

Study of Ethyl Cellulose Based Sustained Release Microspheres of Naproxen Sodium

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ABSTRACT: The present study was conducted to prepare sustained release microspheres of naproxen sodium using ethyl cellulose (Ethocel 20 cps) polymer. Three different plasticizers namely polyethyleneglycol 600 (PEG 600), polyethyleneglycol 6000 (PEG 6000) and triethyl citrate (TEC) were used at 10% (wt/wt) and 40% (wt/wt) level of the drug content. Prepared microspheres were characterized with respect to drug loading, microsphere particle size, microsphere surface morphology and release behavior. Surface morphology of the microspheres was examined in a scanning electron microscope. Drug release was observed in phosphate buffer solution of pH 6.8 for 8 hours. At 10% level of the plasticizers, percent release was 93.36%, 93.02% and 92.67% for PEG 600, PEG 6000 and TEC respectively after 8 hours. On the other hand, at 40% level, percent release was 81.12%, 70.06% and 51.12% for PEG 600, PEG 6000 and TEC respectively after the same duration. Release mechanisms followed case I or fickian model.

Key words: Naproxen sodium, Ethocel 20 cps, Sustained release, Microsphere, Scanning electron microscope.

INTRODUCTION

Naproxen sodium (NS) has been proved to be effective in both experimental and clinical pain like rheumatoid arthritis, osteoarthritis, juvenile arthritis and acute gout without any serious cardiovascular or respiratory side effects.^{1,2} The drug is lipid soluble, practically insoluble at low pH and freely soluble at high pH. One of the most important commonly used methods for controlling drug release is to form a matrix system with the help of hydrophilic, inert and hydrophobic polymers. Ethyl cellulose (EC) is hydrophobic polymer and is essentially tasteless, odorless, colorless and physiologically and pharmacologically inert. It has been extensively used as a pharmaceutical solid vehicle in preparing microcapsules,³ coating material for tablets and

granules⁴⁻⁶ and matrix forming material for sustained release dosage forms.^{7,8} But EC is considered as an ideal polymer for microencapsulation technology and it has been proved that EC can be used successfully for both oil-in-water and water-in-oil emulsion solvent evaporation technique.⁹⁻¹³

Microencapsulation is one process used to control drug release and hence prolong therapeutic activity.¹⁴ In pharmaceutical sustained release preparations, the uniqueness of microcapsules lies in the wide distribution throughout the gastrointestinal tract. This potentially improves drug absorption and reduces side effects related to localized build-up of irritating drugs against the gastrointestinal mucosa.¹⁵

In this study, EC was used to prepare sustained release microspheres of NS. Plasticizers at different concentrations were used in the matrix to observe their effect on microsphere properties. However, plasticizer content variation was considered as independent variable and microsphere morphology, size distribution, drug loading, release property of NS were considered as dependent variables.

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MATERIALS AND METHODS

NS was received as generous gift from SQUARE Pharmaceuticals Ltd., Bangladesh. The following chemicals were obtained from the respective sources and used as received: ethyl cellulose (ETHOCEL 20 cps, Colorcon, UK), polyethyleneglycol 600 (PEG 600, BASF, Germany), polyethyleneglycol 6000 (PEG 6000, BASF, Germany), triethyl citrate (TEC, Morflex Inc. USA), liquid paraffin (Merck, Germany), methanol (Merck, Germany), span 60 (BDH Chemicals, England), petroleum ether of 40:60 grade (Merck, Germany).

Preparation of ethyl cellulose-naproxen sodium microspheres. Microspheres were prepared using the emulsification (water-in-oil) and organic solvent evaporation technique¹⁶ which is a slight modification of the Tsai technique.¹⁷

Table 1. Formulations of naproxen sodium microspheres

Materials (mg)	F1	F2	F3	F4	F5	F6
Naproxen sodium	2	2	2	2	2	2
Ethocel 20 cps	1.8	1.8	1.8	1.2	1.2	1.2
PEG 600	0.2			0.8		
PEG 6000		0.2			0.8	
Triethyl citrate (TEC)			0.2			0.8

Surface morphology study. To observe the microspheres surface morphology, a Scanning Electron Microscope (SEM, S-3400N, Hitachi, Japan) was used. SEM images at different magnifications were taken for comparative study.

