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Preparation and *in vitro* Characterization of pH-triggered Naproxen-loaded Microsphere of Eudragit L100-55

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Abstract

Naproxen, a non-selective NSAID, is used as an analgesic and anti-inflammatory drug. Being a BCS class II drug, it suffers bioavailability problem due to its poor aqueous solubility. Also, naproxen has the potential to cause gastric injury by ion trapping method. The aim of the study is to improve the solubility of naproxen and reduce the potential gastric injury caused by direct contact of the drug with gastric mucosa by formulating pH responsive microspheres. The naproxen microspheres were prepared by solvent evaporation method using Eudragit L100-55 as enteric polymer. *In vitro* evaluations like entrapment efficiency (%EE), dissolution study, surface morphology (SEM) and drug-excipient interaction (FTIR) were done following the formulation. The entrapment efficiency was found to be the highest and lowest for N6 (1500 mg of Eudragit L100-55) and N1 (250 mg of Eudragit L100-55) formulations, respectively. The microspheres didn't release any drug in acidic media during dissolution and showed an improved solubility in the pH 6.8 buffer media, indicating site specific drug release in small intestine. In morphological evaluation by SEM, N2 (500 mg of Eudragit L100-55) microspheres were found to be spherical and less than 200 µm in size. Additionally, the FTIR study revealed the compatibility of the drug with the excipients of the formulations. Although enteric microspheres of naproxen seemed to be promising to improve bioavailability and reduce gastric irritation from *in vitro* perspective, further *in vivo* evaluation is required to confirm the findings.

Key words: Naproxen, microsphere, eudragit L100-55, solvent evaporation, bioavailability, gastric intolerance.

Introduction

Naproxen, a potent nonsteroidal anti-inflammatory drug (NSAID) of BCS class II, is used for its antipyretic, analgesic and anti-inflammatory properties (Todd & Clissold, 1990). Like most NSAIDs, gastrointestinal irritation is one of the major side effects reported after oral administration of naproxen (Sweetman, 2009).

NSAIDs like naproxen damage gastric mucosa by two mechanisms: prostaglandin dependent and prostaglandin independent mechanism. In prostaglandin dependent mechanism, naproxen damages gastric mucosa by non-selectively inhibiting COX1 and COX2 enzymes, resulting in a decreased level of prostaglandins responsible for maintaining the integrity of gastric mucosa. On the other hand, prostaglandin independent mechanism causes gastric injury by coming in direct contact with gastric surface cells (Matsui *et al*., 2011; Wallace, 2000).

Naproxen is a weak acid. In acidic gastric environment, the drug is non-ionized and lipid soluble. These molecules diffuse across gastric

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mucosal epithelial cell membranes into cytoplasm, where pH is neutral. In neutral environment, molecules are re-ionized and converted into more lipophobic form. Therefore, they are trapped and accumulated within the cells (Laine, 1996). These accumulated naproxen molecules inhibit oxidative phosphorylation in mitochondria and release reactive oxidative species, resulting in cellular apoptosis (Brand *et al.*, 2004).

Since gastrointestinal intolerance of naproxen results from the inhibition of the protective prostaglandin synthesis as well as acute local contact of the drug with the gastric mucosa (Bjorkman, 1996), the development of an enteric multiparticulate drug delivery system might reduce the gastromucosal irritation by avoiding immediate gastric contact of the drug. Naproxen-loaded enteric microsphere can be a viable option for oral delivery of this NSAID which offer several advantages over other conventional dosage forms. Conventional dosage forms available in the market are suspension and uncoated tablet with or without a PPI in combination. These formulations might be effective in avoiding prostaglandin dependent injury, but unable to prevent naproxen to come in direct contact with gastric mucosa, resulting in higher risk of prostaglandin independent gastric injury. Moreover, naproxen being a BCS class II drug, oral absorption of the drug is greatly hampered by its poor solubility. Formulating the drug in microsphere can dramatically improve the solubility and consequent drug absorption from GIT. Also employing pH responsive enteric polymers like Eudragit L100-55 in microsphere formulation will enable the drug release in small intestine rather than in the stomach, causing a minimization of local damage to the GIT (Bjorkman, 1996; Newman, 2015; Shah *et al.*, 2014).

