Biological Forum – An International Journal **15(5a): 510-520(2023)**

ISSN No. (Print): 0975-1130
ISSN No. (Online): 2249-3239

Formulation and Development of Sustained Release Oral Drug Delivery System Comprising Naproxen Sodium Microspheres

Pagar Madhumanjiri K.[1*], Gangurde Avinash B.[2], Pagar Rahul Y.[3] and Bairagi Vinod A. [4]
[1]Department of Pharmaceutics, KBHSS Trust's Institute of Pharmacy,
Malegaon, Dist. Nashik (Maharashtra), India.
[2]Professor, Department of Pharmaceutics,
KBHSS Trust's Institute of Pharmacy, Malegaon, Dist. Nashik (Maharashtra), India.
[3]Assistant Professor, Department of Pharmaceutics,
KBHSS Trust's Institute of Pharmacy, Malegaon, Dist. Nashik, (Maharashtra), India.
[4]Principal, Department of Pharmaceutics,
KBHSS Trust's Institute of Pharmacy, Malegaon, Dist. Nashik (Maharashtra), India.

(Corresponding author: Pagar Madhumanjiri K.)*
(Received: 09 March 2023; Revised: 25 April 2023; Accepted: 05 May 2023; Published: 16 May 2023)
(Published by Research Trend)

ABSTRACT: Designing a sustained release formulation can be complex, as it requires a deep understanding of the drug's physicochemical properties, release kinetics, and compatibility with various excipients. Finding the right combination of polymers, fillers, and other excipients to achieve the desired release profile can be challenging. In the present study, naproxen-loaded polymeric microspheres were compressed into naproxen sustained-release tablets. To prevent the GI side effects of the drugs, research aimed to create simple, affordable sustained-release tablets containing microspheres loaded with naproxen. To formulate the microspheres, an O/W emulsification method was used. An analytical method was developed using a UV- spectrophotometer for about 200-400nm of wavelengths. Later for formulation development, qualitative determination of Naproxen and ethyl cellulose was done in different solvents. Evaluation of microspheres prepared was done in 6.8 phosphate buffer by determining drug loading, percentage of yield, drug release study, X-ray diffraction (XRD), scanning electron microscopic (SEM) analysis, Fourier transform infrared (FT-IR), and In vitro dissolution study and the formulation batches F1, F2, F3, F4, F5, and F6, had DR 100 % at 4 h, 8h, 10h, 12h, 14h, and 24h respectively. The tablets were created using the optimized microsphere formulation naproxen. For the characterization of granules, certain parameters like tapped density, bulk density, a range for angle of repose, Hausner ratio, and Compressibility index were determined for all 5 batches B1, B2, B3, B4, and B5. For the characterization of the tablet, certain parameters like weight, thickness, hardness, friability, and DT were determined.

Keywords: Ethyl cellulose, Microsphere, Naproxen sodium, Oral drug delivery system, Sustained release.

INTRODUCTION

Naproxen sodium (NS) is known as efficient in both performing experiments and also clinical settings like osteoarthritis, juvenile arthritis, rheumatoid arthritis, and acute gout with no severe respiratory or cardiovascular side effects (Uziel *et al.*, 2000; Sajeev *et al.*, 2002). It is a non-steroidal anti-inflammatory drug (NSAID) and its use is frequently limited due to serious gastrointestinal side effects. It has been discovered that the total dosage form has a lower tendency to attach to the esophagus. The medication is readily soluble at high pH and lipid-soluble at low pH when it is nearly insoluble. The formation of a matrix system using inert, hydrophobic, and hydrophilic polymers is the most significant and often utilized technique for controlling drug release. Ethyl cellulose (EC) is a hydrophobic polymer. It is tasteless, odorless, colorless, and inert physiologically and pharmacologically. In the of microcapsule preparation (Hashkes *et al.*, 2003), coating materials for tablets and granules (Pearnchob and Bodmeier 2003; Sadeghi *et al.*, 2003; Dashevsky *et al.*, 2004), and matrix forming materials for sustained release dosage forms (Zabed *et al.*, 2002; Katikaneni *et al.*, 1995), seen to be widely utilized as a solid vehicle pharmaceutically. However, is seen to be demonstrated that EC may be utilized effectively for both water-in-oil and oil-in-water emulsion solvent evaporation procedures (Thies, 1995; Finch, 1990; Jacobs and Mason, 1993), making it a preferred polymer for microencapsulation technology.

One method for regulating drug release and prolonging therapeutic action is microencapsulation (Deasy, 1984). The distinctiveness of microcapsules in pharmaceutical sustained release formulations resides in their extensive diffusion throughout the gastrointestinal (GI) system. As a result, there may be a reduction in side effects and the localized building up of irritant drugs contrary to the GI mucosa (Kondo, 1979). Microencapsulation of NSAIDs reduced the occurrence and severity of gastrointestinal and CNS side effects when compared to

traditional tablet and capsule formulations, according to a thorough literature review. Sustained release drug delivery systems have a variety of benefits over conventional dosage forms (Lachman *et al.,* 1976; Li *et al.,* 1988). Because of its short half-life, naproxen was chosen as the model drug, of side effects in the gastrointestinal tract, as well as the fact that it is soluble in alcohol but not in water (Kumar and KB, 2016).

The purpose of this research was to compress naproxen-loaded polymeric microspheres into naproxen sustained-release tablets. The study aimed to develop simple and cost-effective sustained-release tablets containing naproxen-loaded microspheres to avoid the GI complications associated with the drug. The microspheres were formulated by an O/W emulsification method. An analytical method was developed using a UV- spectrophotometer for about 200-400nm of wavelengths. Later for formulation development, qualitative determination of Naproxen and ethyl cellulose was done in different solvents. For the characterization of microspheres, the yield was determined.

MATERIALS AND METHODS

Materials

Naproxen sodium was received as a generous gift from Dr. Reddy's Limited, Hyderabad, India. The given chemicals were acquired from the specific sourcing utilized as received: ethyl cellulose (Loba Chemie, Mumbai, India), Tween 80 (Sigma-Aldrich, Mumbai, India), Microcrystalline cellulose (MCC) (JRS Pharma, India), Lactose anhydrous (DFE Pharma, India), Cross carmelose sodium (Signet, Mumbai, India), Magnesium stearate (Nikita Chemicals, Nagpur, India), Dichloromethane (Loba Chemie, Mumbai, India), Methanol (Loba Chemie, Mumbai, India).