Particle size determination. Microsphere size distribution was analyzed by laser diffraction technique using Mastersizer 2000 (MALVERN, UK). Particle size distribution was measured by Dry dispersion technique. Volume mean diameter (D [4, 3]) was used to express average particle size in μm . Specific surface area (m^2/gm) of the microspheres was also determined.

Drug content analysis. Aqueous solutions of NS (0 to 20 $\mu\text{g}/\text{ml}$) in phosphate buffer (pH 6.8) were prepared and the absorbance was measured at 332 nm by a Shimadzu UV-VIS Spectrophotometer (UV mini-1240, Shimadzu Corp., Japan). A linear line was obtained while absorbance values were plotted against concentrations ($R^2 > 0.99$).

50 gm light liquid paraffin (LLP) and 1% (wt/wt of the LLP) of span 60 were taken in a beaker (external phase). Drug, polymer and plasticizers (according to table 1) were dissolved in 15 gm methanol (internal phase) and a clear solution was made with the help of a vortex mixer (Digisystem laboratory instruments inc. Taiwan). The internal phase was then incorporated into the external phase with continuous stirring by a high speed stirrer (Heidolph No. 5011, Heidolph, Germany) at 3000 rpm and maintaining the temperature at 25°C. After 2 hours of stirring, microspheres were filtered and washed with petroleum ether (40:60) for three times and finally dried in a vacuum dryer (Veego, India). Microspheres were then sieved with 1 mm sieve to remove any lump present.

Drug loaded microspheres of each batch were finely powdered in a glass mortar and 10 mg powder was taken in a volumetric flask. A clear solution was made using the same phosphate buffer after proper sonication (Power Sonic 505, Hwashin Technology Co., Korea). Then the solution was filtered through 0.45 μm filter and analyzed spectrophotometrically for drug content.^{18,19}

The weight of NS theoretically contained in the microspheres was compared with the weight actually obtained from the drug content studies, i.e., the quantity loaded into the microspheres formulated, to get the NS loading efficiency.²⁰ Following equation was used for the calculation.

$$\text{Drug-loading efficiency (\%)} = (C_p/C_t) \times 100 \quad (1)$$

where, C_p and C_t were the actual and theoretical drug content in NS loaded microspheres of EC polymer, respectively.

In vitro dissolution study. *In vitro* dissolution was carried out in a USP XXX apparatus 2 (Paddle Apparatus) in 900 ml phosphate buffer (pH 6.8) at $37 \pm 0.5^\circ\text{C}$ at a rotational speed of 50 rpm. Dissolution samples were withdrawn at predetermined intervals and were filtered through $0.45 \mu\text{m}$ filters. The drug content was determined in the filtrate either directly or after appropriate dilution with the dissolution media.

RESULTS AND DISCUSSION

EC was used as the wall material due to its safety, stability, hydrophobicity and perfect film forming nature among other polymers. Besides, EC has good release retardant property also.^{21,22} However, NS microspheres were successfully

prepared by water-in-oil emulsion solvent evaporation technique using EC as the wall material and PEG 600, PEG 6000, TEC as plasticizers.

However, EC microspheres showed good encapsulation efficiency of NS. It was above 85% for both 10% and 40% level of the plasticizers (Table 2). No difference in NS load was seen even though different plasticizers at different ratios were used i.e. variation of plasticizers did not affect the encapsulation efficiency of EC.

Figure 1 shows the SEM photographs of the microsphere formulated using 40% TEC. Surface appeared smooth at the lower magnification. At higher magnification, microsphere surface appeared embedded with TEC where very few numbers of small pores were seen.

Table 2. Microsphere properties of the optimized batches

Batch	EE (%) ^a	Particle Mean Diameter (μm) ^b	SSA ($\text{m}^2/\text{g} \times 10^{-2}$) ^c	Analysis of "Higuchi" plot	
				SLP (K_h) ^d	K_h/SSA
F1	85.36	656.14 ± 18.96	1.34	22.23	16.58
F2	88.44	659.19 ± 19.90	1.34	20.52	15.31
F3	89.34	670.64 ± 17.43	1.25	14.23	11.38
F4	90.16	656.25 ± 29.54	1.32	17.36	13.15
F5	86.79	651.32 ± 31.12	1.37	18.19	13.27
F6	91.48	671.23 ± 19.23	1.22	11.41	9.35

