Targeted Drug Delivery

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Abstract

Purpose: *To formulate and evaluate a novel pH-responsive mini-tablet for ileo-colonic targeted delivery of naproxen in chronotherapeutic treatment of rheumatoid arthritis.*
Methods: *Core mini-tablets were prepared by direct compression method. These prepared core mini-tablets were then coated with enteric coating polymers, i.e., Eudragit L100 and Eudragit S100 in different ratios and concentrations and filled into an empty hydroxypropyl methylcellulose (HPMC) capsule. Fourier transform infrared spectroscopy (FTIR) and diffraction scanning calorimetry (DSC) studies on the pure drug and its combination with polymers were performed to assess compatibility. The formulations were also characterized for drug content, in-vitro drug release and stability.*
Results: *FTIR and DSC data show that there was no interaction between the drug and the polymers. All the physicochemical properties of the core mini-tablets were within acceptable limits. Drug content was 99.42 ± 0.15 %. Optimized formulation F12 released drug after a lag time of 5.02 ± 0.4 h, with 99.40 ± 0.4 % of the drug released at the end of 8 h. It was also stable for a period of 6 months based on International Conference on Harmonization ICH guidelines.*
Conclusion: *A novel pH-responsive mini-tablet formulation of naproxen has been successfully developed for the chronotherapeutic treatment of rheumatoid arthritis*

Keywords: *Ileo-colonic targeted delivery, Naproxen, Mini-tablets, Hydroxypropyl methylcellulose , Chronotherapeutic, Enteric coat, Rheumatoid arthritis*

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory syndrome which mainly causes the destruction of joints integrity. The patients with this disease have symptoms which mainly persist in the early morning hours such as joint pain and functional disability [1]. Rheumatoid arthritis can be well treated by the concept of chronotherapy to maintain the highest concentration of drug in the bloodstream, so that peak pain and stiffness of the disease can be overcome [2,3]. Drugs can be targeted as per the circadian behavior of the diseases by using pulsatile dosage forms [4]. When intentionally delayed absorption of drug is needed in order to have a uniform therapeutic effect, then colon targeting of the drug would be useful for the treatment of diseases that have peak symptoms in the early morning times after awakening. Rheumatoid arthritis is one of such diseases [5,6].

Dew *et al* developed the first colon targeted pH responsive drug delivery system [7,8]. This type of delivery system is most specifically referred to as 'ileo-colonic targeted drug delivery' rather than colon-targeted drug delivery system [9,10]. Control of size and size distribution of pellets is more critical prior to the coating process. Therefore, to achieve a tight and reproducible release profile both a desirable pellet size and a narrow particle size distribution are important and which is not easy to achieve. Unlike granules which have high porosity and irregular shapes hence making coating difficult [11].

Mini-tablets are very small tablets compared to normal tablets having diameter between 2 to 3 mm. Other advantages of mini tablets include: they are more uniform in size so very less unit-to-unit variation in drug occur and accurately weighed amounts of drug can be loaded into mini-tablets. It is relatively easy to manufacture mini-tablets, and is even possible to coat them in order to delay the drug release because of their excellent smooth surface area. They can also be filled in capsules like other multiple unit dosage forms. Therefore they resemble good substitutes for pellets and granules [11,12].

Naproxen has been found to be effective in both clinical and experimental pain of rheumatoid arthritis and it is a derivative of naphthylpropionic acid. It belongs to the class of NSAID's [13]. By keeping in view the need to target naproxen during the time of its greatest need, this work was designed to develop a novel pH-responsive mini-tablets-filled capsule for chronotherapeutic delivery of naproxen.

EXPERIMENTAL

Materials

Naproxen was obtained as gift sample from IPS Pharma Training Institute, Hyderabad, India. Sodium starch glycolate (SSG) was purchased from Rajesh Chemicals, Mumbai. PVP-K-30 was purchased from Himedia Chem. Lab, Mumbai. Magnesium stearate, lactose, acetone, triethyl citrate and isopropanol were purchased from S.D Fine Chem. Lab, Mumbai, India. Aerozil was obtained from Sisco Research Laboratories Pvt. Ltd. Mumbai. Talc was purchased from Loba Chemie Pvt. Ltd, Mumbai. pH sensitive methacrylic acid co-polymers (Eudragit® L-100 and S-100) were supplied as gifts samples by Degussa India Pvt. Ltd., Mumbai, India. Empty HPMC capsules (almost all sizes) were obtained as a gift sample from ACG Associated Capsules Pvt. Ltd. Mumbai. All the remaining materials used were of analytical grade.

