ORIGINAL ARTICLE

Design of Novel Nanogel Formulation of Naproxen Sodium for Enhanced Anti-inflammatory Effect

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Abstract

Objective: The main aim and objective of this project study are to developed the nanogel of naproxen sodium and evaluate them. Naproxen sodium has been used as non-steroidal anti-inflammatory drug (NSAID's) for its anti-inflammatory and analgesic effect. Topical NSAIDs will penetrate the skin and help reduce pain locally. Oral route causes irritation and ulceration of GIT to avoid this reaction naproxen sodium given topically. The aim of the present study is to formulate naproxen sodium-loaded nanodispersion and then incorporated into a gelling agent to produce nanogel which will improve solubility as well as skin permeation of drug. **Materials and Methods:** Formulations were developed with varying concentrations of polymers like Eudragit RS100 and sodium alginate using modified emulsification-diffusion method. Differential scanning calorimetric and Fourier transforms infrared (FTIR) analysis was performed to ensure the compatibility of the drug and excipients. The gels were tested for clarity, viscosity, spreadability, surface pH, drug content uniformity, *in vitro* drug diffusion study, and skin irritation study using rat abdominal skin. **Results:** FTIR studies showed no evidence on interactions between drug, polymers, and excipients. The formulations are characterized for the particle size and found to be below 150 nm. The drug content in the formulations was found satisfactory. The best *in vitro* drug release profile was achieved with the formulation F4 batch exhibited 6 h sustained drug release, that is, 93.05% with desired therapeutic concentration which contains the drug. The formulation showed optimum stability and possessed a sustained drug release during the study period. The nanogel formulation showed the favorable alternative to oral administration for naproxen sodium. **Conclusion:** From the overall study, it was concluded that the nanogel of nanodispersion-loaded naproxen sodium was successfully formulated and evaluated.

Key words: Anti-inflammatory effect, nanodispersion, nanogel, naproxen sodium, topical non-steroidal anti-inflammatory drugs

INTRODUCTION

The topical preparation are generally used for the localized effect at the site of application by the efficacy of the drug penetration into the layers of the skin or mucous membrane. In topical drug delivery system, the application of the drug is directly on the skin to treat and cure the skin disorder. These topical drug delivery systems are generally used to treat for local skin infection or used on that place where other route of the drug administration is not useful. Topical drug delivery system involved the exploration of the drug to the surface area of the body, in the formulation which can be absorbed.[1] The main advantage of the topical drug delivery system is to skip the first pass metabolism to avoid

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the risks and problems regarding of the intravenous therapy and of varied condition of absorption such as pH changes, presence of enzyme, and gastric emptying time are often advantage of topical preparation. Topical drug administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal, and skin as topical routes. The larger body part is covered by the skin and skin is one of the most easily accessible organ on human body for topical administration and is main route of topical drug delivery system.[2]

The major limitation of conventional drug delivery system such as short contact time between active drug and site of application, lower transdermal permeability, and less bioavailability can be overcome by application of novel drug delivery system. The novel drug delivery system helps enhancing the transdermal permeability of drug, avoid the first pass metabolism of the drug, and enhances the bioavailability of the drug molecule. In the form of novel drug delivery system, an existing drug molecule can get a new life.

Nanodrugs involve the direct application of micronization and ultrafine powder technologies to the processing of drugs into nanoparticles. Nanoparticles are colloidal particles with sizes of approximately 10–1000 nm. These particles may be divided into nanocarriers and nanodrugs. Nanocarriers refer to materials prepared by the dissolution or dispersion of drugs with a variety of nanoparticles, which may be classified as either nanospheres or nanocapsules.[3] Nanoparticles offer advantages such as: Increased bioavailability, dose proportionality, and smaller dose form. Increased surface area results in a faster dissolution of the active agent in an aqueous environment, such as the human body. Faster dissolution generally equates greater absorption and bioavailability. Smaller drug doses less toxicity, reduction in fed/fasted Variability etc.[3]

Nanogels are innovative drug delivery system that can play an integral part in pointing out many issues related to old and modern courses of treatment such as nonspecific effects and poor stability. Nanogels may be defined as highly cross-linked nanosized hydrogels range from 20 to 200 nm. They can be administered through various routes, including oral, pulmonary, nasal, parenteral, and intraocular. They have a high degree of drug loading capacity and it shows better permeation capabilities due to smaller size. They release the drug by pH responsive, thermos sensitive, volume transition, photochemical internalization, and photo isomerization mechanism.[4] Nanogels have found an application dermatology and cosmetology as topical delivery systems of non-steroidal anti-inflammatory drugs (NSAIDs) and for the treatment of allergic contact dermatitis and psoriatic plaque. Nanogels are ideal for this application since they can overcome the major limitation of topical delivery systems, which is the relatively short contact time between active drugs and the application site. This is done by retaining water into the gel matrix and forming a uniform a dispersion of the nanogel. Oleic acid was used for surface modification. A variety of inflammatory disorders can be treated using this nanogel system as it can effectively permeate to deep layers of the skin.[4]

The main aim of the research study was to formulate the nanogel of the naproxen sodium. Naproxen sodium is BCS Class II drug which is widely used as NSAID's for its anti-inflammatory and analgesic effect. In this study, an attempt was made to formulate novel formulation of naproxen sodium to enhance solubility as well as skin permeation for the treatment of pain associated with inflammation.