^aEE = encapsulation efficiency; ^bparticle diameter = mean \pm standard deviation; ^cSSA = specific surface area; ^dSLP = slope of Higuchi plot

Microsphere size was $656.14 \mu\text{m}$, $659.19 \mu\text{m}$ and $670.64 \mu\text{m}$ for PEG 600, PEG 6000 and TEC at 10% level of the plasticizers respectively (Table 2). While the plasticizers were used at 40% level, mean particle sizes were $662.5 \mu\text{m}$, $661.32 \mu\text{m}$ and $678.23 \mu\text{m}$ for the plasticizers respectively. Particle size distribution curves of the 10% plasticizers were unimodal in nature where as those of 40% plasticizers were little bimodal in nature.

In vitro release of NS from EC microspheres was observed for 8 hours in phosphate buffer of pH 6.8. Figure 2 shows the zero order release curves of NS. Microspheres were firstly prepared using 10% of plasticizers and release of NS from these batches is shown in figure 2a. At this level of the plasticizers,

almost similar release curves were found for all the plasticizers. Percent release of NS was 93.36% for PEG 600, 93.02% for PEG 6000 and 92.67% for TEC.

However, at 40% level of the plasticizers, significant differences in the release curves of NS were observed (Figure 2b). Release was 81.12% for PEG 600, 70.06% for PEG 6000 and only 51.12% for TEC.

PEG is a plasticizer and this plasticizing activity of PEG has been utilized as a good release retardant while used with different types of polymers in different formulations.²³⁻²⁶ Due to this plasticizer activity, PEG 600 and PEG 6000 were used in this experiment and they retarded release of NS

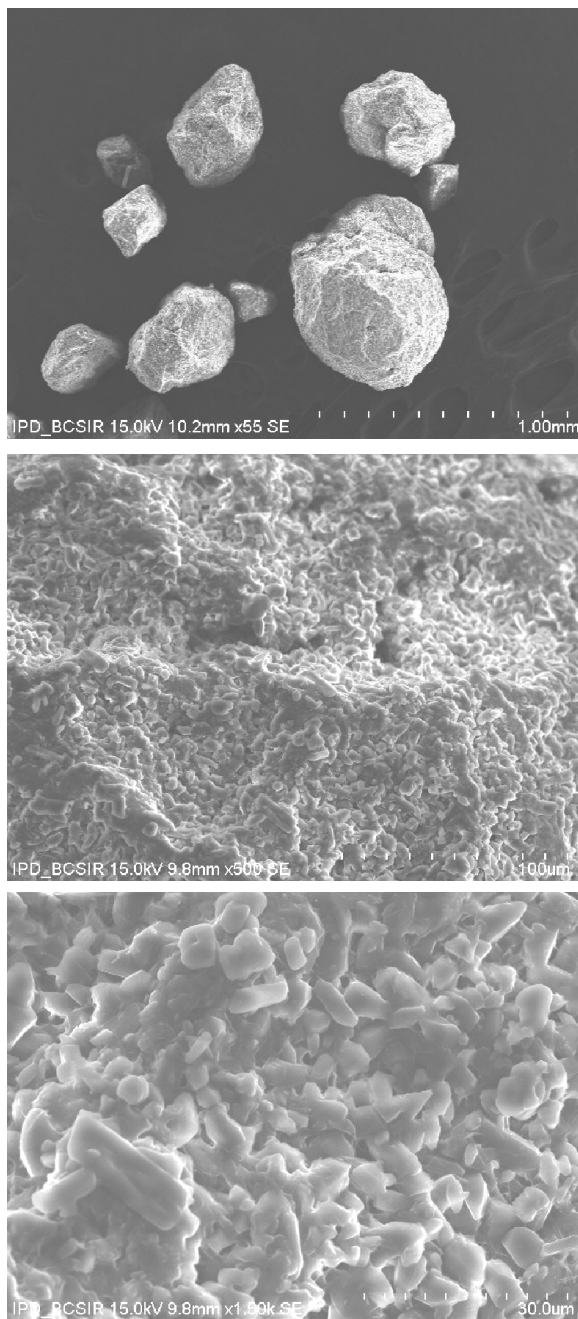


Figure 1. SEM photograph of Ethocel 20cps microspheres of NS containing 40% of TEC at three different magnifications

significantly specially at 40% level. But triethyl citrate (TEC) reduced the release of NS mostly. It is a good plasticizer and is the most widely used plasticizer in aqueous and organic film coatings.²⁷⁻²⁹ TEC is also the most compatible plasticizer for the polymer used in this study. TEC reduces the minimum film forming temperature (MFT) of EC more than any other plasticizer.^{30,31} This plasticizer