Identification of absorption maxima (λmax)

The pure drug, naproxen, was mixed in varying pH solutions (pH 1.2, 6.5, 6.8 and 7.2) to a concentration of 10 µg/ml. These prepared solutions were scanned between 200-400 nm regions on UV Spectrophotometer in order to identify the absorption Maxima (λmax).

Fourier Transform Infrared (FTIR) spectral analysis

The pure drug, naproxen, polymers and physical mixture of drug and polymers used under this experimental condition were evaluated for compatibility. The evaluation was performed by taking 2 mg sample in 200 mg KBr (Perkin Elmer, spectrum-100, Japan). The range of scanning was 400 to 4000 cm^{-1} and the resolution was 1 cm^{-1}.

DSC studies

DSC thermograms of pure drug naproxen and physical mixture were recorded using Diffraction scanning calorimeter (DSC 60, Shimadzu, Japan). The measurement was performed between 30 and 350 ^{o}C at heating rate 10 ^{o}C/min [14].

Preparation of mini-tablets of naproxen

The core mini-tablets were prepared using the wet granulation method. The ingredients such as naproxen, intragranular quantity of sodium starch glycollate, PVP K30 and lactose as mentioned in Table 1 were passed separately through 60 mesh sieve and mixed in dry condition. After dry-mixing the blend at a slow speed in a double-cone blender for a period of 10 min, it was granulated with ethanol. This wet granulated mass was then immediately passed through a sieve of 16 mesh size. The granules obtained after sieving were dried in a hot air oven at 30 to 35 ^{o}C for a period of 1 h. These granules after drying were allowed to pass the same sieve of 16 mesh size in order to break the irregular shaped lumps and finally mixed with extra-granular quantity of sodium starch glycollate. Finally, these dried granules after lubrication with magnesium stearate and Aerosil. were compressed into 25 mg weighing mini-tablets using 3 mm round concave punches in a rotary tablet press (Karnavati Engineering, Ahmadabad) [15].

Table 1: Composition of core mini-tablets

Ingredient	Core mini-tablet (mg)
Naproxen	16.666
Sodium starch glycollate	2.5
PVP K30	1.0
Lactose	4.334
Magnesium stearate	0.25
Aerosil	0.25
Total weight (mg)	25.0

Preparation of coating solution

First, the combination of eudragit polymers were added in 50 % of the solvents and were stirred for a period of approximately 30 - 60 min till both the polymers are completely dissolved. Secondly, triethyl citrate and talc were added in the remaining solvent mixture and stirred with a high speed mixer for 10 min. Then, this solution of triethyl citrate and talc was poured slowly into the polymer solution in the stirring motion and finally passed through a 0.5 mm sieve. The composition of the coating solution is shown in Table 2.

Table 2: Composition of coating solution

Ingredients	Quantity (g)
Eudragit L 100 and/or Eudragit S 100	6.00
Triethyl citrate	0.600
Talc	3.00
Acetone	34.69
Isopropanol	51.42
Water	4.29
Total weight (g)	100

Preparation of pH-responsive mini-tablets

Sufficient quantity of naproxen core mini-tablets along with placebo tablets were coated with the coating solution as per the experimental design shown below in Table 3 in a 6 inches lab scale coating pan using a spray gun (United Technologies, Mumbai). The prepared mini-tablets were coated with 500 ml of coating solution. The operating parameters were - tablets charge 100 g; preheating temperature 40 ± 5 °C; preheating time 20 min; inlet air temperature 45 ± 5 °C; nozzle diameter 1.0 mm, atomization pressure 2.0 bar, spray rate 8 – 10 ml/min.

Preparation of enteric coated mini-tablet-filled capsule formulations

For preparing the capsule formulation 15 enteric coated mini-tablets equivalent to 250 mg of naproxen were filled into size 1 HPMC capsule [15]

Table 3: Composition of enteric-coated mini-tablet-filled capsule systems

Formulation code	Eudragit L 100: Eudragit S 100	Coating level (%)
F1	1:0	10
F2	1:0	15
F3	1:0	20
F4	2:1	10
F5	2:1	15
F6	2:1	20
F7	1:1	10
F8	1:1	15
F9	1:1	20
F10	1:2	10
F11	1:2	15
F12	1:2	20
F13	0:1	10
F14	0:1	15
F15	0:1	20

Pre-compression tests

The granules containing drug, polymers and various excipients were evaluated for pre-compression parameters to study their flow properties, and maintain uniformity of mini-tablets weight.