MATERIALS AND METHODS

Materials

Naproxen sodium was obtained as a gift sample from Lupin Limited, Pune. Tween 80, Sodium alginate, Carbopol 940, Glycerol, Oleic acid, Triethanolamine, Hydroxyl methyl propyl cellulose K15 M, Methyl paraben, Propylene glycol, and Eudragit S100 were purchased from Modern Science, Nashik. All the materials used were of AR/LR grade or the best possible grades available, supplied by the manufacturer without further purification or investigation.

Methods

Preformulation studies

Characterization of the drug naproxen sodium

Naproxen sodium was obtained as a gift sample from Lupin Limited. Pune, and was subjected to the following characterization tests or preformulation studies.An investigation of physical, chemical, and mechanical property of drug substance alone and when combined with the Excipient to develop safe, effective, and stable drug.[5]

Organoleptic properties

The organoleptic properties of the drug were studied and compared with the reported standards.

Melting point

Melting point was determined using capillary tube method. A small amount of drug was taken in capillary tube closed at one end and it was placed in melting point apparatus and the temperature at which the drug melts was noted. Observed value was compared with reported value.[6]

Solubility study

The solubility of naproxen sodium was determined in methanol, distilled water, and phosphate buffer pH 7.4.

An adding excess amount of drug was added to 10 ml of respective solvent. The contents were stirred continuously for 24 h at 37°C and allowed to equilibrate. After 24 h, the sample was withdrawn and filtered through membrane filter and analyzed in UV-visible spectrophotometer (Shimadzu UV-2600).[6]

Ultraviolet – visible spectroscopy

The naproxen sodium was subjected to UV spectroscopic analysis to find out the wavelength (λmax) at which it shows maximum absorbance. Drug was accurately weighed and dissolved in solvent to obtain stock solution of 1000 µg/ml. This solution was then suitably diluted with same solvent to get solution of concentration 100 µg/ml. Then, the UV spectrum of this concentration was recorded over the wavelength range 200–400 nm. The UV spectrum of drug was taken in solvent methanol.[5]

Preparation of calibration curve by UV-visible spectrophotometric method

Calibration curve in phosphate buffer

The stock solution of 100 g/ml was prepared in pH 7.4 phosphate buffer and was used to prepare different dilutions in the range of 2–25 g/ml. The absorbance of the resulting solutions was measured at 272 nm by a UV-visible spectrophotometer. The solution was then scanned in the range of 200–400 nm using a Shimadzu-2600 UV/Vis spectrophotometer to determine the absorption maximum.[6,7]

Construction of Beer's Lamberts plot in 7.4 phosphate buffer

The stock solution of 7.4 phosphate buffer was used to prepare different dilutions. The absorbance of different dilutions was measured at 272 nm using 7.4 phosphate buffer as blank by UV-visible spectrophotometry.

Fourier Transforms Infrared spectroscopic (FTIR) studies

The infrared absorption spectrum of naproxen sodium (1 mg) was recorded with KBr (10 mg) over the wave number 4000–400 cm^{-1} using FTIR spectrophotometer (Shimadzu; 8400S). The dried sample of drug was mixed with KBr in the ratio 1:99, the sample triturate and finally placed in sample holder. The spectrum was run over the wave number 4000–400 cm^{-1} using FTIR spectrophotometer. The spectral analysis was done by standard absorbance of the functional groups. Compatibility study was carried out using Fourier transform infrared spectrophotometer. FTIR study was carried on pure drug and physical mixture of drug and polymers. Physical mixtures were prepared and samples kept for 7 days at 40°C.[7]

Differential scanning calorimetric (DSC) studies

The DSC analysis of drug sample of naproxen sodium was performed using DSC instrument. Small amount of naproxen sodium (2–3 mg) was accurately balanced in aluminum pan, hermetically sealed with the help of crimper and sample pan and reference pan are kept in DSC analyzer than the sample was heated from ambient temperature 40°C to 400°C, with the heating rate of 10°C/min. Inert atmospheres were provided by purging nitrogen gas flowing at 100 ml/min. The DSC analysis of drug sample of naproxen sodium and polymer sodium alginate was performed using DSC instrument. Small amount of naproxen sodium and sodium alginate physical mixture (2–3 mg) was accurately balanced in aluminum pan, hermetically sealed with the help of crimper and sample pan and reference pan are kept in DSC analyzer than the sample was heated from ambient temperature 40°C to 400°C, with the heating rate of 10°C/min. ++ Inert atmospheres were provided by purging nitrogen gas flowing at 100 ml/min.[7]

Formulation of naproxen sodium loaded nanodispersion using modified emulsification-diffusion method

The nanodispersion of the naproxen sodium was prepared by modified emulsification- diffusion method. Naproxen sodium-loaded nanodispersion was prepared using polymer sodium alginate and Eudragit S100 and penetration enhancer oleic acid. 200 mg of naproxen sodium was weighed and dissolved in 5 ml methanol containing polymer and oleic acid. This organic phase containing drug polymer mixture was added into aqueous phase containing Tween 80, with constant stirring at 5000–10,000 rpm. Addition of organic phase was done with the help of syringe positioned with needle directly into the aqueous stabilizer solution at the rate of 0.5 ml/min. The resulting dispersion was stirred for 6 min at 8000- rpm and was subjected to the sonication for 5–10 min. Then, double distilled water was added slowly to the dispersion with subsequent stirring for 1 h to induce diffusion of organic solvent into the continuous phase and then organic solvent remove by evaporation for approximately 50 min under reduced pressure leading to the formation of nanodispersion. The formula for the nanodispersion of naproxen sodium is represent in the Table 1.[8,9]

Characterization of nanodispersion

Physical appearance

Physical appearance of nanodispersion was observed visually.