Among many methods, solvent evaporation is the most commonly used technique for the microencapsulation of the drug. Here the drug is dissolved, dispersed or emulsified in an organic polymer solution, which is then emulsified in an external aqueous or oil phase. As the organic solvent is removed by evaporation, the drug and polymer are precipitated in the droplets, thus forming the microspheres (Maghsoodi, 2009).

The objective of this work was to produce microsphere by the solvent evaporation method using Eudragit L100-55 as enteric polymer and investigate the pharmaceutical nature and potential gastric tolerance to the formulations *in vitro*.

Materials and Methods

Materials

Naproxen, eudragit L100-55, span 80, acetone, methanol, liquid paraffin and n-hexane were used in the preparation of six different formulations. Naproxen was a generous gift from Beximco Pharmaceuticals Limited, Bangladesh. Eudragit L100-55 was provided by Evonik Industries, Bangladesh. Span 80 (Merck, Germany) was acquired from the laboratory of Department of Pharmaceutical Technology, University of Dhaka. The remaining components were all of BP and USP pharmaceutical quality and they were procured from the local market.

Preparation of naproxen microsphere: Solvent evaporation method was used for the preparation of microspheres (Table 1). For organic phase, naproxen, and eudragit L100-55 were measured and dissolved in a solvent system comprising of methanol (15 ml) and acetone (5 ml) in a magnetic stirrer for 15 minutes at 500 RPM until a clear solution is formed. This organic phase was continuously injected into the liquid paraffin containing span 80 while stirring at 1200 RPM in an overhead stirrer for 4 hours. Then the liquid paraffin was decanted and microspheres were washed with n-hexane three times. Then the formulated microspheres were collected and dried in oven at 40°C for 24 hours and stored in labelled vials in desiccator (Newman, 2015; Shah *et al*., 2014).

Entrapment efficiency (%EE): To measure the % EE, 50 mg of microsphere sample was measured and

vortexed with 5 ml of buffer solution (pH 6.8, phosphate buffer) for 45 minutes. Then the solution was filtered and diluted appropriately to take an UV absorbance at 332 nm. The entrapment efficiency was calculated using the following formula (Maghsoodi, 2009):

$$\%EE = \frac{\text{Measured concentration}}{\text{Theoretical concentration}} X\ 100$$

Table 1. Formulations of naproxen enteric microsphere.

Code	naproxen (mg)	EudragitL100-55 (mg)	Acetone (ml)	Methanol (ml)	Span 80 (ml)	Liquid paraffin (ml)
N1	250	250	15	5	1	60
N2	250	500	15	5	1	60
N5	250	750	15	5	1	60
N4	250	1000	15	5	1	60
N5	250	1250	15	5	1	60
N6	250	1500	15	5	1	60

In vitro dissolution study: The release profiles of naproxen from enteric Eudragit L100-55 microspheres were investigated according to a previously published method (Hao *et al*., 2013). In the first 2 hrs, naproxen loaded microspheres and 2 ml 0.1 N HCl solution (pH 1.2) were put into a dialysis tube and then the dialysis tube was placed into 22 ml HCl solution at 37ºC. Following that, the pH of dissolution medium was changed to pH 6.8 by adding 8 ml 0.2 M tribasic sodium phosphate solution. At specific time intervals (0, 1, 2, 3, 4,5, 6, 7, and 8 Hr), sample was taken and replaced with fresh release medium. The concentration of the released drug into medium was determined by UV spectrophotometer at 332 nm. The analysis was performed three times for each sample.

Model-dependent dissolution kinetics: Model-dependent mathematical kinetics, including zero-order, first-order, Hixson- Higuchi's square root equation and Korsmeyer-Peppas were used to investigate the *in vitro* release kinetics and mechanism of drug release. The best-fitted model was considered to have the lowest Akaike Information Criterion (AIC) value (Simionato *et al*., 2018).