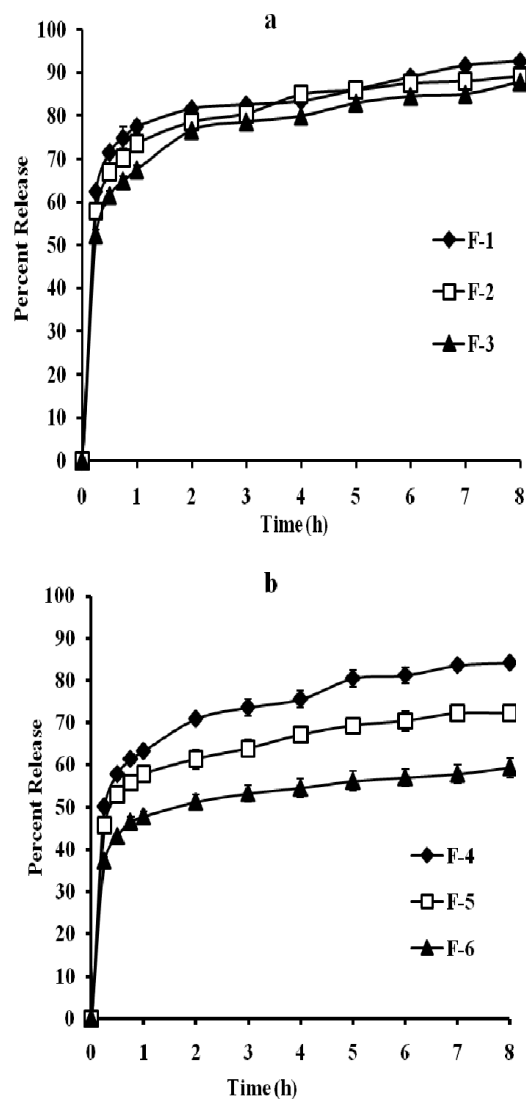


Figure 2. Zero order release of NS from EC microspheres contacting (a) 10% plasticizers and (b) 40% plasticizers

has an official monograph in the current USP/NF.³² This highly plasticizing activity of TEC might be attributable to the most retarded release of NS from the microsphere formulations. Besides, changes in surface of the microspheres are clearly seen from figure 1 and this also elucidates the release controlling behavior of TEC.

Plasticizers generally are used in different sustained release formulations due to their ability of lowering the glass transition temperature (T_g) of different polymers. As the T_g of the polymers are lowered, they become more flexible at a

comparatively lower temperature which ultimately renders the polymers to act as more release retarding agent. For the same purpose, three different plasticizers were considered in this experiment at two different levels. After the addition of the plasticizers at 10% level in the microsphere formulations, NS release was nearly 90% after 8 hours for all the plasticizers where almost 75% of NS was released within first 1 hour. That is, plasticizers at 10% level were quite unable to delay the initial burst release of the drug. But at 40% level of the plasticizers, better release was found. At this level, 62%, 59% and 48% drug was released from PEG 600, PEG 6000 and TEC respectively after first hour of dissolution. In figure 4, percent release of NS after 1 hour is shown for 10% plasticizer (white bars) and 40% plasticizer (black bars) where it is clearly seen that initial burst release of the drug was successfully delayed due to the presence of higher level of the plasticizers.

Release rates (K_h) of NS were also calculated from Higuchi plots (Figure 3). There was a direct

relationship between the rates (K_h) and percent excipient contents (Figure 4). Release rates were significantly smaller while the plasticizers were used at 40% level. When the individual release rates (K_h) were normalized by dividing with the respective microcapsule specific surface area (SSA), there was also a linear relationship between these values (K_h/SSA) and the percent amount of excipients. These values (K_h/SSA) were found to decrease linearly in the order of PEG 600 > PEG 6000 > TEC for both 10% and 40% level (Table 2).