Drug entrapment efficiency

Accurately weighed 10 mg of manodispersion were suspended in 100 ml of phosphate pH 7.4 buffer solution. After that, the solution was filtered through filter paper and from filtrate appropriate dilution was made and absorbance was measured at 232 nm using UV-visible spectrophotometer.[10]

$$\text{Drug entrapment efficiency} = \frac{\text{Actual drug contentin nanodispersion}}{\text{Theoretical drug content}} \times 100$$

Actual drug content

Precisely weighed equivalent quantity (10 mg) of nanodispersion containing drug was kept in 100 ml of phosphate buffer pH 7.4 solution for an hour with continuous stirring. Filtered samples were further analyzed at 272 nm next to blank using UV-visible spectrophotometer.[10]

Actual Drug content (%) = (Nact/Nms)×100

Where Nact =actual Naproxen sodium content in weighed quantity of nanodispersion, Nms = weighed quantity of nanodispersion and

Particle size and zeta potential determination

The zeta potential was measured for the determination of the movement velocity of the particles in an electric field and the particle charge. In the present work, nanodispersion was diluted 10 times with distilled water and analyzed by Zetasizer Instrument.[11]

Morphology scanning electron microscopy (SEM)

SEM technique was used for detailed particle structural characterizations and morphological structures of nanodispersion. Sample was deposited on a glass slide and was kept under vacuum. The samples were coated with a thin gold/palladium layer using a sputter coater unit of SEM.[11,12]

Preparation of naproxen sodium nanogel

Gels of the prepared nonodispersion were prepared by dispersing a gel forming agent HPMC K15 M or carbopol 940 soaked in hot water for 24 h and then nanodispersion of naproxen sodium is added in that solution under homogenous stirring using high speed homogenizer (8000–10,000 rpm). The pH was adjusted to the 7.0 using triethanolamine to form the gel and naproxen sodium-loaded gels were stored at room temperature. The composition of the excipients used in preparation of nanogel is illustrated in Table 2.[11,12]

Evaluation of nanogel

Evaluation parameter for nanogel is description, selection of gelling agent, pH, viscosity, drug content, spreadability skin irritation test, *in vitro* diffusion test, and stability. Nanogel was verified for by visual inspection after set in the container. Homogeneity and clarity were observed. pH of formulation was measured using digital pH meter.

Drug content

1 g of nanogel which was quantity equivalent to dose, that is, 1% of drug was dissolved in 100 ml of phosphate buffer pH 7.4, a sample (5 ml) was taken from this solution and

Table 1: Formula for nanodispersion of naproxen sodium

Formulation code	Ingredients					
	Drug (mg)	Methanol (ml)	Eudragit S 100 (mg)	Sodium alginate (mg)	Oleic acid (mg)	Tween 80 (ml)
N1	200	5	100	-	25	0.5
N2	200	5	200	-	25	0.5
N3	200	5	300	-	25	0.5
N4	200	5	-	100	25	0.5
N5	200	5	-	200	25	0.5
N6	200	5	-	300	25	0.5

Table 2: Composition of excipients used for preparation of nanogels

Sr. No.	Ingredients	F1	F2	F3	F4	F5	F6
1	Nanodispersion of naproxen sodium (ml)	1.0	1.0	1.0	1.0	1.0	1.0
2	Carbopol 940 (g)	0.5	1.0	1.5		-	-
3	HPMC K15 M K15 M (g)	-	-	-	0.5	1.0	1.5
4	Propylene glycol (ml)	10	10	10	10	10	10
5	Triethanolamine (ml)	1.0	1.0	1.0	1.0	1.0	1.0
6	Methyl paraben (g)	0.1	0.1	0.1	0.1	0.1	0.1
7	Propyl paraben (g)	0.5	0.5	0.5	0.5	0.5	0.5
8	Water (ml)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

diluted to 25 ml, then naproxen sodium concentration was determine by measuring the absorbance at 272 nm using UV-visible spectrophotometer (Shimadzu, UV-2600) and calculate the drug content on the basis of slope and intercept obtained from linearity equation, that is, Y= mx + C of pure drug.[10]

Spreadability

To determine spreadability of the gel formulation, two glass slides of standard dimension were selected. The formulation whose spreadability was to be determined was placed over one slide and other slide was placed over them such that gel is sandwiched between the two slides. The slides were pressed on each other so as to displace any air present and the adhering gel was wiped off. The slides were placed on stand such that only the lower slide is held firm by the opposite fangs of clamp allowing upper slide slip off freely by the force of weight tie to it. 125 g weight was tied to the upper slide carefully. The time taken by the upper slide to complete detached from the lower slide was noted and calculation of spreadability was done using the formula.[10]

$$S=m.l/t$$

Where, S = spreadability, m = weight tied to upper glass slide, *l* = length of glass slide, t = time (sec)

Viscosity

Viscosity of prepared gel was measured using Brookfield at different RPM viscosity that was measured and noted. The measurement was made over whole range of speed settings from 50–200 rpm with 10 s between two successive speeds.[13]