Particle size and surface morphology: Scanning electron microscopy (SEM) was used to examine the surface morphology of naproxen microsphere (N2, N4, N6) and evaluate the particle size. The field emission scanning electron microscope (JSM-7610F) was employed for surface morphology evaluation according to a previously published method. A small volume of microsphere dispersion was drop-cast onto a carbon coated copper grid and vacuum dried. The dried samples were sputtered coated with a thin layer of platinum and examined at an accelerating voltage of 5-15 kV (Bhattacharjee, 2016).

Drug-excipient compatibility: The compatibility between the drug and excipients of microsphere was assessed using fourier transform infrared spectroscopy (FT-IR) analysis. The FT-IR spectra of the N1 formulations were recorded. FTIR study was conducted to evaluate the ability of the microsphere formulations to protect the integrity of the naproxen molecules. As N1 formulation have the lowest amount of eudragit L100-55, investigating its ability to protect the drug molecules can be extrapolated to the higher polymer ratios in microspheres. N1 microsphere sample was set on the instrument's sample platform (Perkin Elmer, L160000A, USA) and IR spectra in the 4000-650 cm^{-1} range were acquired using Spectrum 10 software (Song *et al*., 2020).

Result

% EE: % EE was found to be the highest for N6 formulation and the lowest for N1 formulation (Figure 1, Table 2). An increase in drug entrapment was observed with an increase in drug-polymer ratio. Similar observation was observed in another research where an increase in polymer/drug ratio resulted in improved encapsulation of naproxen, probably due to greater proportion of polymer (Maghsoodi, 2009).

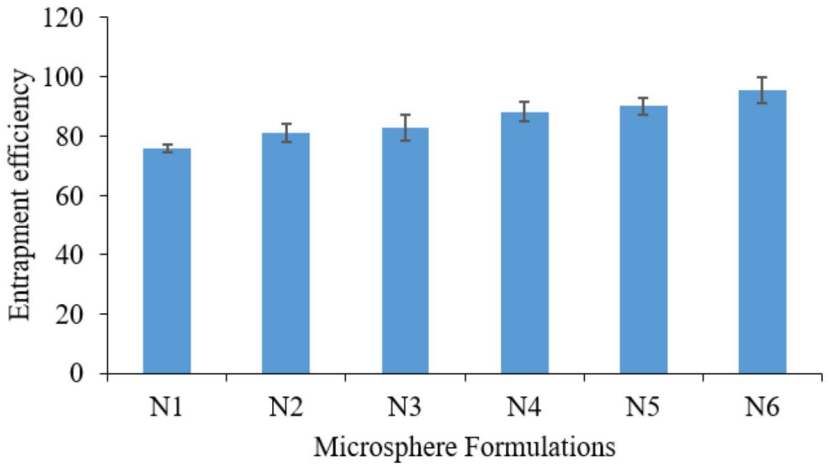


Figure 1. Comparative assessment of entrapment efficiency of formulations (mean ± SD, n=3). SD value is presented by error bar.

Table 2. % EE of the microsphere formulations (mean ± SD, n=3).

Formulation code	N1	N2	N3	N4	N5	N6
% EE	75.88 ± 1.23	81.03 ± 2.96	82.92 ± 4.39	88.26 ± 3.3	90.09 ± 2.9	95.47 ± 4.49
Drug: Polymer	1:1	1:2	1:3	1:4	1:5	1:6

In vitro dissolution: To evaluate the pH-dependent release profiles of naproxen from the samples, *in vitro* release tests were performed under sink condition in pH 1.2 acidic media and pH 6.8 phosphate buffer. In the dissolution medium at pH 1.2, no formulations released drug more than 4% in the first 2 hours and drug release commenced after placing the microspheres in pH 6.8 buffer solution. As clearly shown in figure 2, a burst drug release behavior was observed for all microspheres at pH 6.8 buffer solution initially. The formulation with smallest drug polymer ratio exhibited the highest amount of initial release (N1) where N6 formulation having the highest drug polymer ratio showed minimum amount of burst release. After the initial release, all the microspheres released drug in a sustained release fashion till the end of study. Since the polymer is insoluble in the release media with pH 1.2, the microspheres might be only slightly swollen and remained intact in this case. N2 and N5 formulations exhibited highest and lowest drug release respectively at the end of 8hr study (Table 3, Figure 2). The observations from the dissolution tests clearly indicated the formulation's potential of reducing gastric intolerance due to its inability to release naproxen in the acidic environment of stomach.