Time for 50% drug release (t_{50}), 75% drug release (t_{75}) and mean dissolution time (MDT) were also calculated to assess the kinetic parameters of the release data (Table 3). Minimum t_{50} and t_{75} were for PEG 600 comprising formulations. On the other hand, maximum t_{50} and t_{75} were for TEC comprising formulations suggesting that these formulations showed more sustained release activity. MDT value of the formulation comprising TEC was also maximum and it was more than 10 hours.

Table 3. Kinetic parameters of naproxen sodium release curves

Batch	r^2 values		n	k	t_{50} (h)	t_{75} (h)	MDT (h)
	Zero	Higuchi					
F1	0.51	0.92	0.097	0.751	0.01	0.99	1.7
F2	0.59	0.96	0.1161	0.714	0.04	1.53	1.9
F3	0.53	0.97	0.1367	0.666	0.12	2.35	2.3
F4	0.57	0.95	0.1441	0.63	0.2	3.33	3.0
F5	0.52	0.97	0.1237	0.566	0.36	9.79	□10
F6	0.67	0.98	0.1204	0.465	1.82	□10	□10

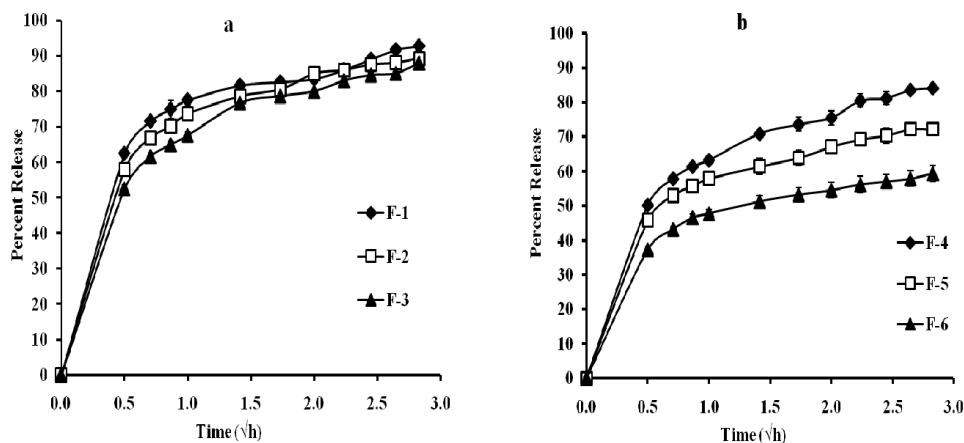


Figure 3. Higuchi release model of NS from EC microspheres contacting (a) 10% plasticizers and (b) 40% plasticizers

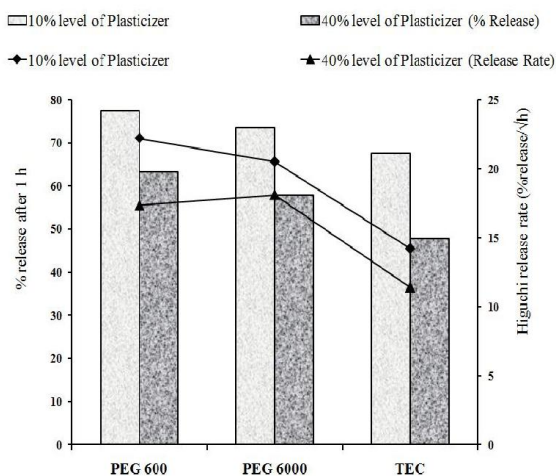


Figure 4. Percent release (bar) and Higuchi release rate (line) of NS from EC microspheres

CONCLUSION

It can be inferred that Ethocel 20 cps can be a good choice to prepare sustained release microspheres of drugs like NS. Optimized batches showed good drug loading capacity having microsphere size within a satisfactory range. All the plasticizers showed good release controlling capacity. Optimized batches showed good release controlling capacity while containing only 40% level of plasticizer in their matrix. But, batches formulated with TEC were comparatively better than others. So, Ethocel 20 cps microspheres comprising TEC could be a good choice to release NS for more than 8 hours in the treatment of arthritis.

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