In vitro drug release study

Diffusion study was carried out by modified Franz diffusion cell of 20 ml capacity. Cellophane membrane is soaked in dissolution medium for 12 h before carrying out experiment. In modified Franz diffusion cell, 0.6 g of nanogel was placed in donor compartment of cell. The entire surface of membrane was in contact with the receptor compartment containing 20 ml of phosphate buffer pH 7.4. The receptor compartment was continuously stirred at 50 rpm using magnetic stirrer with temperature maintained at 37 ± 20°C constant temperature by circulating water bath. The study was carried out for 6 h, with the interval of 15, 30, 45, 60, 90, 120, 180, 240, and 360 min for up to 6 h. The sample was withdrawn at predetermined time interval and same volume was replaced with fresh buffer. The absorbance of withdrawn sample was measured by spectrophotometrically at 272 nm.[14]

Skin irritation test

In this study, all the experiments were carried out with the animal ethical committee permission (CPCSEA) and all the guidelines were followed for care and handling of animal. The permission from the ethical committee was obtained in the form of MGV/PC/CPCSEA/XXX1V/01/2019/12. Skin irritation test was performed as per the procedure three male and three female Wistar rat were used.

Procedure – The hair of the dorsal portion will be removed physically with help of sharp surgical scissors and chemical depilatory, then skin was washed properly 1 day before use, the animals were divided into two experimental groups with three animals in each group.

Group 1: Control and 0.8% formalin solution and Group 2: Control and medicated gel (with drug). Observed for any sensitivity after 24 h, 48 h, and 72 h.

Stability studies

The aim of stability study is to predict the shelf life of a product by accelerating the rate of decomposition, ideally by increasing temperature and relative humanity (RH) condition Stability studies were carried out as per ICH Q1A guidelines. The Naproxen sodium nanogel of optimized batch were packed with aluminum strips and stored for 3 months. Samples were analyzed after 3 months for physical appearance and drug entrapment efficiency. The formulations were evaluated mainly for their physical characteristics at the predetermined intervals of 1 month such as appearance/clarity, pH, viscosity, and drug content.[15]

RESULTS AND DISCUSSION

Preformulation studies organoleptic properties

The sample of drug received was studied for its organoleptic characters which shows white color, odorless in nature, and non-hygroscopic in nature.

Melting point determinations

Melting point of pure naproxen sodium is found in 255–256°C which is found to be nearly standard melting range of naproxen sodium. That indicates that the gifted samples obtained were of pure quality.

Determination of solubility

The solubility of naproxen sodium was found soluble in distilled water, methanol, and 7.4 phosphate buffer. The solubility of pure naproxen sodium in water, methanol, and 7.4 phosphate buffer was found to be 4.7 and 10.5, respectively. The inference was found to be that the naproxen sodium was freely soluble in methanol and 7.4 phosphate buffer and soluble in distilled water.

UV-visible spectrophotometric analysis of naproxen sodium

Determination of absorbance maximum wavelength (λmax) of naproxen sodium in 7.4 phosphate buffer

The UV spectrum of naproxen sodium solution in phosphate buffer pH 7.4 exhibited a wavelength of absorbance maximum at 272 nm is represented in Figure 1.

Construction of Beer's lamberts plot of Naproxen Sodium in 7.4 phosphate buffer

The Beer's lamberts plot for naproxen sodium in 7.4 phosphate buffer was constructed. The regression coefficient of the lines obtained to be 0.9933 which is shown in Figure 2. The linearity in phosphate buffer was found in the concentration range of 2–10 µg/ml. Calibration curve was found to be linear in the concentration range of 2–10 µg/ml having coefficient of regression value $R^2 = 0.9933$ and Slop y = 0.0065x + 0.063 in 7.4 phosphate buffer.[5,6]

The powdered mixture of naproxen sodium and KBr was taken in a sampler and the spectrum was recorded by scanning in the wavelength region of 4000–400 cm^{-1} using FTIR spectrophotometer.

The principle peaks were obtained at wave number 534.28 cm^{-1} for C-Br Stretching, 810.10 cm^{-1} for C-C Stretching, 921.97 cm^{-1} for C-O Stretching, and 1392.61 cm^{-1} for C-H Bending. The FTIR interpretations indicated that naproxen sodium is compatible with the excipients sodium alginate, eudragit RS 100, and oleic acid and no interactions were observed in all formulations of nanodispersion. The FTIR spectrum of pure naproxen sodium is shown in Figure 3.[5,6]

Figure 4 shows FTIR spectrum of naproxen sodium with sodium alginate. The mixture of naproxen sodium and sodium alginate contains all major peak with pure naproxen sodium. The principle peaks were obtained at wave number 2194 cm^{-1} for C=C stretching, 3035 cm^{-} for C-H Aliphatic stretching, and 1055 cm^{-1} for C-N stretching 659 cm^{-1} for C- Cl stretching DSC studies.

Figure 5 shows the DSC thermogram for naproxen sodium DSC studies indicated a sharp endothermic peak at 258.59°C corresponding to the melting of the pure drug indicating the purity of sample.