Methods

Preformulation studies

Solubility study. Phosphate buffer pH 7.4, 6.8, and 5.8 and distilled water were used to determine the solubility of naproxen. The excess drug was added to 10ml of respective solvent and the stirring of the solution was done for 24 hours at 37^0C and was readily equilibrated. After 24 hours the sample was withdrawn and filtered via a membrane filter and then analyzed in a UV-visible spectrophotometer (Kumar *et al.,* 2015).

Preparation of Naproxen-loaded microspheres of ethyl cellulose by O/W emulsification method

Weighed quantity of tween 80 was added to the beaker containing water (Aqueous phase) as an external phase and kept for 30 min with stirring. Weighed quantities of drug and polymer were dissolved in DCM and sonication was done for 10 min to obtain a transparent and clear solution. Drug polymer solution (Organic phase) was moved in a 10 ml syringe, addition was done dropwise into the aqueous phase at constant RPM of the overhead stirrer according to the formula to give O/W. Table 1 enlists the formula composition of the initial batches. Optimization of Naproxen-loaded microspheres of ethyl cellulose by O/W emulsification method. Table 2 enlists the formula composition of Optimisation batches.

Table 1: Formula composition of initial trials.

Sr. No.	Name of the ingredients					
Batch No.	**Naproxen**	**Ethyl Cellulose**	**Tween 80**	**DCM**	**Water**	**RPM**
1	200 mg	200 mg	0.3 ml	20 ml	100 ml	1000
2	200 mg	400 mg	0.3 ml	20 ml	100 ml	1000
3	200 mg	600mg	0.3 ml	00 ml	100 ml	1000

Table 2: Formula composition of optimisation batches.

Sr. No.	Ingredients					
Batch No.	**Naproxen**	**Ethyl Cellulose**	**Tween 80**	**DCM**	**Water**	**RPM**
1	200 mg	600 mg	0.3 ml	20 ml	100 ml	1000
2	200 mg	700 mg	0.3 ml	20 ml	100 ml	1000
3	200 mg	800 mg	0.4 ml	30 ml	100 ml	1000
4	200 mg	900 mg	0.4 ml	30 ml	100 ml	1000
5	200 mg	1000 mg	0.5 ml	40 ml	100 ml	1000
6	200 mg	1200 mg	0.5 ml	40 ml	100 ml	1000

Characterization of Microspheres

The yield of microspheres

Each batch of naproxen-loaded microspheres was precisely weighed, and the formula was used to determine the yield of microspheres (Khairnar *et al.,* 2014).

% Yield= Weight of dried microsphere/Weight of drug + Weight of polymer×100 …(1)

DL determination

Microspheres containing 10 mg of Naproxen after weighing were mixed with enough DCM to dissolve the polymeric coating. The addition of a suitable quantity of 6.8 phosphate buffer was done in the solution to extract the drug. Stirring was continued until all of the DCM had evaporated. Whatman filter paper was used to filter the dispersion. A UV spectrophotometer was

used to examine the drug-containing filtrate following dilutions at 240
nm. The following formula was used to compute DL from an absorbance (Masaeli *et al.,* 2016).

% DL = Drug Entrapped / Weight of Microspheres ×100 ...(2)

In vitro dissolution studies

The XXVIII equipment, Type I, was used to conduct in vitro dissolution studies for 12 hours by utilizing the rotating paddle method. Naproxen-loaded microspheres containing 60 mg of NTG were added to the dissolution media (6.8 phosphate buffer) at a speed of 100 rpm at a temperature of 37 ± 0.5°C. The aliquots of the dissolution medium were taken at regular intervals and replaced with new dissolution media to keep the sink condition. Whatman filter paper no 41 was used to filter the samples. A UV spectrophotometer was used to evaluate the samples spectrophotometrically at 240 nm. Three different determinations were assigned their means. Any errors resulting from EC were corrected.

Fourier transforms infrared spectroscopy study (FTIR)

Using an FTIR spectrophotometer, the Naproxen infrared spectra, EC, and Naproxen-loaded microspheres were achieved by utilizing the potassium bromide pellet technique. Sample (1 mg) and potassium bromide (40 mg) were mixed and made into a disc by hand. Spectra were collected in the scan range of 4,400–500 cm^{-1}.

X-ray diffraction study (XRD). X-ray diffraction was used to investigate the physical condition (crystalline or amorphous) of Naproxen, EC, and Naproxen-loaded microspheres. X-ray diffractometer employed with Ni-filtered Cu-ka radiation (k = 1.5406 A), with a voltage of 40 kV, and a current of 40 mA was used to perform a powder X-ray diffractometer. The scanning rate was 0.06/min, over a 2h range of 20°C –80°C.

Scanning electron microscopy (SEM)

SEM was used for the evaluation of microsphere features such as size, shape, and surface. At a distance of 8.6–8.7 mm the SEM was used with a 1.0 kV accelerating voltage.

Development of fast disintegrating sustained-release tablets containing Naproxen sodium microspheres by direct compression method

The direct compression process was used to make Naproxen sustained-release tablets. The tablets were created using the optimized microsphere formulation naproxen. All of the materials were weighed and sieved #40 before collection and mixing in a specified geometric order. Separately weighed 50 mg equivalent Naproxen microsphere and addition was done to the aforesaid mixture of components. Tablet compression with a 15 mm punch using a tablet compression machine to produce 1200 mg tablets was done. Table 3 shows the formula composition of all batches. The produced tablets were utilized in the following tests.

Table 3: Formula composition of tablets.

