Research Article

Formulation and Evaluation of Etoricoxib Nanogel

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ABSTRACT

This project aimed to formulate and evaluate a nanogel of Etoricoxib to increase the therapeutic action and reduce side effects associated with oral administration. Etoricoxib is a non-steroidal anti-inflammatory drug possessing antipyretic, analgesic, and potential anti-neoplastic properties. It exhibits adverse effects like vertigo, drowsiness, nausea, hypersensitivity, gastrointestinal bleeding and, peptic ulceration on oral administration. To avoid the adverse effects of orally administered Etoricoxib, it is formulated as topical nanogel. Nanogel was formulated by emulsion-solvent diffusion technique using polymers like Polyvinyl alcohol and ethyl cellulose in different ratios. Preformulation studies were carried out. Nanogels were prepared by varying the concentrations of polymers and were evaluated for physical appearance, pH, viscosity, spreadability, particle size, zeta potential, drug content determination, in-vitro diffusion studies and, in-vivo animal studies. Formulation F4 containing a high concentration of polyvinyl alcohol and ethyl cellulose showed a higher drug release of 103.8±0.76%. in 6 hours. The particle size of the formulation F4 was found to be 211.2 nm and a polydispersity index of 0.481. The In-vivo anti-inflammatory test was done by carrageenan-induced paw edema method and it was found that Etoricoxib nanogel showed 81.8 % inhibition of paw edema whereas conventional gel showed 77.2 % inhibition. In-vivo animal studies showed that the Etoricoxib nanogel could inhibit edema effectively. It was concluded that Etoricoxib nanogel is an ideal and effective formulation.

Keywords: Nanogel, Etoricoxib, Homogenization, formulation.

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INTRODUCTION

The term Nanogels is defined as the nanosized particles formed by physically or chemically cross-linked polymer networks that swell in a good solvent.[1] These are potential polymeric nanoparticulate systems having tremendous biomedical applications which include high biocompatibility, high drug loading capacity, high biodegradability, good permeation capabilities and, tissue-mimicking properties. Due to their strong affinity for aqueous solutions, nanogels can swell or deswell when submerged in an aqueous media. The advantages of nanogels include their biocompatibility, biodegradability, permeability, high drug loading capacity and, both hydrophilic and lipophilic drugs can be encapsulated. However, nanogels also possess various disadvantages like the presence of traces of polymers or surfactants and the expensive removal of solvent and surfactant. They can be administered through various routes like oral, pulmonary, nasal, parenteral, intra-ocular, and topical route.[2] Etoricoxib is a non-steroidal anti-inflammatory drug with antipyretic, analgesic, and potential anti-neoplastic effects. It acts by inhibiting the effect of the cyclooxygenase enzyme which is responsible for converting arachidonic acid into prostaglandins. It is a BCS class II drug, with low water solubility. The adverse effects of orally administered etoricoxib include vertigo, nausea, vomiting, gastrointestinal bleeding, and peptic ulceration.[3] To avoid the adverse effects occurred by oral administration, it is prepared as topical nanogel. Various excipients were studied for the preparation of nanogel which includes Poly vinyl alcohol a hydrophilic polymer, Ethyl cellulose is a hydrophobic polymer, tween 80 used as a stabilizer and emulsifier, carbopol 934 is used as a gelling agent, as the drug is water insoluble Dichloromethane is used as solvent and triethanolamine is used to maintain the pH.

MATERIALS AND METHODS

Materials

Etoricoxib was a kind gift from the Jangoan Institute of Pharmaceutical Sciences, Yeshwanthpur, Jangoan, Telangana. Ethylcellulose, polyvinyl alcohol, carbopol 934, dichloromethane, and sodium lauryl sulphate were procured from S D Fine Chem Limited, Mumbai. Poly ethylene glycol was purchased from Merck Specialities Private Limited, Mumbai. Tween 80 from Sisco Research Laboratories Pvt Ltd, Maharashtra. Carrageenan powder was purchased from Bakersville India Pvt Ltd, Indore, Madhya Pradesh.

Methodology

Preliminary studies:

Determination of λmax of Etoricoxib

10µg/ml standard (stock-C) solution of Etoricoxib was scanned in the range of 200-400nm using a UV-Visible Spectrophotometer and λmax was determined.

Construction of Calibration curve of Etoricoxib

Dilutions were prepared with pH 7.4 phosphate buffer saline with 1% SLS (60:40) to get concentrations of 2, 4, 6, 8, 10, 12, and 14 µg/ml. The absorbance of these dilutions was measured at 235nm using UV-Visible Spectrophotometer. pH 7.4 phosphate buffer saline was used as blank. The calibration curve was drawn by taking concentration on X-axis and absorbance on Y-axis.