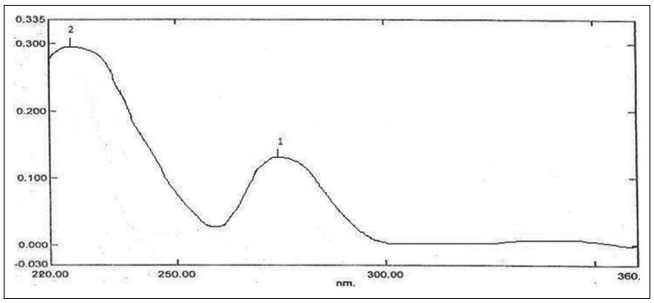

Figure 1: UV spectra of naproxen sodium drug in 7.4 phosphate buffer

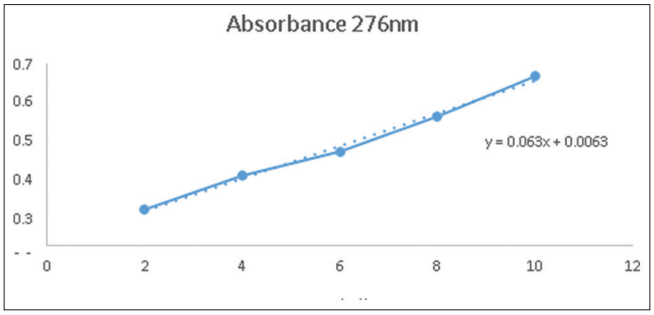

Figure 2: Construction of Beer's lamberts plot in phosphate buffer FITR analysis

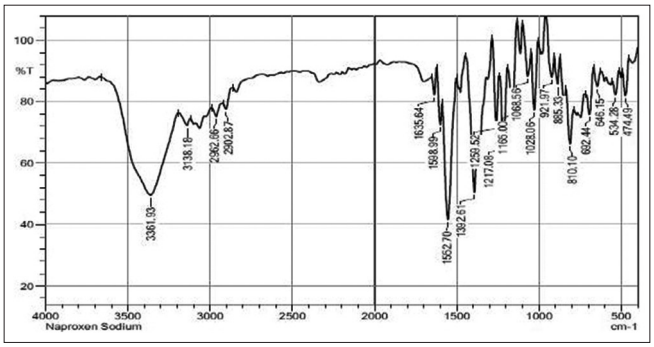

Figure 3: FTIR spectrum of naproxen sodium

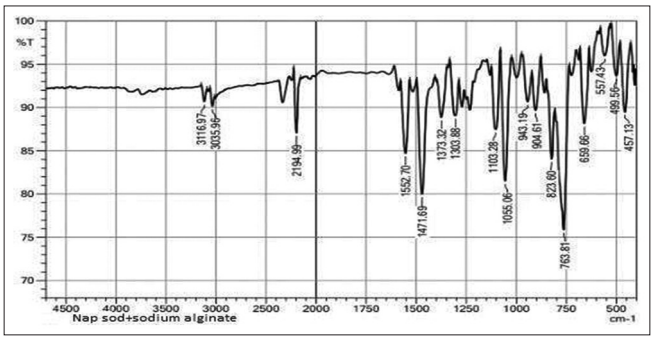

Figure 4: Infra-red spectrum of drug with polymers

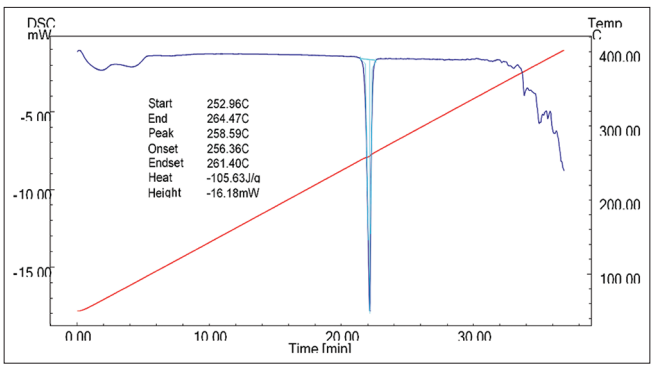

Figure 5: DSC thermogram of naproxen sodium

Figure 6 shows the DSC thermogram of naproxen sodium and polymers. DSC was also performed to check interaction between drug and polymer. The DSC thermogram of pure drug shows sharp endothermic peak which corresponds to the melting point of drug at 259.97°C.

Formulation of naproxen sodium nanodispersion

The different batches were evaluated for the appropriate concentration of drug naproxen sodium. On the basis of entrapment efficiency, the strength of drug was selected. From these, 85.47% drug entrapment was observed that maximum 200 mg of drug can load into the formed nanodispersion. Hence, this concentration of drug was used for further batch optimization study. The different batches were evaluated for the appropriate concentration of sodium alginate and oleic acid. From these, it is observed that the separately prepared concentration of Drug: sodium alginate, Drug: Eudragit RS100, and Drug: Oleic acid in Tween 80 was formed the suitable nanodispersion, respectively.[8,9] Increased the concentration of sodium alginate increased the entrapment efficiency. Nanodispersion batch N5 having more drug entrapped as compare to other batches. The composition naproxen sodium in nanodispersion is represent in Table 3.

Evaluation of naproxen sodium nanodispersion

Evaluations of prepared naproxen sodium nanodispersion were carried out for entrapment efficiency, % drug content, and particle size and morphology study.