Sr. No.	Ingredient Name	B1	B2	B3	B4	B5
1	Naproxen Microspheres eq. to 50 mg	437	437	437	437	437
2	MCC 101	365	359	353	347	341
3	Lactose	368	362	356	350	344
4	CCS	24	36	48	60	72
5	Mg. stearate	6	6.0	6.0	6.0	6.0
6	Total	1200	1200	1200	1200	1200

Characterization of granules

Bulk density. A 50 cm^3 (blend) sample was cautiously placed in a 100ml graduated cylinder. For two seconds, drop the cylinder three times from a height of one inch onto a hardwood surface. Divide sample weight in gms by the final volume in cubic meters for calculating the Bulk density (Ziyaur *et al.,* 2006) and the formula is

Bulk density (Bd) = Mass of the powder (M) / Bulk volume (VB) ...(3)

Tapped density. By tapping the powder 500 times, the volume was obtained. Tapped density tester was used to do the mechanical tapping of the cylinder and the tapped volume was taken. (Bodea and Leucuta, 1997). It is given by the formula

Tapped density (Td) = Mass of the powder (M) / Tapped volume (VT) ...(4)

The angle of repose. The angle of repose used the funnel method to determine the powder blend. The accurate weight of the powder blend was removed in the funnel. The funnel height adjustment was done such that the funnel tip should touch the powder blend apex. The powder blend was made to flow via the funnel on the surface freely. The powder cone diameter was calculated and the angle of repose was also determined using the following formula. (Dortus and Gunal, 1994). The angle of repose specifications as per IP is given as

$$\text{Tan } ° = h/r \quad ...(5)$$

Where, h = height of the powder cone, r = radius of the powder cone, °=angle of repose.

Carr's index or % compressibility and Hausner ratio (Qureshi *et al.,* 2014). Expressed in percentage and given by the formula

% Compressibility (% I) = Td – Bd / Td × 100...(6)

Where Td is tapped density and bd is bulk density.

Characterization of the tablets

Weight variation test. By weighing tablets, the weight variation test was done and the average weight was calculated. Each tablet shall stay within certain limits. If NMT two tablets are outside the percentage limit and no tablet differs by more than two times the percentage limit, the tablets are subjected to the USP test (Soppimath *et al.,* 2001).

Uniformity of thickness and diameter. A Vernier caliper was used to measure the diameter and thickness of tablets at three different positions. The mean (±SD) of three measurements was used to report the results (Soppimath *et al.*, 2001).

Hardness. The hardness of the tablets was determined by a Monsanto hardness tester. Each's average hardness was found. The tensile strength of a tablet is measured by the load/pressure required for crushing it by placing it on its edge (Soppimath *et al.*, 2001).

Friability. Friabilator, a laboratory friability tester is used to determine the friability of the tablets. The percentage loss in tablet weight before and after 100 tablet revolutions was determined, and the percentage friability was calculated. The weight loss should not be more than 1 % (Modi and Seth 2010).

Disintegration test. The disintegration test apparatus is used to perform this on six tablets. The disintegration medium was 900 mL saline pH 7.4 phosphate buffer at 37 0.50 °C, and the time it took for the tablet to completely disintegrate without any palpable mass left in the apparatus was measured in seconds (Modi and Seth 2010).

Dissolution test. For the drug release study, prepared tablets containing Naproxen were employed. The in vitro dissolution studies were carried out in triplicate at 100 rpm using USP apparatus type II. The dissolution medium was 900 mL of saline pH 7.4 phosphate buffer kept at 37 0.50 C. At different times, aliquots of dissolution media were extracted and filtration was done through a 0.22-micron filter. Drug release was determined when the samples were analyzed at 240 nm (Modi and Seth 2010).

RESULTS

Preformulation study

Saturation solubility. On UV analysis, drug concentration in each medium was reported in Table 4.

The solubility study indicates that the drug has a solubility that is pH-dependent as solubility is raised with rising pH. The present study shows lower drug solubility in distilled water (100µg/ml) when compared to pH buffer 5.8 and 6.8. Naproxen showed the least solubility (10µg/ml) in 0.1N HCl. It was observed that naproxen showed good solubility in buffer pH 7.4 (650µg/ml). The comparative solubility of naproxen in respective solvents can be studied (Fig. 1).

The solubility of naproxen is due to the unionization of the drug at lower pH ranges. Although the unionized drug is facilitated through the membrane ensuring its permeability, the solubility becomes a problem. The results of the solubility study show a similar trend as indicated in the literature.

Development of Naproxen-loaded microspheres of ethyl cellulose by O/W emulsification

Preliminary batches of naproxen-loaded microspheres

Preliminary batches were prepared according to the given formulation and microsphere formation was observed. The following results were reported in Table 5.

Table 4: Saturation solubility of Naproxen.

Sr. No.	Medium	Concentration
1.	Distilled water	100µg/ml
2.	0.1N HCl	10 µg/ml
3.	Buffer pH 5.8	200 µg/ml
4.	Buffer pH 6.8	350 µg/ml
5.	Buffer pH 7.4	650 µg/ml

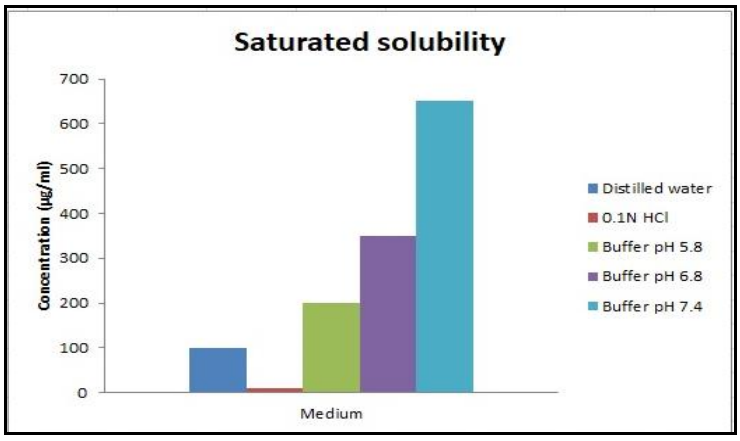

Fig. 1. Saturated Naproxen solubility in various mediums.

Table 5: Observation of naproxen-loaded microspheres.

Ingredient (Batch No)	Naproxen	Ethyl Cellulose	Observation
1	200 mg	200 mg	No microspheres observed
2	200 mg	400 mg	No microspheres observed
3	200 mg	600 mg	Microspheres Observed

It has been observed that no microspheres were formed in the initial two preliminary trials. In the third batch, microspheres were observed by using the O/W solvent emulsification method. Further optimization in terms of the concentration of polymer.

Characterization of Optimised Microspheres

Yield of microspheres. The microsphere's yield was seen to be in the range of 96.8–98.8 % of total solid content employment through the microsphere's formulations. Table 6 and Fig. 2 represent the information on the yield of microspheres. The percentage yield of microspheres was found to be more. It was seen that polymer and microspheres from the external phase were collected properly which is a reason for the high percentage yield.

Table 6: Yield of microspheres.