Drug kinetics: The drug release data from the formulations were treated in different kinetic orders such as zero order, first order, Korsmeyer-Peppas & Higuchi kinetics and their AIC values were determined to identify their release mechanism

(Table 4). The best fitted model had the lowest AIC value. It appeared from release kinetics that except N2 formulation, all the formulations were best fitted in first order kinetics. For N2 formulation the best fitted model was Korsmeyer-Peppas and drug release mechanism can be assumed as anomalous transport (as the particles were sphere and $0.43<n<0.85$). So, the drug release was due to both Fickian diffusion and swelling and relaxation of the drug delivery system matrix. On the other hand, in other formulations, rate of drug release was concentration dependent ("Mathematical Models of Drug Release," 2015).

Particle size and surface morphology: In SEM analysis three microsphere samples were analyzed (N2, N4 and N6). In the SEM study of N2, spherical particles were observed where the size might be less than 200 µm. The surface of the microspheres appeared rough. In case of N4, the microspheres were similar to N2 in shape and surface morphology, but appeared larger. Lastly, no spherical structure was observed in the SEM analysis of N6 sample, the sample appeared flaky in nature (Figure 3).

Table 3. Release of naproxen from pH-triggered microspheres into pH 1.2 HCl and pH 6.8 phosphate buffer media (mean ± SD, n=3).

Time (Hr)	Cumulative % drug release					
	N1	N2	N3	N4	N5	N6
0	0	0	0	0	0	0
1	1.16 ± 0.8	2.12 ± 0.5	2.81 ± 0.9	1.98 ± 0.7	2.67 ± 1.1	3.11 ± 1.5
2	1.29 ± 0.7	2.15 ± 1.1	3.78 ± 2.1	2.33 ± 1.3	3.43 ± 1.6	3.3 ± 0.9
3	39.34 ± 1.5	35.86 ± 1.9	30.57 ± 1.7	27.7 ± 2.9	25.33 ± 1.2	23.53 ± 3.7
4	53.88 ± 1.2	49.04 ± 2.7	39.7 ± 3.1	35.47 ± 2.2	37.97 ± 2.5	31.92 ± 3.6
5	58.77 ± 2.3	54.19 ± 2.3	50.01 ± 3.2	43.41 ± 2.5	46.74 ± 3.3	44.95 ± 2.3
6	62.59 ± 1.7	65.74 ± 2.2	63.19 ± 1.2	51.81 ± 3.3	55.74 ± 1.6	52.71 ± 2.9
7	69.56 ± 2.5	68.08 ± 1.5	74.22 ± 2.6	68.36 ± 3.9	68.19 ± 2.1	65.55 ± 4.3
8	73.74 ± 1.9	72.3 ± 2.9	77.97 ± 2.2	78.02 ± 1.7	79.08 ± 3.4	73.04 ± 2.5