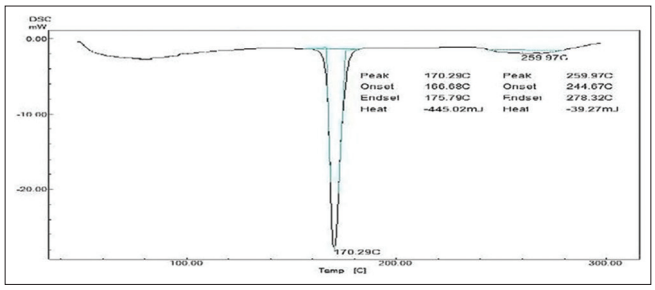

Figure 6: Differential scanning calorimetry of naproxen sodium and sodium alginate

Physical appearance

Physical appearance of nanodispersion was observed visually. It was found to be off white viscous odorless nanodispersion.

pH

The pH of naproxen sodium nanodispersion was found in the range 6.6–7.1 from batch N1 to N6.

Entrapment efficiency

Percentage entrapment efficiency of batches N1-N6 was in range from 72.14 to 88.21%. Highest % entrapment efficiency is shown in N5. Six batches were 72.14%, 78.45%, 81.81%, 76.32%, 88.21%, and 85.44%, respectively, as listed in Table 4. From this, it was concluded that the concentration of sodium alginate increase then percentage entrapment efficiency increase.[9]

Actual drug content

The uniform dispersion of naproxen sodium in nanodispersion can be determined by drug content analysis. It was observed that around 42.33 ± 0.12 to 80.36 ± 0.10% drug can be incorporated in the nanodispersion. Nanodispersion N5 batch shows the uniform dispersion of drug.[10] Drug content analysis is shown in Table 5.

Particle size and zeta potential determination particle size

Particle size was done by zeta sizer of optimized batch N5. The particle size was found to be 149.2 nm. Graph was observed, in which the particle size ranges from 100 to 250 nm which is in increasing order due to increase in concentration of excipients but after certain concentration, the ratio of drug to excipients was increased the particle size decrease. This was because of high drug to excipients ratio; amount of the excipients available was less. Hence, it was concluded that particle size varies with the concentration of drug excipients ratio. The average particle size of optimized batch N5 was

Table 3: Composition of naproxen sodium in nanodispersion

Formulation code	Ingredients					
	Drug (mg)	Methanol (ml)	Eudragit R S 100 (mg)	Sodium alginate (mg)	Oleic acid (mg)	Tween 80 (ml)
N1	200	5	100	-	25	0.5
N2	200	5	200	-	25	0.5
N3	200	5	300	-	25	0.5
N4	200	5	-	100	25	0.5
N5	200	5	-	200	25	0.5
N6	200	5	-	300	25	0.5

Table 4: *In vitro* drug diffusion profile of naproxen sodium nanogel percent drug release (mean±S.D.)

Time (min)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
15	5.5±0.01	5.47±0.02	4.59±0.01	9.43±0.021	5.40±0.02	5.29±0.01
30	9.48±0.03	8.42±0.01	8.11±0.02	10.64±0.04	8.68±0.03	8.10±0.02
45	15.65±0.01	12.34±0.02	11.70±0.02	14.81±0.01	13.35±0.01	11.14±0.03
60	20.05±0.03	17.5±0.01	15.34±0.02	22.17±0.04	20.22±0.01	15.89±0.02
90	27.37±0.02	23.51±0.02	21.27±0.03	27.61±0.02	22.64±0.02	21.73±0.01
120	34.06±0.01	33.82±0.03	32.87±0.02	44.64±0.01	32.52±0.01	29.88±0.03
180	49.25±0.02	41.39±0.02	36.28±0.02	58.12±0.01	44.80±0.01	43.39±0.03
240	61.05±0.02	54.55±0.02	53.65±0.01	84.88±0.021	64.63±0.02	53.94±0.01
360	86.42±0.02	82.76±0.02	70.29±0.02	93.05±0.01	84.12±0.01	74.32±0.03

Table 5: Entrapment efficiency and actual drug content of naproxen sodium

Sr. No.	Batch code	% Entrapment in nanodispersion	Actual drug content
1.	N1	72.14	42.33±0.12
2.	N2	78.45	64.56±0.21
3.	N3	81.81	55.98±0.23
4.	N4	76.32	71.23±0.10
5.	N5	88.21	80.36±0.15
6.	N6	85.44	72.70±0.18

observed 149.2 nm.[11] The particle size of optimized batch was shown in Figure 7.

Zeta potential analysis

Zeta potential gives the type of charge present on the surface of the nanodispersion and stability of the prepared formulation. It is used for the quantification of the magnitude of the charge. The zeta potential of optimized batch is −17.2 m, the nanodispersion formulation of optimized batch is having moderate stability.[11] The zeta potential of optimized batch is displayed in Figure 8.

Figure 9 shows the morphology of the SEM. By SEM, the surface morphology of drug particles can be studied. From the SEM photographs of optimized batch N5, the figure conforms that nanodispersion was spherical in shape, size, and surface structure of nanodispersion and also showed the porous surface with no drug crystal on the surface. The size affected by the encapsulation. The sample was observed under SEM at 50 KX magnetic resonance.

Evaluation of naproxen sodium nanogel

Physical characteristics

The formulated naproxen sodium nanogel was evaluated for appearance, pH viscosity, and spreadability. Obtained results are shown.