Angle of repose (θ)

The angle of repose was determined by taking accurately weighed granules into the funnel. The height of the funnel was adjusted as the tip of the funnel touched the apex of the blend. Then the blend was allowed to flow through the funnel freely on to the surface. From the formed powder cone, height and radius was measured and the angle of the repose was calculated using the following equation.

$\tan \theta = h/r$……………………………………(1)

where, h and r are the height and radius of powder cone respectively.

Bulk and tapped density

For the prepared granules both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Two gram of granules from each batch, which previously was shaken to break any formed agglomerates, was introduced into 10 ml of measuring cylinder. Noting the initial volume, the cylinder was allowed to fall under its own weight over a hard surface from the height of 2.5 cm at 2 sec intervals. Tapping was continued until no further change in volume was noted. LBD was computed as the ratio of granule weight to the untapped volume of the granules while TBD was obtained as the ratio of the granule weight to the tapped volume of the granules.

Hausner's ratio

Hausner's ratio is considered as an indirect index of the ease of the powder flow. It was computed as the ratio of tapped density (ρt) to bulk density (ρd).

Carr's (compressibility) index

The compressibility index of the granules was determined by Carr's compressibility index. Carr's Index (%) was calculated as in Eq 2.

Carr's Index (%) = TBD-LBD/TBD x 100 ..... (2)

Post-compression tests

The mini-tablets were evaluated for post-compression parameters to determine their physicochemical properties.

Hardness test

The hardness of mini-tablets was determined using Pfizer hardness tester. From each formulation batch three mini-tablets were randomly taken and the values were calculated.

Friability test

The test was performed by initially weighing 20 mini-tablets and then transferring into a Veego friabilator. The friabilator was operated at 25 rpm for 100 revolutions and the mini-tablets weighed again. Friability was computed as percent loss in weight.

Weight variation test

From each formulation batch twenty mini-tablets were randomly taken and weighed individually to determine variation.

Uniformity of thickness

From each formulation batch, six mini-tablets were randomly taken and measured for thickness using a micrometer screw gauge [12,14].

Drug content uniformity

For estimation of drug content first 50 mini-tablets were taken and then crushed into fine powder in the mortar. Then this fine powder equivalent to 250 mg of naproxen was extracted in pH 7.2 phosphate buffer. This solution was filtered through a Millipore filter of 0.45 µm pore size. After suitable dilutions drug content was spectrophotometrically determined at a wavelength of 331 nm.

***In vitro* disintegration time**

The disintegration time of core mini-tablets was determined using disintegration test apparatus as per the specifications of Indian Pharmacopoiea. One mini-tablet was placed in each of the six tubes of the basket. To each tube the disc was added and the apparatus was run using 900 ml of pH 7.2 phosphate buffer as the immersion liquid. The assembly was raised and lowered between 30 cycles per minute in buffer maintained at 37 ºC. The time in minutes for complete disintegration of the core mini-tablets with no palpable mass remaining in the tube was measured and recorded.

***In vitro* dissolution test**

Dissolution studies were carried out by using USP XXIII dissolution test apparatus using basket method. For dissolution testing of core mini-tablets, fifteen mini-tablets were immersed completely at a time, as they are equivalent to 250 mg of naproxen and evaluated in pH 6.5, 6.8 and 7.2 dissolution media. For dissolution testing of enteric coated mini-tablets filled capsule formulations, one capsule filled with fifteen mini-tablets were immersed completely at a time. To match the changes in pH along the GI tract, four dissolution media with pH 1.2, 6.5, 6.8 and 7.2 were used sequentially. These four media represents the stomach, proximal part of the small intestine, lower 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 6.5 phosphate buffer. After 1 h the medium was again replaced with fresh pH 6.8 dissolution medium and after 2 h was further replaced with pH 7.2 phosphate buffer for a period of 3 h. In the first 2 h, 750 ml of pH 1.2 dissolution medium was used, and the test was subsequently continued in 900 ml of medium at other pH conditions.