Sr. No.	Batch No	% Yield	% DL
1	F1	96.8	12.5
2	F2	97	16.8
3	F3	98.5	22.5
4	F4	98	25.9
5	F5	97.5	28.12
6	F6	98.8	33.14

Determination of DL and DR. The drug loading was obtained to be in the range of 12.5 % (F1) to 33.14 % (F6). Table 8 shows the DL of all batches. The DL value measurement for all batches is seen to have huge variation. It was observed that as the concentration of ethyl cellulose was raised in the formulation from F1 to F6, drug loading was seen to increase from a minimum of 12.5 % (F1) to a maximum of 33.14 % (F6).

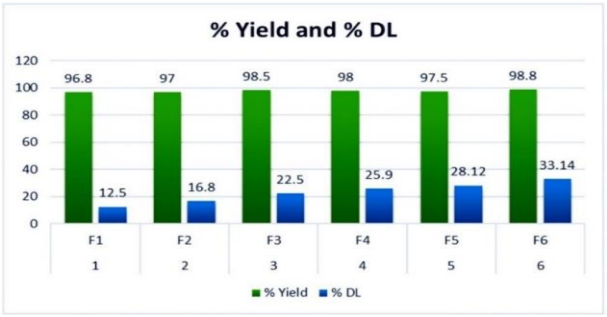

Fig. 2. % Yield and % DL.

***In vitro* dissolution studies.** In 6.8 phosphate buffer *in vitro* dissolution study was performed and the formulation batches were F1, F2, F3, F4, F5, and F6, which had DR 100 % at 4 h, 8h, 10h, 12h, 14h, and 24h respectively as given in Table 7. Ethylcellulose acts as a sustained-release polymer and helps in tight encapsulation of the microsphere. As its concentration is increased in the formulation it leads to the slow release of the drug. The optimized batch was found to be F6 with 100% DR for 24h concerning drug release as ethyl cellulose concentration was highest in the batch. The comparative drug release profile of microspheres in pH 6.8 phosphate buffer can be seen in Fig. 3.

Table 7: Microsphere's in vitro dissolution studies.

Time (Hr)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	40	32	27	22	14	9
2	70	62	52	35	22	15
4	100	82	70	49	32	27
8		100	90	65	51	35
10			100	89	79	52
12				100	92	65
14					100	78
24						100

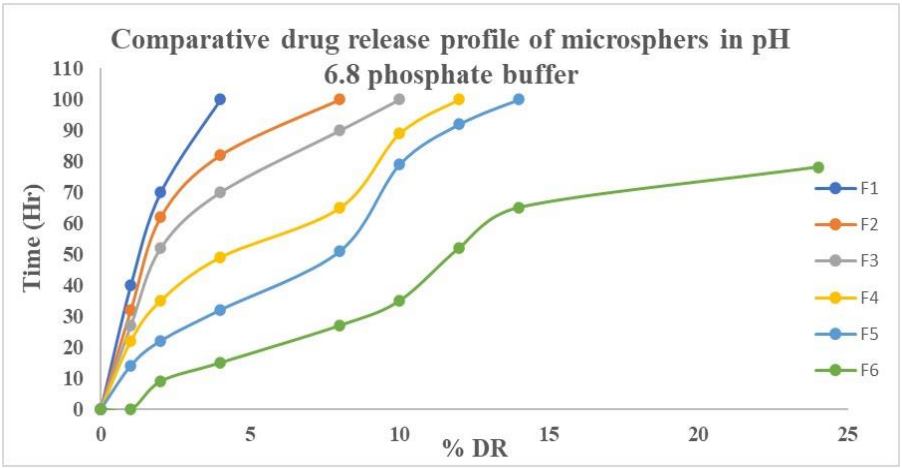

Fig. 3. The comparative drug release profile of microspheres in pH 6.8 phosphate buffer.

Fourier transform infrared spectroscopy study (FTIR). In Fig. 4 the FT-IR spectra of the drug, polymers, and its physical mixtures are shown. A= naproxen, B= Ethylcellulose, C= Microspheres. The drug sample shows characteristic functional group peaks at 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}. The ethylcellulose FT-IR spectrum shows a distinctly seen band at 3482 cm^{-1} that attributes to -OH stretching vibration. The asymmetric band was found for 2970-2870 cm^{-1} might be because of C-H stretching vibration. The FT-IR of the physical mixture of microspheres formulation showed a characteristic peak of the drug, and the polymer revealed that all peaks were easy to detect in the physical mixture. Hence there was no interaction between drug and excipient and therefore, no incompatibility is seen.

X-ray diffraction (XRD) study. In Fig. 5 (A), the distinctly seen sharp peaks of naproxen are seen to be acquired at the diffraction angles 14.50, 17.73, and 27.45. Hence, the nature of pure naproxen being crystalline is evident from its XRD spectrum. The ethylcellulose (B) showed no sharp peaks hence, it is found to be amorphous. Pure Naproxen showing crystalline peaks of the drug disappear in Naproxen-loaded ethyl cellulose microspheres (C). Naproxen was found to be of some percentage crystalline and amorphous nature when converting in microspheres of ethyl cellulose. This evidence shows an indication that Naproxen is extremely distributed and disordered and homogeneously in microspheres in an amorphous form.

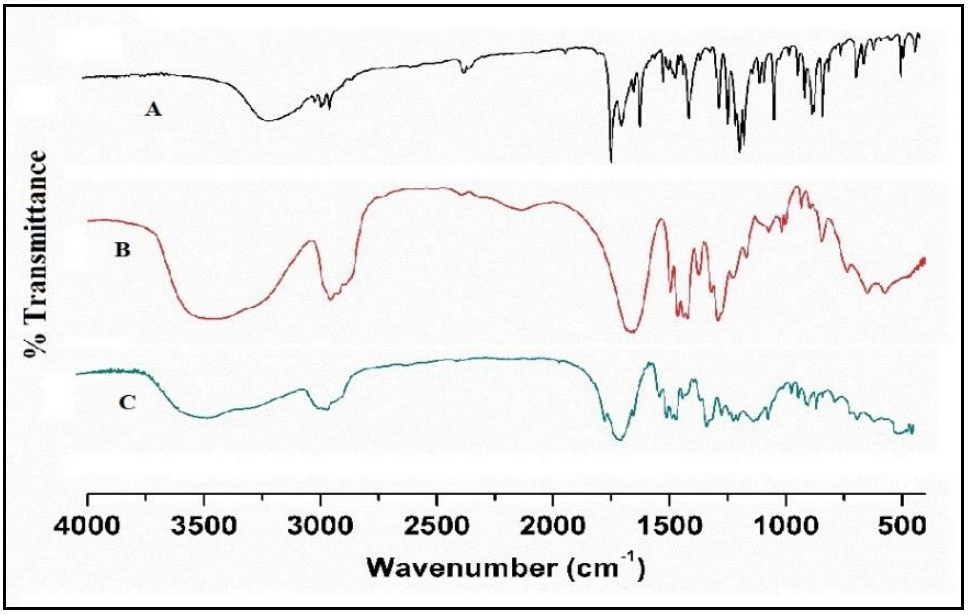

Fig. 4. FT-IR spectra of drug, polymer, and its physical mixtures (microspheres), where A= naproxen, B= Ethylcellulose, C= Microspheres.