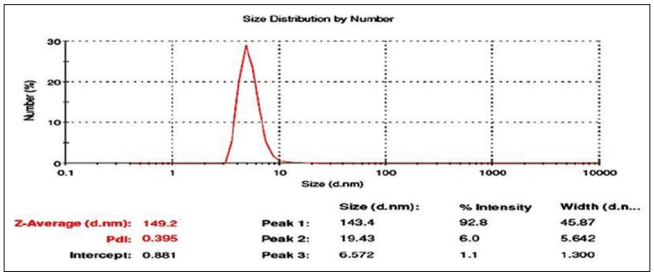

Figure 7: Particle size of optimized batch

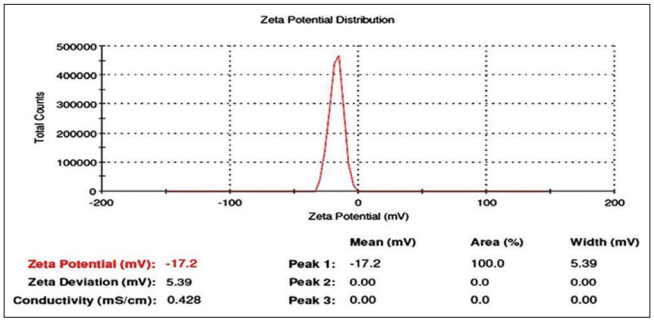

Figure 8: Zeta potential of optimized batch SEM

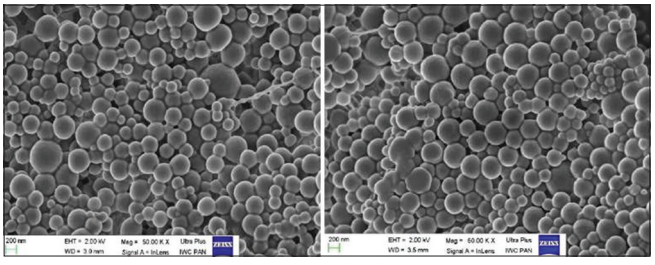

Figure 9: SEM image of optimized nanodispersion N5 batch

Appearance

All formulations of nanogel F1 to F6 batches are shown smooth and gel like appearance.

pH

The pH of formulation F1 to F6 is shown in between 6 and 6.8. In all formulation, the F4 batch shows proper pH.[10]

Actual drug content

The prepared formulation was analyzed for drug content. It was observed that the drug content in the prepared nanogel was satisfactory and the drug was uniformly distributed in all the formulation. The percentage drug content was found to be in between 91.21 ± 0.034 and 76.12 ± 0.012.[10] The actual drug content of formulated nanogel is illustrated in Table 6.

Spreadability determination

The spreadability of optimized formulation (F4) and marketed formulation was studied and it shows that spreadability is 18.41±0.02.[10]

Viscosity

Viscosity of nanogel is taken in different RPM such as 60, 100, 150, and 200, respectively, for all the formulations, the torque is setup at 95% for constant viscosity. F4 formulation batch shows good viscosity as compare to other batches. Viscosity v/s rpm plots for formulations show decrease in viscosity as shear rate (rpm) was increased which indicate that gel has the pseudo plastic flow. As pH was increased, the increased in viscosity was observed. Concentration of HPMC K15 M was a major factor affecting viscosity of formulations.[13] The viscosity of the nanogel formulation is present in Table 7.

Entrapment efficiency

After preparing nanodispersion, unentrapped drug is separated by dialysis method described above and the drug remained entrapped in nanogel is determined by spectrophotometric method.

$$EE\% = \frac{Wt - Wf}{Wt} \times 100$$

Nanogel consisting different kind of surfactants displayed diverse % EE. Maximum %EE (85.98%) was obtained from nanogel prepared with Tween 80 F5 batch.[14] The percent entrapment efficiency of various batches of naproxen sodium is shown in Table 8.

In vitro drug release study

The *in vitro* drug diffusion profile of naproxen sodium nanogel is shown in Table 4 and Figure 10. About 93.05% in table formulation F4 batch show higher drug release at 360 min.[14]

Mathematical models for drug release

In *in vitro* study of diffusion, kinetic model is shown in following table and formulation containing F4 batch shown higher value of all the zero order of kinetics and Higuchi model. The plot of Higuchi model of optimized batch F4 is represent in Figure 11.

Table 6: Drug content in nanogel

Formulation code	Actual drug content
F1	76.12±0.012
F2	82.30±0.023
F3	84.55±0.027
F4	91.21±0.034
F5	83.96±0.049
F6	87.85±0.061

Table 7: Viscosity nanogel formulation

Formulation Code	Torque %	RPM	Viscosity (cp)
F1	96	50	1080
	98	100	2672
	96	150	3600
	95	200	5240
F2	98	50	2142
	96	100	3943
	99	150	4283
	95	200	5656
F3	93	50	1245
	92.3	100	2554
	94	150	4253
	94	200	3525
F4	98	50	1056
	92	100	2826
	96	150	3521
	94.01	200	4623
F5	95	50	1114
	91	100	4264
	91.03	150	3224
	94.1	200	4241
F6	91	50	2079
	92	100	3143
	93	150	4422
	94	200	5567

Table 8: Entrapment efficiency of naproxen sodium nanogel

Sr. No.	Batch code	% Entrapment in nanogel (mean±SD, *n*=3)
1	F1	61.76±0.49
2	F2	55.38±0.13
3	F3	76.02±0.71
4	F4	85.98±0.45
5	F5	78.38±0.27
6	F6	65.83±0.042