Rotation speed was 100 rpm and temperature was maintained at 37 ± 0.5 °C. At predetermined time intervals, 5 ml of dissolution media were taken and then replaced with fresh dissolution media. The withdrawn samples were analyzed at 230 nm, 329 nm, 329 nm and 331 nm for pH 1.2, 6.5, 6.8 and 7.2 buffers, respectively, by UV absorption spectroscopy and the mean cumulative percentage drug release was calculated over the sampling times [8].

Stability studies

Tests were performed in both room temperature and accelerated stability conditions. The conditions used for storing in room temperature were 30 ± 2 °C and 65 ± 5 % RH, and for accelerated stability studies, the mini-tablets were stored at 40 ± 2 °C and 75 ± 5 % RH in a humidity chamber. At intervals of 2, 3 and 6 months, samples were withdrawn and subjected to stability testing. First, drug content was evaluated for the enteric-coated mini-tablets formulations. Secondly, after filling these mini-tablets into HPMC capsules, whole optimized formulation which was identified was evaluated for dissolution studies to determine the effect of lag time during storage [16].

Statistical analysis

The data were expressed as mean ± standard deviation and the experimental tests were performed in triplicate. Experimental wise error rate (α) of 0.05 which was used to determine level of significance among all possible pairs of formulations. The level of statistical significance was set at $p \leq 0.05$.

RESULTS

Absorption maxima (λmax)

When pure drug naproxen was scanned in between 200 - 400 nm region spectrophotometrically, absorption maxima were 230, 329, 329 and 331 nm at buffer pH of 1.2, 6.5, 6.8 and 7.2, respectively. Thus, these values of absorption maxima were used in plotting the release profile of naproxen.

FTIR spectra

FTIR spectral analysis showed no chemical interaction between pure drug and Eudragit polymers as all the peaks remained intact at their positions as shown in Figure 1. When pure drug naproxen was scanned in different pH buffers (1.2, 6.5, 6.8 and 7.2) it was found that there was significant variation in wavelength as the pH increases. The FT-IR spectral peaks found are: Naproxen: OH- 3166 cm^{-1}; OCH3- 3002 cm^{-1}; CH3- 2963 cm^{-1}; C=O- 1727 cm^{-1}, Eudragit L100: OH- 3258 cm^{-1}; OCH 3- 2997 cm^{-1}; CH3- 2952 cm^{-1}; C=O- 1731 cm^{-1}, Eudragit S100: OH- 3225 cm^{-1}; OCH 3- 2998 cm^{-1}; CH 3- 2953 cm^{-1}; C=O- 1727cm^{-1}, Naproxen + Eudragit L100+ Eudragit S100: OH- 3198 cm^{-1}; OCH 3- 2998 cm^{-1}; CH 3- 2960 cm^{-1}; C=O- 1728 cm^{-1}.

Thermal properties

The thermogram of pure naproxen gave a sharp exothermic peak at 160.22 ºC. DSC results of the physical mixture of naproxen and Eudragit polymers did not show any significant shift in exothermic peak i.e. its peak was found at