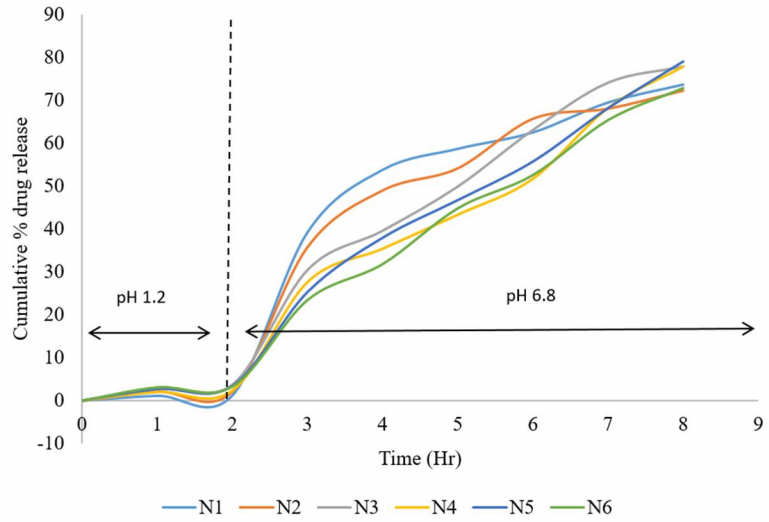
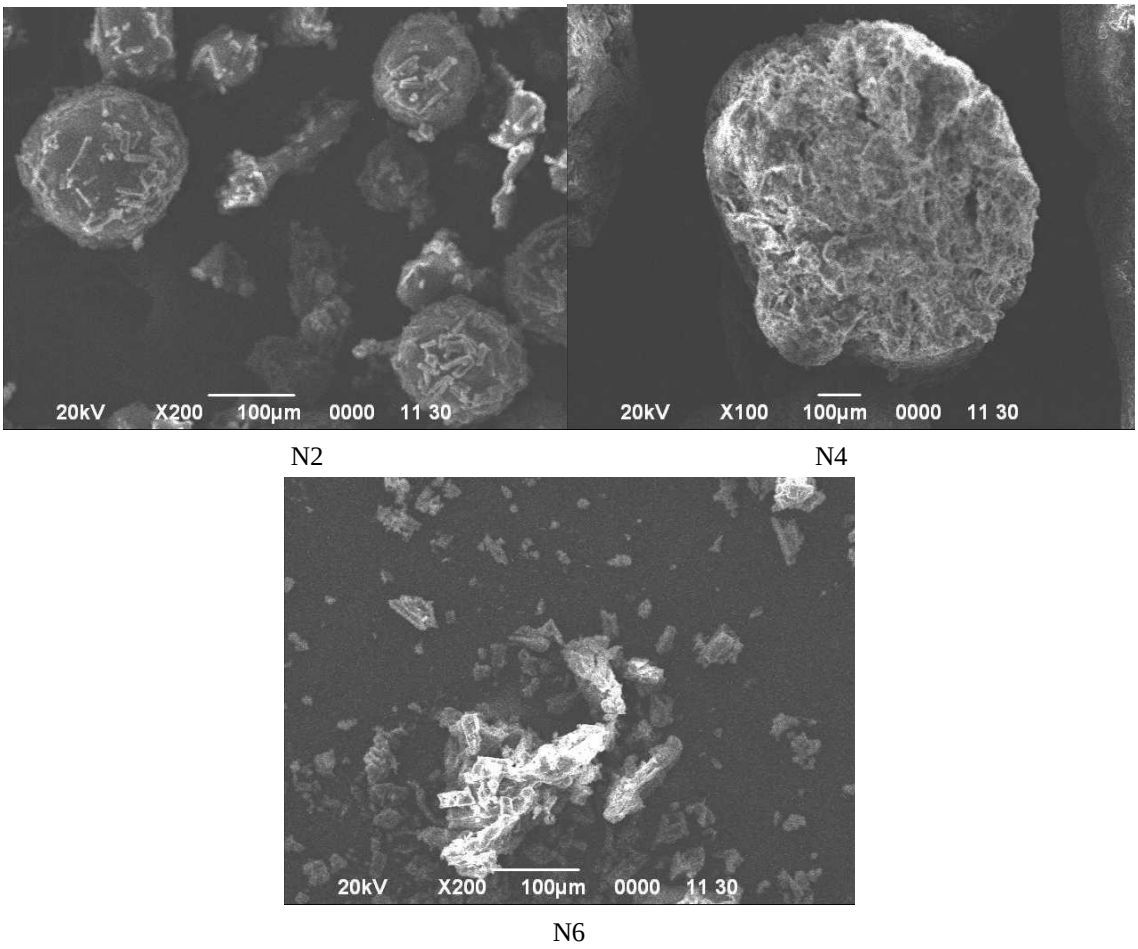


Figure 2. Release pattern of naproxen from pH-triggered microsphere into pH 1.2 HCl media and pH 6.8 phosphate buffer.