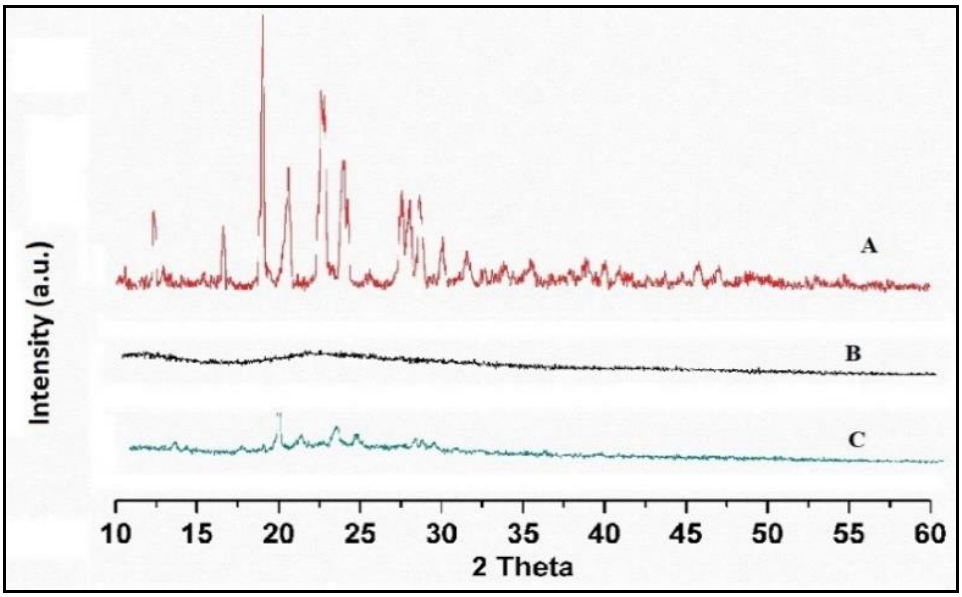

Fig. 5. PXRD spectrum of pure naproxen, polymer, and their physical mixtures (microspheres), where A= naproxen, B= Ethylcellulose, C= Microspheres.

DSC study. The DSC curve of Naproxen profiles (Fig. 6-A) clear view of the endothermic peak at 155^0C was observed corresponding to its melting point (152^0C) & indicating its purity & shows the drug in crystalline form. XRD of ethyl cellulose (B), shows crystallinity in the systems to some extent. The sharp endothermic peak vanishes in curve C of the microspheres and is not seen at any temperature. This is an indication of proper encapsulation of the drug in the microsphere and its conversion from crystalline to amorphous form. As the drug is properly encapsulated temperature has not reached up to the encapsulated drug and hence, it is not melted at its melting point.

Scanning electron microscopy (SEM). By using SEM, the surface morphology of Naproxen-loaded microspheres was analyzed. The FE-SEM photograph of the microsphere's surface showed in Fig. 7. The microspheres were seen to be spherical, smooth, and with no surface cracks, also they were free-flowing and discrete. The sphericity of the microspheres was good.

.

The particle size of the microspheres was seen to be less than 5 µm and up to a maximum of 5 µm. With no erosion and cracking the microsphere surface was regular and smooth. The surface of the microsphere had no pores. Because of no pores and cracks, there will be fewer possibilities of the drug leaching out the ethylcellulose from the polymeric coat which maybe results in the sustained release of the drug from the microspheres.

Developing fast disintegrating sustained-release tablets containing Naproxen sodium microspheres by direct compression method.

Characterization of granules

Bulk density. The Bulk density was obtained as 1.15, 1.19, 1.27, 1.3, and 1.35 for B1, B2, B3, B4, and B5 respectively as given in Table 10.

Tapped density. The Tapped density was found to be 1.22, 1.25, 1.32, 1.39, and 1.4 for B1, B2, B3, B4, and B5 respectively as given in Table 8.

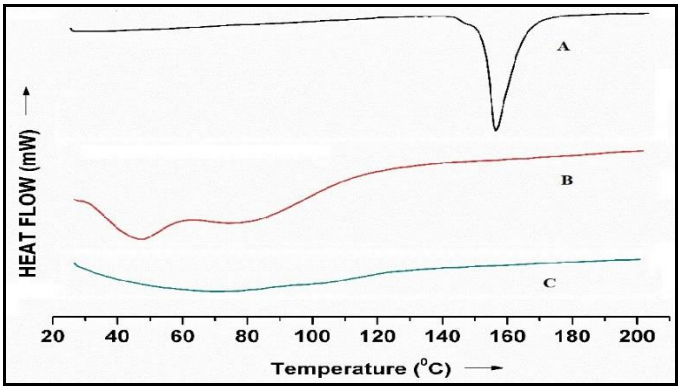

Fig. 6. DSC curve of the drug, polymer, and their physical mixtures (microspheres), where A= naproxen, B= Ethylcellulose, C= Microspheres.

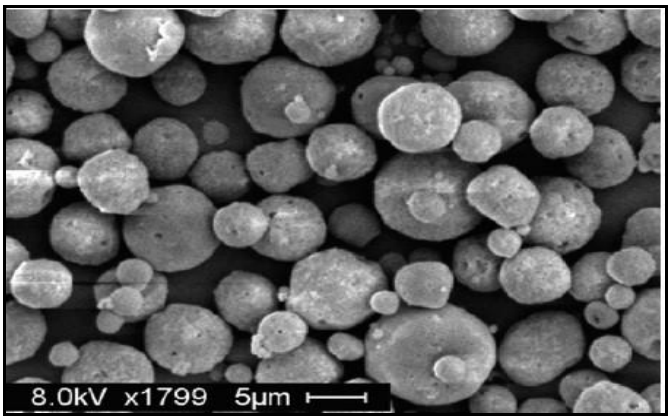

Fig. 7. Photographs of FE-SEM of microspheres surface.