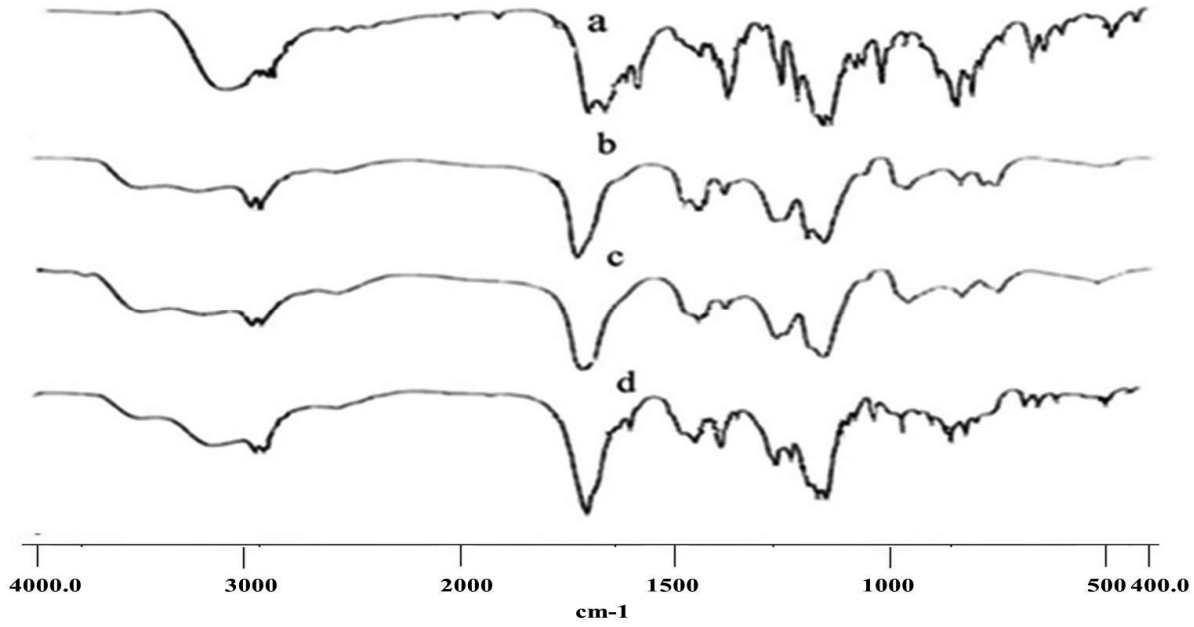

Figure 1: FTIR spectra of (a) pure naproxen (b) Eudragit L100 (c) Eudragit S100; and (d) Naproxen + Eudragit L100 + Eudragit S100

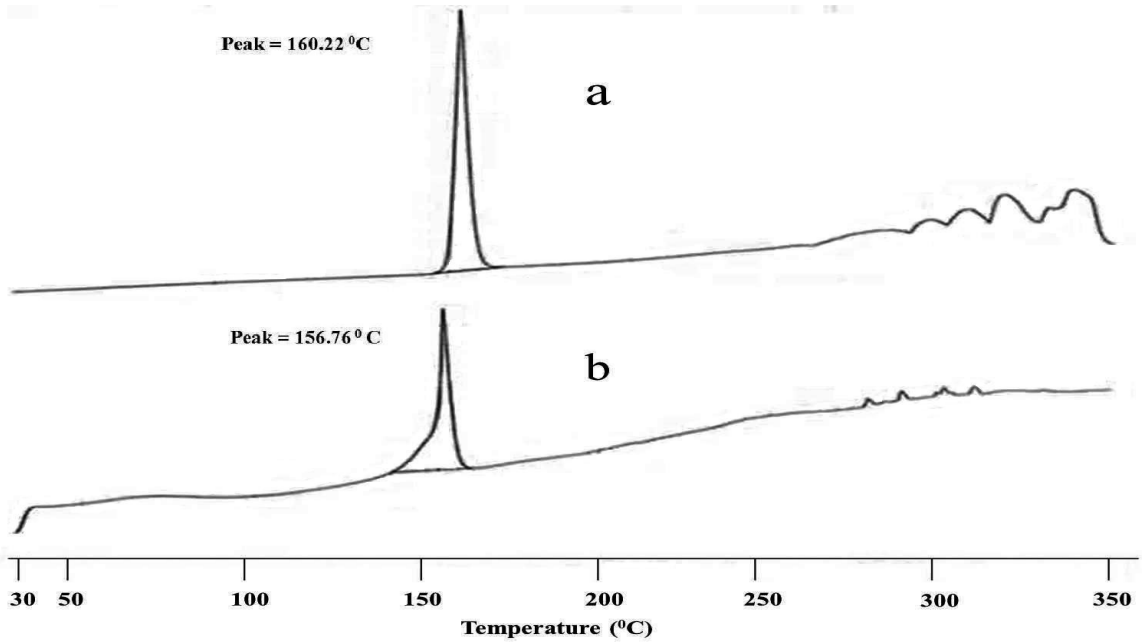

Figure 2: DSC thermogram of (a) pure naproxen and (b) naproxen + Eudragit L100 + Eudragit S100

156.76 ºC. FTIR results were further confirmed by DSC. DSC data confirm that there was no interaction between the drug and polymers as there was no significant shift in the exothermic peak as shown in Figure 2.

Granule characteristics

The angle of repose for the granules of core mini-tablets was found to be 23.48 ± 0.11 º. The values for both loose bulk density and tapped bulk density were found to be 0.54 ± 0.01 and 0.63 ± 0.01 gm/cc respectively. The value of compressibility index for the blend was found to be 14.28 ± 0.91 %. The value for Hausner's ratio was found as 1.16 ± 0.03. These results indicate that the granules were of good flow properties.