Drug-excipient compatibility studies

The Drug-excipient studies are done to study any possible interaction between the drug and excipients. FTIR spectrum of both pure drug and drug with excipients were taken and compared. The excipients should be compatible with the drug to formulate a nanogel.[6]

Preparation of Etoricoxib nanogel

The Etoricoxib nanogel was formulated by the Emulsion-solvent diffusion method. Accurately weighed quantities of drug, ethyl cellulose were dissolved in dichloromethane. The Aqueous phase was prepared by adding carbopol 934, polyvinyl alcohol in water with continuous stirring and heating followed by adding tween 80. The drug-containing phase is then added into the aqueous phase drop by drop under homogenization to form an emulsion. Homogenization was then continued for 2 hours. Tri ethanolamine was then added to form the gel with continuous stirring and to maintain the pH of nanogel.[4,5] The compositions of formulations were given in table 1.

Table 1: Formulation table of Etoricoxib Nanogels

S.no	Ingredients	F1	F2	F3	F4
1	Drug (mg)	100	100	100	100
2	Ethyl cellulose (mg)	100	100	200	200
3	Polyvinyl alcohol(mg)	100	200	100	200
4	Carbopol 934 (mg)	200	200	200	200
5	Dichloromethane(ml)	10	10	10	10
6	Tween 80 (ml)	4	4	4	4
7	Triethanolamine (ml)	QS	QS	QS	QS
8	Distilled water	QS	QS	QS	QS

Evaluation of Nanogels

Physical Appearance of nanogels:

The formulated Etoricoxib nanogel formulations were visually inspected for their color, appearance, and homogeneity after the gels were allowed to settle in the container. They were then tested to check the presence of any aggregates.[7]

pH measurement:

The pH values of formulated nanogels were determined using a Digital pH meter (Syntronics®, India). The pH meter was initially calibrated with standard buffer tablets of pH 4.0, pH 7.0, and pH 9.0. 1gm of prepared nanogel was dissolved in 100ml of distilled water to make a 1% aqueous solution. The pH was measured by dipping the glass electrode into the prepared aqueous solution. The pH is measured in triplicate and the standard deviation was calculated.[6] To avoid any irritation the pH of the formulated gel should be ideally near the pH of the skin.

Spreadability:

The spreadability is done to denote the extent of the area in which the gel spreads readily on application to the skin. The gels were placed between 2 horizontal plates of 20×20 cm and a standard weight of 200gm was added to the upper plate to determine the spreadability. The spreading diameter was noted after one minute. The diameter obtained was measured in cm and calculated by using the formula.[6]

$$S = M \times L / T$$

Extrudability study:

The gels were filled into the collapsible tube. The weight in grams needed to extrude a 0.5 cm ribbon nanogel from the collapsible tube in 10 seconds was used to measure the formulation's extrudability. The extrudability was measured and calculated by using the formula[4],

Extrudability = applied weight to extrude the nanogel from tube (in gm) / Area (in cm^2).

Viscosity study:

The viscosity of the prepared nanogels was determined by Brookfield viscometer using spindle no 64 at 10 rpm and the temperature was maintained at 25℃. The nanogel formulations were taken in a beaker and allowed the spindle to rotate. The reading was then recorded.[7]

Drug content determination:

1gm of formulated nanogel was diluted with pH 7.4 phosphate buffer saline and the mixture was filtered through the membrane filter. The absorbance was then determined by scanning the sample using UV-Spectrophotometer at 235 nm.[8,9]

Particle size and polydispersity index (PDI):

The particle size of the formulated nanogel was determined by photon correlation spectroscopy that analyzes the fluctuations in light scattering due to the Brownian motion of the droplets using a zeta sizer (Malvern Master sizer 2000 MS). 1 ml of nanogel was dissolved in 10 ml of distilled water and diluted to get a clear solution. The droplet size, polydispersity index, and zeta potential were then determined using Malvern zetasizer.[6]

Selection of Dissolution Medium

Solubility studies

Many criteria are taken into consideration while selecting dissolution media. The Drug should have adequate solubility in the dissolution media without impacting the sink condition. The drug Etoricoxib is poorly water soluble, solubility studies were done to determine the solubility of the drug in various buffers. To conduct the solubility studies, excess Etoricoxib was dissolved in various ratios of pH 7.4 phosphate buffer saline: PEG 400, pH 7.4 phosphate buffer saline: 1% SLS, pH 7.4 phosphate buffer: PEG 400, pH 6.8 phosphate buffer: PEG 400, pH 7.4 phosphate buffer with 1% SLS, and pH 7.4 phosphate buffer with PEG 400. These solutions were then sealed in vials and kept on a rota shaker for 72 hours. Following filtering, the samples are examined using a UV-Spectrophotometer set at 235 nm.