Table 8: Flow properties of the granules.

Batch No	B1	B2	B3	B4	B5
BD (g/ml)	1.15	1.19	1.27	1.3	1.35
TD (g/ml)	1.22	1.25	1.32	1.39	1.4
CI	5.74	4.8	3.79	6.47	3.57
HR	1.06	1.05	1.04	1.07	1.04
Angle of repose	34	32	29	27	26

Angle of repose. The angle of repose was obtained as 34^0, 32^0, 29^0, 27^0, and $26^0$for B1, B2, B3, B4, and B5 batches respectively which is mentioned in Table 8. The range was found to be between 26□ to 34□ and hence the granules have excellent flow properties.

Car's index. CI was found to be 5.74, 4.8, 3.79, 6.47, and 3.57 for B1, B2, B3, B4, and B5 batches respectively which is mentioned in Table 8. The range was found to be < 10 and hence the granules have excellent flow properties.

Hausner ratio. Hausner ratio was found to be 1.06, 1.05, 1.04, 1.07, and 1.04 for B1, B2, B3, B4, and B5 batches respectively which is mentioned in Table 8. The range was found to be between 1.00–1.11 and hence the granules have excellent flow properties.

Considering BD, TD, Angle of repose, Hausner ratio, and Compressibility index, the tablet blend shows excellent flow properties. So, there were no compressibility issues encountered.

Characterization of the tablets

Weight variation test. The weight of the tablet for B1, B2, B3, B4, and B5 was found to be 1200, 1199, 1200, 1198, and 1200g respectively as given in Table 9. There is uniformity seen in the weights of the tablets in all 5 batches.

Uniformity of thickness and diameter. The tablet thickness for B1, B2, B3, B4, and B5 was found to be 7.3, 7.3, 7.4, 7.5, and 7.6mm respectively and the diameter was 14.9, 15, 14.8, 14.9, 15mm respectively and which is in close range in all the batches and hence is seen to be uniform throughout as given in Table 9.

Hardness. The Hardness was obtained in the range of 3-4 N for all tablets in the 5 batches. This was seen to be uniform throughout as given in Table 9.

Friability. The friability of the tablet for B1, B2, B3, B4, and B5 was found to be 0.59, 0.67, 0.58, 0.62, and 0.52 respectively as given in Table 9. As the range of friability is NMT 1% the compressed tablets have good resistance.

Disintegration test. The DT of the tablet for B1, B2, B3, B4, and B5 was found to be 1200, 1199, 1200, 1198, and 1200 sec respectively as given in Table 9. The DT is found to decrease from B1 for 82 sec to B5 for 19 sec. This effect is seen due to the increased concentration of croscarmellose as a super disintegrant from B1 to B5. Hence, tablet disintegration occurs faster in the optimized batch B5 for about 19 sec leading to faster release of microspheres.

Dissolution test. From Fig. 8. and Table 10, at the end of 24h batch, B5 achieves a 100% drug release and hence is considered the optimized batch. If we make such microsphere-containing formulations a sustained-release activity can be achieved. An alternate medication strategy is introduced by not only using the pure drug but by formulating naproxen-loaded ethyl cellulose microspheres. This will lead to sustained release and later can be encapsulated in a tablet dosage form. Such tablet dosage form will give drug release up to 24h and ultimately it will reduce the dosing frequency. There might be no need for multiple administration of doses.

Table 9: Characterization of the tablets.

Batch	Tablet weight	Thickness (mm)	Diameter (mm)	Hardness (N)	Friability (%)	DT (sec)
B1	1200	7.3	14.9	3	0.59	82
B2	1199	7.3	15	3.5	0.67	75
B3	1200	7.4	14.8	4	0.58	55
B4	1198	7.5	14.9	3	0.62	40
B5	1200	7.6	15	3.8	0.52	19

Table 10: In pH 6.8 phosphate buffer: Dissolution profile of tablets.

Time (Hr)	B1	B2	B3	B4	B5
0	0	0	0	0	0
1	35	31	29	21	20
2	60	65	69	30	29
4	75	89	84	45	43
8	90	93	92	70	56
10	100	100	97	89	62
12			100	95	84
14				100	92
24					100

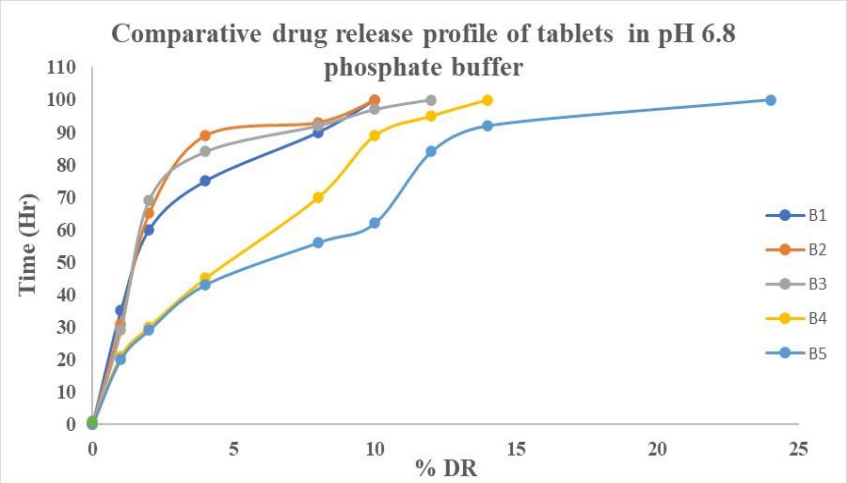

Fig. 8. The comparative drug release profile for tablets in pH 6.8 phosphate buffer.