Physical characteristics of core mini-tablets

The mean weight of mini-tablets was 26 ± 0.12 mg. The hardness of core mini-tablets was 3.22 ± 0.22 kg/cm^2. Friability was 0.67 ± 0.04 % and it also showed that mini-tablets have sufficient mechanical strength. The thickness was 2.12 ± 0.00 mm. Good uniformity in drug content was observed in the uncoated core mini-tablets, and percentage drug content was 99.42 ± 0.04 %. The uncoated mini-tablets also passed the disintegration test as they disintegrated within 6 ± 0.56 min.

***In vitro* dissolution properties**

The uncoated core mini-tablets released 99.28 ± 0.4, 99.53 ± 0.3 and 99.77 ± 0.4 % of naproxen in pH 6.5, 6.8 and 7.2 phosphate buffers, respectively within 15 min. The dissolution rate of naproxen increased with increase in pH of the dissolution medium.

Of all the formulations, HPMC capsule disintegrated and released the enteric coated mini-tablets within 9 min in pH 1.2 dissolution media. When enteric coated mini-tablets-filled-capsule formulations prepared with 10, 15 and 20 % coating level were subjected to dissolution studies (as represented in Figure 3 - 5), it was found that formulations FI, F2, F3, F4, F5, F6, F7, F8 and F10 prevented naproxen release in pH 1.2 dissolution media but not in pH 6.5, 6.8 and 7.2 dissolution media. On the other hand, formulations F9, F11 and F13 prevented naproxen release in pH 1.2 and 6.5 dissolution media but not in pH 6.8 and 7.2 dissolution media.

It was also observed that formulations F12, F14 and F15 completely prevented naproxen release in pH 1.2, 6.5 and 6.8 dissolution media. However, formulations F14 and F15 failed to release maximum percentage of drug at the end of 8 h. So, it does not meet chronotherapeutic release pattern (which means releasing the drug

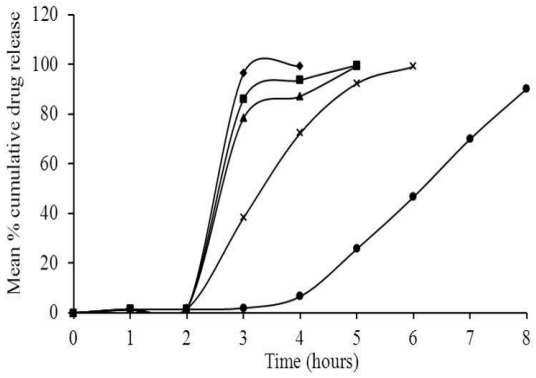

Figure 3: *In-vitro* release profiles of enteric coated mini-tablets-filled-capsule system with 10 % coating level. ***Key:*** F1=♦, F4= ■, F7=▲, F10= ×, F13=●; (n = 3)

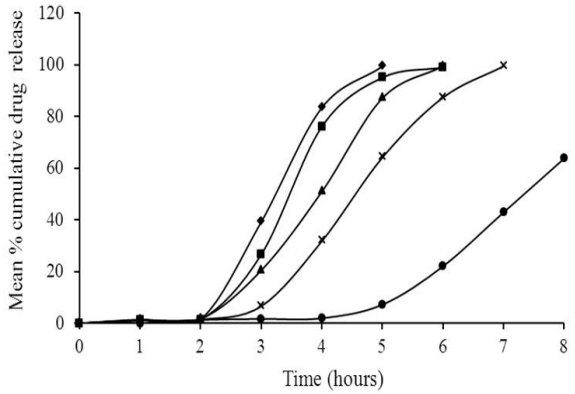

Figure 4: *In-vitro* release profiles of enteric coated mini-tablets-filled-capsule system with 15 % coating level. **Key:** F2=♦, F5= ■, F8=▲, F11= ×, F14=●. (n = 3)