Table 4. Analysis of kinetic drug release models of microsphere formulations.

Formulation code	AIC			
	Zero order	First order	Higuchi	Korsmeyer-Peppas
N1	75.6247	53.2487	60.0781	60.5018
N2	61.6444	57.5073	67.2201	56.1200
N3	77.9043	45.2884	61.3672	62.1331
N4	75.3164	44.0024	51.0711	48.6193
N5	79.1917	41.5742	58.7056	60.1842
N6	73.9316	54.9359	51.4130	52.2630



N2 N4

N6

Figure 3. Scanning electron microscopy of naproxen microsphere formulations.

Drug-excipient compatibility: Naproxen gives its characteristics peaks in FTIR around 1252 cm^{-1} due to C–O stretching (acid), 1583 cm^{-1} due to COO– stretching, C–C aromatic stretching at 1631 cm^{-1} and C–H aliphatic stretch at 2840 cm^{-1} (Sharma *et al*., 2013). These characteristic peaks were observed in the FTIR analysis of N1 microsphere sample although the peaks were slightly shifted probably due to electrostatic interactions with the excipients. This observation ensured the integrity of the molecular structure of naproxen in the microsphere (Figure 4).

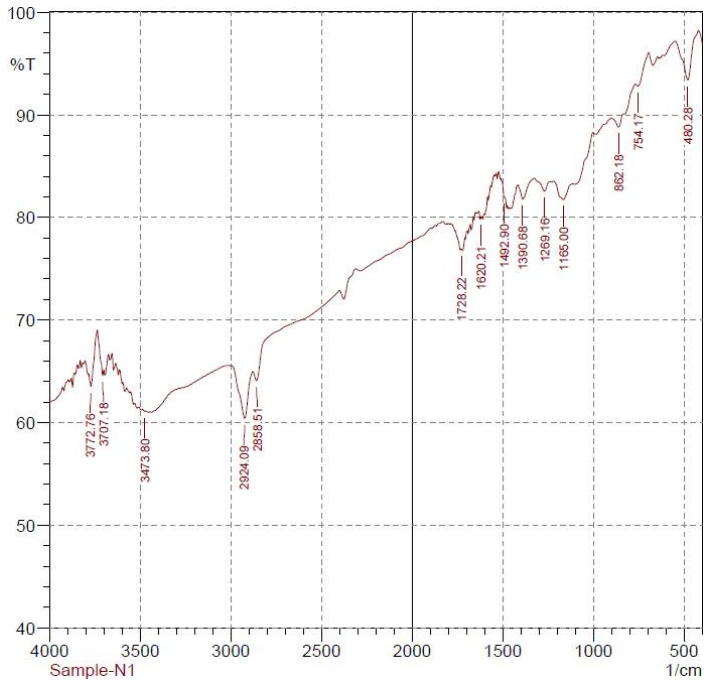


Figure 4. FTIR study of N1 microsphere sample.

Discussion

In this study, an effort was made to formulate naproxen microspheres to improve its bioavailability and gastrointestinal tolerance of the drug. Naproxen, a drug of BCS class II, suffers a poor bioavailability due to its low aqueous solubility. Also the drug can irritate the gastric mucosa on local contact with stomach cell surface by an 'Ion-trapping' method (Bjarnason *et al.*, 2018). To solve these issues and make a gentler version of naproxen solid oral dosage form, polymeric microsphere formulations were prepared using solvent evaporation method. Eudragit L100-55 was used as enteric polymer which is an anionic copolymer and contains carboxyl groups allowing it to have greater water solubility in neutral pH (small intestine) unlike in acidic pH (stomach) (Loh *et al*., 2022).

The % EE of the formulations was evaluated to understand how much drug was encapsulated in microspheres. A correlation was predicted between the amount of polymer and entrapment where drug encapsulations were observed to be proportional with the amount of enteric polymer, probably due to higher polymeric content provided enough space to embrace the drug. This might have diminished the solubilization of hydrophobic naproxen molecule by the surfactant, resulting in improved drug entrapment (Wang *et al*., 2022).