DISCUSSION

The purpose of this research was to compress naproxen-loaded polymeric microspheres into naproxen sustained-release tablets. The study aimed to develop simple and cost-effective sustained-release tablets containing naproxen-loaded microspheres to avoid the GI complications associated with the drug. The microspheres were formulated by an O/W emulsification method (Nakashima *et al.,* 2000, Nag *et al*., 2022). Later for formulation development, qualitative determination of Naproxen and ethyl cellulose was done in different solvents. For the characterization of microspheres, the yield was determined and was found to be in the range of 96.8–98.8 % of total solid content utilized for the formulation of microspheres. The microspheres form the external phase and the polymer was collected properly which is a reason for the high percentage yield. The observation of there increase in the concentration of ethyl cellulose there was an increased in the formulation from F1 to F6 and therefore, drug loading was seen to increase from a minimum of 12.5 % (F1) to a maximum of 33.14 % (F6). In 6.8 phosphate buffer performance of in vitro dissolution study was done and the formulation batches F1, F2, F3, F4, F5, and F6, had DR 100 % at 4 h, 8h, 10h, 12h, 14h, and 24h respectively. Ethylcellulose acts as a sustained-release polymer and helps in tight encapsulation of the microsphere. As its concentration is increased in the formulation it leads to the slow release of the drug (Khandbahale, 2020). The optimized batch was found to be F6 with 100% DR for 24h. as the concentration of ethyl cellulose was highest in the batch and also by considering other parameters like the yield, and DL.

The FT-IR of the physical mixture of microspheres formulation did show the drug's characteristic peak, and the polymer revealed that all peaks were easy to detect in the physical mixture. Therefore, no interaction between drug and excipient is seen and hence no incompatibility is seen. XRD studies show that Naproxen was seen as crystalline and amorphous to some percentage while converting into microspheres of ethyl cellulose. Naproxen is seen to be highly disordered and homogeneously distributed in an amorphous form in microspheres as per the evidence. The sharp endothermic peak is seen to vanish in the DSC curve of the microspheres and is not seen at any temperature. This is an indication of proper encapsulation of the drug in the microsphere and its conversion from crystalline to amorphous form. As the drug is properly encapsulated temperature has not reached up to the encapsulated drug and hence, it is not melted at its melting point. Scanning electron microscopy was utilized for analyzing the surface morphology of Naproxen-loaded microspheres. The FE-SEM photograph of the surface of the microspheres was determined to be spherical, smooth, and with no surface cracks. The microsphere particle size was determined to be less than 5 µm and up to a maximum of 5 µm. As no pores and cracks are seen, it will show fewer possibilities for drug leaching out from the ethyl cellulose polymeric coat and hence result in the sustained release of the drug from microspheres.

A direct compression process was used to make fast disintegrating Naproxen sustained-release tablets. The tablets were created using the optimized microsphere formulation naproxen. For the characterization of granules, certain parameters were determined for all the 5 batches B1, B2, B3, B4, and B5; the bulk density was found to be 1.15, 1.19, 1.27, 1.3, and 1.35 respectively, the tapped density was found to be 1.22, 1.25, 1.32, 1.39, and 1.4 respectively. The range for angle of repose was found to be between 26°C to 34°C, for CI the range was found to be < 10, and for the Hausner ratio, the range was found to be between 1.00–1.11. Considering BD, TD, Angle of repose, Hausner ratio, and Compressibility index, the tablet blend shows excellent flow properties (Tan *et al.,* 2015). So, there are was no compressibility issues encountered.

For characterization of the tablets, certain parameters were determined for the batches B1, B2, B3, B4, and B5 where the weight of the tablet was found to be 1200, 1199, 1200, 1198, and 1200g respectively, and the thickness of the tablet was found to be 7.3, 7.3, 7.4, 7.5, and 7.6mm respectively and the diameter was 14.9, 15, 14.8, 14.9, 15mm respectively. In the range of 3-4 N, hardness was found for all the tablets in the 5 batches. All these values are in close range in all the batches and hence show uniformity throughout (Parashar *et al.,*

2012). The friability of the tablet was from ranging 0.52- 0.67 respectively**.** As the range of friability is NMT 1% the compressed tablets have good resistance. The DT of the tablet for all 5 batches was found to be 1200, 1199, 1200, 1198, and 1200 sec respectively**.** The DT is found to decrease from B1 for 82 sec to B5 for 19 sec. This effect is seen due to the increased concentration of croscarmellose as a super disintegrant from B1 to B5. Hence, tablet disintegration occurs faster in the optimized batch B5 for about 19 sec leading to faster release of microspheres. At the end of the 24h batch, B5 achieves a 100% drug release and hence is considered the optimized batch (Nandy *et al.*, 2011). If we make such microsphere-containing formulations a sustained-release activity can be achieved.

CONCLUSION

An alternate medication strategy is introduced by not only using the pure drug but by formulating naproxen-loaded ethyl cellulose microspheres. This will lead to sustained release and later can be encapsulated in a tablet dosage form. Such tablet dosage form will give drug release up to 24h and ultimately it will reduce the dosing frequency. There might be no need for multiple administration of doses. By O/W emulsification technique, fast disintegrating tablets were made by conversion of microspheres. Later we can successfully make formulations that show reduced dosing frequency which will help to avoid the GI complications associated with the pure drug. The tablets might enhance patient compliance by improving the taste and swallowing ability of pediatric and geriatric patients. There may be less chance of missing the dose.

FUTURE SCOPE

We still have only the *in vitro* data whereas the *in vivo* study is needed to check its behavior in the biological system. Hence, there is a need to perform preclinical studies. *In vitro- in vivo* correlation is significant as part of the formulation development strategy. So, the prospects of the studies will include proper preclinical studies in suitable animal models.

Acknowledgment. The authors are grateful to thank for the Respected Principal Dr Vinod Bairagi for providing facilities to complete this research work.
Conflict of interest. None.

REFERENCES

Bodea, A. and Leucuta, S. E. (1997). Optimization of hydrophilic matrix tablets using a D-optimal design. *International journal of pharmaceutics, 153*(2), 247-255.

Dashevsky, A., Kolter, K. and Bodmeier, R. (2004). Compression of pellets coated with various aqueous polymer dispersions. *International journal of pharmaceutics, 279*(1-2), 19-26.

Deasy, P. B. (1984). Microencapsulation and Related Drug Processes (New York: Marcel Dekker, Inc.), 361.

Dortus, B. and Gunal, I. V. (1994). Development and in vitro evaluation of acetazolamide SR formulation. *Int. J. Pharm., 112*, 46-56.

Finch, C.A. (1990). Ullman's Encyclopedia of Industrial Chemistry. VCH Publishers, New York, *16*(5), 575-588.