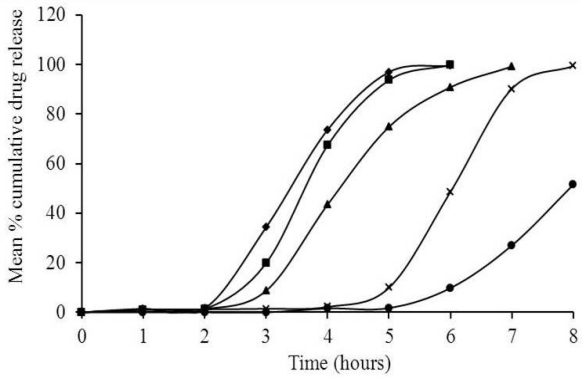

Figure 5: *In-vitro* release profile of enteric coated mini-tablets-filled-capsule system with 20 % coating level. ***Key:*** F3=♦, F6= ■, F9=▲, F12= ×, F15=●. (n = 3)

during the time of its greatest need). On the other hand, formulation F12 prepared with 1:2 ratio of Eudragit L100: Eudragit S100 with 20 % coating level released naproxen after a lag time of 5.02 ± 0.4 h and 99.40 ± 0.4 % at the end of 8 h. Thus, we found this formulation to be the most suitable because it met our desired criteria.

Formulation stability

When optimized enteric coated mini-tablets batch F12 was subjected for evaluation of drug content, it was found that the drug was reduced only by 0.90 ± 0.55 % in a period of 6 months suggesting that the drug was stable. When stability studies were performed for in-vitro drug release profile it was observed that there was very small variation (i.e., < 1 %) in both lag time and drug release profile for the optimized formulation F12. While performing statistical analysis it was found that there was no significant difference during before and after stability studies ($p \leq 0.05$).

DISCUSSION

Both the FT-IR and DSC studies confirm that there was no chemical interaction between drug and polymers as all the peaks were intact. The particle data indicate good flow properties of the granules. All the evaluated post-compressional tests were within acceptable Indian pharmacopoeia (I.P) limits and also indicate that the core mini-tablets possess sufficient mechanical strength to resist breakage during coating.

In the present research work, the aim was to target naproxen as per the circadian rhythm of rheumatoid arthritis. As the symptoms of this disease mainly persists in the early morning hours, by keeping this fact in view we aimed to design a novel pulsatile formulation using mini-tablets-filled-capsule drug delivery system. The developed capsule device was based on pH-sensitive delivery. The device was formulated in three steps First, naproxen was prepared as fast disintegrating core mini-tablets using sodium starch glycolate as a disintegrant; second naproxen core mini-tablets were coated with different ratios and concentrations of Eudragit-L-100 and Eudragit-S-100. Third, these enteric coated mini-tablets were then filled into an empty HPMC capsule body and capped.

The objective in dissolution testing was to identify a suitable ratio and coating level of enteric polymers which releases the drug after a lag time (< 10 %) of at least 5 h or at ileo-colonic junction and maximum portion of the drug till the end of 8 h. Based on the study criteria, a suitable formulation should provide adequate lag time in pH 1.2, 6.5 and 6.8 dissolution media but immediately release naproxen in pH 7.2

dissolution media. Thus, formulation F12 has met the desired criteria. This release profile was based on the assumption that if it was taken during night hours (i.e., before going to bed at 10 pm) then starts releasing naproxen 5 h later with complete naproxen release achieved by 6:00 am. Thus, maximum drug will be available between 4 and 6 am which is the period when rheumatoid arthritis symptoms are at their peak. In all these formulations, neither Eudragit L100 nor Eudragit S100 could individually target the naproxen release to ileo-colonic junction. Also, it was found that as the concentration of Eudragit L100 was decreased or Eudragit S100 was increased, lag time also increased. This was due to the fact that Eudragit L100 is soluble above pH 6 and Eudragit S100 is soluble above pH 7. Therefore, mini-tablets coated with a higher concentration ratio of Eudragit L100 released maximum proportion of the drug in pH 6.5 phosphate buffer (which represents the proximal part of the small intestine), whereas mini-tablets coated with more concentration ratio of Eudragit S100 released maximum portion of the drug in pH 7.2 phosphate buffer (which represents the terminal ileum).

When stability studies were performed for drug content and *in vitro* drug release profile it was observed that there was very small variation (i.e., < 1 %) in both drug content, and drug release profile for the optimized formulation F12. Thus, it was confirmed that our optimized formulation was stable for a period of 6 months as per ICH guidelines.

CONCLUSION

By varying the combination ratio and coating levels of Eudragit L100 and Eudragit S100 polymers, mini-tablets of naproxen can be targeted successfully in the chronotherapeutic treatment of rheumatoid arthritis As the prepared mini-tablets of this research work are more uniform in size, shape, weight and drug content they can be used as a better substitute to overcome many drawbacks of pellets and granule coatings.

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