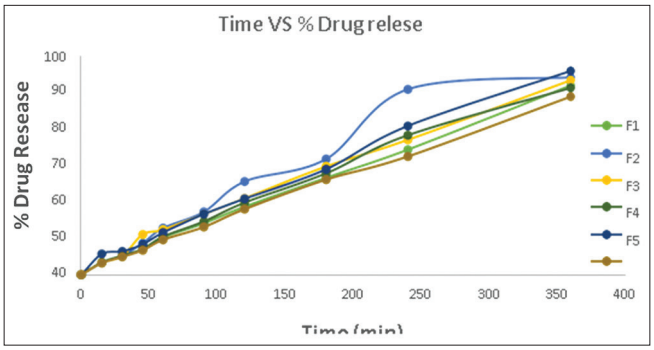

Figure 10: Percent drug release of nanogel formulation batches F1-F6

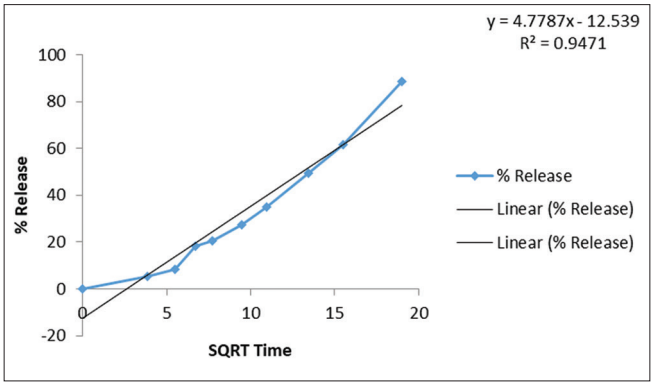

Figure 11: Plot of Higuchi model of optimized batch F4

Figure 12: Skin irritation test F4 batch after (a) 24 h, (b) 48 h, and (c) 72 h stability study

The regression coefficient R^2 was used as criteria to choose best model to fit drug release from the naproxen sodium nanogel. The R^2 values of all models are given in table. In almost all case, the R^2 of Higuchi model is higher than any other model indicating that the drug release from the formulation followed Higuchi diffusion mechanism. The release exponent n for optimized batch F4 was found to be 0.9471.[14]

Skin-irritation test

Table 9 represents the data of skin irritation test at the time interval of 24 h, 48 h, and 72 h. Skin irritation test was performed using *in vitro* skin irritation test method. The formulation did not indicate any evidence of skin irritation such as redness of skin or any change in skin. Thus, it may be concluded that formulation does not have skin irritation

Table 9: Skin irritation test

Formulation	Presence of edema 24 h	Presence of edema 48 h	Presence of edema 72 h
Control	0	0	0
Aqueous formalin solution	3	3	3
Nanogel	1	0	0

Table 10: Stability study of optimized F4 formulation

Sr. No.	Observation	Before stability testing	After stability testing 3 months
1	Clarity	Clear	Clear
2	Visual appearance	Transparent	Transparent
3	pH	6.8	6.6
4	Viscosity (cp)	2826	2812
5	Drug content	91.24%	90%

potential and is safe for topical application. In the skin irritation test, medicated formulation F4 shows no irritation at 24, 48, and 72 h, respectively. There is no skin irritation occur at different time interval.[15] Skin irritation test F4 batch after 24, 48, and 72 h is shown in Figure 12.

Stability studies of formulation which gave maximum dissolution rate were carried out to point out any visual physical or chemical stability of optimized batch that was assessed at 40 ± 2°C/75 ± 5% RH as per ICH guidelines. The naproxen sodium nanogel of optimized batch was packed with aluminum strips and stored for 3 months. Samples were analyzed after 3 months for physical appearance and drug entrapment efficiency. Formulations at room temperature were found to be stable up to 3 months. There is no change in drug content, clarity, pH, and viscosity.[16] The stability study of optimized F4 formulation at room temperature is briefly explained in Table 10.

CONCLUSION

The formulation of naproxen sodium nanodispersion was done by modified emulsification diffusion method and it is evaluated for entrapment efficiency, % drug content, and particle size and morphology study. The formulated nanodispersion entrapment efficiency was found 88.21% and the particle size was found to be 149.2 nmn. Nanogel formulation containing naproxen sodium was successfully prepared and found to be effective as well as better carrier for the transdermal/topical preparation. The formulated nanogel optimized for appearance, pH, spreadability, viscosity, drug content, *in vitro* drug release, and skin irritation test and stability study. Optimized gel formulation was examined for

visual appearance and it was found to be transparent. The pH of the formulation was found to be in between the skin pH range (6.5–8.5) which is in tolerable range for transdermal route. The value of spreadability indicates that the gel is easily spreadable by small amount of shear, that is, formulation shows good spreadability. Diffusion study resolved that the formulation (F4) showed highest release after 360 min shows 93.05% which was quite higher than released shown by conventional gel. The optimized formulation F4 shows maximum correlation coefficient (R 2 = 0.9471) with Higuchi model. The optimized batch F4 is does not observed skin irritation after 72 h. The optimized formulation F4 showed good stability and no change in any physical characteristics over a 3 months' period at 37 ± 20C. Hence, it can be concluded that developed nanogel formulation shows enhanced solubility as well as skin permeation and found to possible alternative to presently available drug delivery of naproxen sodium.

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