Hashkes, P. J., Tauber, T., Somekh, E., Brik, R., Barash, J., Mukamel, M. and Uziel, Y. (2003). Naproxen as an alternative to aspirin for the treatment of arthritis of rheumatic fever: a randomized trial. *The Journal of pediatrics, 143*(3), 399-401.

Iqbal, Z., Babar, A. and Ashraf, M. (2002). Controlled-release naproxen using micronized ethyl cellulose by wet-granulation and solid-dispersion method. *Drug development and industrial pharmacy, 28*(2), 129-134.

Jacobs, I. C. and Mason N. S. (1993). In Polymeric Delivery Systems, ACS Symposium Series 520 (M. A. El-Nokaly, D. M. Piatt, and B. A. Charpentier, eds.), American Chemical Society, Washington, DC, 1-17.

Katikaneni, P. R., Upadrashta, S. M., Neau, S. H. and Mitra, A. K. (1995). Ethylcellulose matrix-controlled release tablets of a water-soluble drug. *International journal of pharmaceutics, 123*(1), 119-125.

Khairnar, G., Mokale, V. and Naik, J. (2014). Formulation and development of nateglinide loaded sustained release ethyl cellulose microspheres by O/W solvent emulsification technique. *Journal of Pharmaceutical Investigation*, *44*(6), 411-422.

Khandbahale, S. V. (2020). Microencapsulation-A novel approach in drug delivery: a review. *Asian Journal of Research in Pharmaceutical Science, 10*(1), 39-50.

Kondo, A. (1979). Microencapsulation Processing and Technology, Marcel Dekker, New York.

Kumar, L., Suhas, B. S., Pai, G. K. and Verma, R. (2015). Determination of saturated solubility of naproxen using UV visible spectrophotometer. *Research Journal of Pharmacy and Technology*, *8*(7), 825-828.

Kumar, S. and KB, C. S. (2016). Preparation and evaluation of Naproxen Sodium-loaded Chitosan microspheres. *International Journal of Research in Phytochemistry and Pharmacology*, *6*(1), 1-8.

Lachman, L., Lieberman, H. A. and Kanig, J. L. (1976). The theory and practice of industrial pharmacy (pp. 412-428). Philadelphia: Lea & Febiger.

Li, S. P., Kowarski, C. R., Feld, K. M. and Grim, W. M. (1988). Recent advances in microencapsulation technology and equipment. *Drug Development and Industrial Pharmacy, 14*(2-3), 353-376.

Masaeli, R., Kashi, T. S. J., Dinarvand, R., Tahriri, M., Rakhshan, V. and Esfandyari-Manesh, M. (2016). Preparation, characterization, and evaluation of drug release properties of simvastatin-loaded PLGA microspheres. *Iranian journal of pharmaceutical research: IJPR, 15*(Suppl), 205.

Modi, V. C. and Seth, A. K. (2010). Formulation and evaluation of diltiazem sustained release tablets. *Journal of global trends in pharmaceutical sciences, 1*(3), 1-10.

Nag, R., Sahoo, H. S. and Samantaray, S. M. (2022). Dynamic Light Scattering of *Chlorogloeopsis fritschii* BK (MN968818) Mediated Zinc Oxide Nanoparticles at different Temperatures. *International Journal of Theoretical & Applied Sciences*, *14*(1), 19-21.

Nakashima, T., Shimizu, M. and Kukizaki, M. (2000). Particle control of emulsion by membrane emulsification and its applications. *Advanced drug delivery reviews, 45*(1), 47-56.

Nandy, B. C., Mazumder, B., Pathak, K., Saxena, N., Jain, S., Sharma, S. and Saxena, P. (2011). An overview of fast dissolving drug delivery system. *Asian Journal of pharmaceutical sciences and research, 1*(2), 1-30.

Parashar, B., Chauhan, A., Prashar, D., Chandel, A., Kumar, H. and Purohit, R. (2012). Formulation and evaluation

aspects of tablets-An overview. *Am J. Pharm. Tech. Res*, *2*(1), 2249-3387.

Pearnchob, N. and Bodmeier, R. (2003). Dry polymer powder coating and comparison with conventional liquid-based coatings for Eudragit® RS, ethylcellulose, and shellac. *European journal of pharmaceutics and biopharmaceutics*, *56*(3), 363-369.

Qureshi, J., Ijaz, H., Sethi, A., Zaman, M., Bashir, I., Hanif, M. and Azis, M. (2014). Formulation and in vitro characterization of sustained release matrix tablets of metoprolol tartrate using synthetic and natural polymers. *Lat. Am. J. Pharm*, *33*(9), 1533-1539.

Sadeghi, F., Ford, J. L. and Rajabi-Siahboomi, A. (2003). The influence of drug type on the release profiles from Surelease-coated pellets. *International journal of pharmaceutics*, *254*(2), 123-135.

Sajeev, C., Vinay, G., Archna, R. and Saha, R. N. (2002). Oral controlled release formulation of diclofenac sodium by microencapsulation with ethyl cellulose. *Journal of Microencapsulation*, *19*(6), 753-760.

Soppimath, K. S., Kulkarni, A. R. and Aminabhavi, T. M. (2001). Chemically modified polyacrylamide-g-guar gum-based crosslinked anionic microgels as pH-sensitive drug delivery systems: preparation and characterization. *Journal of Controlled Release*, *75*(3), 331-345.

Tan, G., AV Morton, D. and Larson, I. (2015). On the methods to measure powder flow. *Current pharmaceutical design*, *21*(40), 5751-5765.

Thies, C. and Kirk-Othmer. (1995). *Encyclopedia of Chemical Technology*, *16*(4), 628-651.

Uziel, Y., Hashkes, P. J., Kassem, E., Padeh, S., Goldman, R. and Wolach, B. (2000). The use of naproxen in the treatment of children with rheumatic fever. *The Journal of pediatrics*, *137*(2), 269-271.

Ziyaur, R., Kanchan, K., Khar, R. K., Mushir, A., Charoo, N. A. and Shamsher, A. A. (2006). Characterization of 5-fluorouracil microsphere for colonic delivery. *AAPS pharm sci tech*, *7*(2), E47.

How to cite this article: Pagar Madhumanjiri K., Gangurde Avinash B., Pagar Rahul Y. and Bairagi Vinod A. (2023). Formulation and Development of Sustained Release Oral Drug Delivery System Comprising Naproxen Sodium Microspheres. *Biological Forum – An International Journal*, *15*(5a): 510-520.