The dissolution study was conducted using both pH 1.2 HCl media and pH 6.8 phosphate buffer media to simulate the condition of stomach and small intestine. Negligible amount of drug release was observed during the first 2 hours of study in pH 1.2 acidic media probably due to pH dependent feature of the polymer used. Eudragit L100-55, an anionic copolymer, remains unionized below pH 5.5, resulting in poor dissolution of polymer and drug release in acidic media (Dai *et al.*, 2004). All microsphere formulations showed an initial burst drug release, in the range of 23.53% to 39.34% in the first one hour after placing them in pH 6.8 buffer media. This phenomenon could be influenced by several factors, like amorphous unentrapped and entrapped drug close to microsphere surface. This observation agrees with a previous study where diclofenac sodium also showed a burst release from

enteric nanoparticles (Cetin *et al*., 2010). Moreover, eudragit L100-55 is in anionic form above pH 5.5 due to deprotonation of carboxylic acid group, creating a repulsive force between polymer molecules which ultimately release the surface drug molecules (Cetin *et al*., 2010).

The microsphere formulation having the lowest amount of polymer and drug entrapment (N1) showed highest initial release, probably due to highest amount of unentrapped drug on the surface. On the contrary, N6, having the highest drug entrapment might have lower amount of unentrapped drug molecule on surface, thus showing lesser initial release.

Following the immediate drug release, the remaining drugs showed a sustained release patterns, probably due to swelling of polymeric microsphere. Swelling might have increased the average diffusion path length of the encapsulated drug and viscosity of the diffusion media. Hence, slow drug release is expected. Similar results were found in one previous study where initial immediate drug releases were followed by a sustained drug releases, probably due to simultaneous erosion and swelling of pH-sensitive nanoparticles (Cetin *et al*., 2010). This assumption is further supported by drug release kinetics data, where N2 formulation was found to release drug molecules by swelling and fickian diffusion. Also, no precipitation tendency was observed for any formulation, indicating that drug molecules didn't convert into crystalline form during the study period.

SEM analysis was done to evaluate the surface morphology of the microsphere where N2 and N4 formulations appeared to be spherical and rough in surface. The uneven surface might be due to accumulation of drug to the periphery of microsphere. This speculation is further supported by the drug release data where an initial burst release was observed for all the formulations which might have resulted from the surface accumulation of drug molecules. Similar observation was found in another study where eudragit microspheres with abrasions on the surface appeared (Rajesh *et al*., 2017). Moreover, molecular integrity of the drug was ensured from FTIR study, which guaranteed the inherent pharmacological activity of naproxen.

Although *in vitro* evaluations delivered promising results, further *in vivo* assessments with microspheres composed of biocompatible excipients should be considered.

Conclusion

The method employed in this study successfully formulated naproxen microsphere by solvent evaporation method using pH-responsive polymer eudragit L100-55. The formulations resisted drug release in acidic environment and showed biphasic drug release at pH 6.8, which might act as a surrogate parameter of improved bioavailability and gastric tolerance of naproxen, as the drug will not be able to come in contact with gastric mucosa. Also the formulations housed a considerable amount of drug in the microspheres. From SEM study, N2 appeared to be the smallest (<200 µm) and spherical in shape. Lastly drug-excipient compatibility was confirmed from the FTIR study of the formulation, indicating the molecular integrity of the naproxen molecule in the formulations. Overall, the enteric microsphere formulations of naproxen showed a promising potential in the safe delivery of the naproxen in this study.

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Conflict of interests

The authors wish to affirm that this study has no conflicts of interest.

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Author's contributions

Md Asaduzzaman Rakib: Conceptualization, investigation, methodology, writing; faria nasrin: writing - original draft, review & editing, visualization; Muhammad Rashedul Islam: Conceptualization, project administration, writing -

review & editing; Abir Hasan Pranto: methodology, investigation

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