In vitro Release studies

The drug release of the formulation was estimated using **Franz Diffusion Cell**. The diffusion cell consists of receptor and donor compartments and a dialysis membrane was placed between receptor and donor compartments. 1 gram of gel was applied uniformly on the dialysis membrane which is previously soaked in a dissolution medium and the membrane was then fixed to one end of the tube. The entire assembly was positioned so that the lower end of the tube containing the gel touched the surface of the diffusion medium. The setup was placed on the magnetic stirrer and the temperature was maintained at 37°±1°C.[6,9] Samples were withdrawn at different time intervals and then analyzed at 235 nm using UV-Visible Spectrophotometer.

In-vivo studies

The anti-inflammatory activity of Etoricoxib nanogel was evaluated in male albino Wister rats using Carrageenan hind paw method. All the experimental methods and protocols used in this study were reviewed and approved by the Institutional Animal Ethical Committee (IAEC) [1791/Po/Re/S/14/CPCSEA, 2018]. All the ethical guidelines were strictly followed. Healthy albino Wister rats were selected and then divided into 3 groups, each group containing 6 rats. The conventional gel, optimized nanogel, and distilled water were applied externally to the animals of respective groups. 30 minutes later, the rats were challenged by a subcutaneous injection of carrageenan (0.1ml, 1% w/v in normal saline) into the sub-plantar area of the left hind paw. The paw edema was measured using a plethysmometer immediately after injection and 1, 2, 4, 6, and 12 hrs after injecting carrageenan. The % inhibition of paw edema induced by carrageenan was calculated for each group using the following formula. The difference in paw volume between Vo and Vt was taken as a measure of edema.[10]

% inhibition of edema = $V_{control} - V_{treated} / V_{control} \times 100$

Where, $V_{control}$ = mean paw edema volume of rats in the controlled group and

$V_{treated}$ = mean paw edema volume of rats in the test group.

RESULTS AND DISCUSSION

Determination of λmax of Etoricoxib in pH 7.4 phosphate buffer saline with 1% SLS

The Etoricoxib stock (C) solution of concentration 10 µg/ml was scanned in the range of 200-400nm using UV-Spectrophotometer (PG instruments limited). The absorption maxima was found to be 235nm.

Construction of calibration curve of Etoricoxib

The Standard stock solutions of Etoricoxib in the range of concentration 2 µg/ml to 14 µg/ml were prepared using pH 7.4 phosphate buffer saline with 1% SLS and absorbance was measured at 235nm using pH 7.4 phosphate buffer saline as blank. As shown in figure 1 the graph was observed to be linear in the range of 2µg/ml to 12µg/ml with an R^2 value of 0.996 and slope value of y = 0.068 + 0.026. The values were further used for analytical studies.

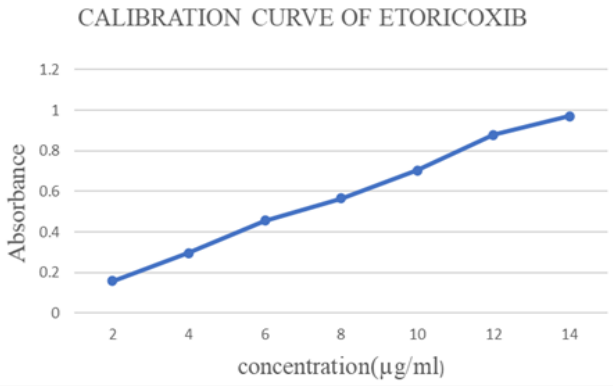

Figure 1: Calibration curve of Etoricoxib in pH 7.4 Phosphate buffer saline

Drug-Excipient compatibility studies

The Drug-Excipient compatibility studies were done by Fourier Transform Infrared Spectroscopy (FTIR) (Shimadzu). The IR spectrum of API was compared with the IR spectrum of a combination of API with all excipients. The obtained frequencies of API and API with excipients were given in table 2 and peaks were shown in figure 2.

Table 2: Characteristic IR peaks of API and API with excipients

Functional groups	Reported frequency (cm^{-1})	Observed frequency (cm^{-1})	
		Peaks of API	Peaks of API with excipients
C-Cl	800 - 600	781.71 cm^{-1}	771.19 cm^{-1}
C-CH_3	1470 - 1430	1432.39 cm^{-1}	1432.39 cm^{-1}
N=C	1750 - 1550	1599.03 cm^{-1}	1640.57 cm^{-1}
S=O	1500 - 1000	1082.79 cm^{-1}	1069.55 cm^{-1}

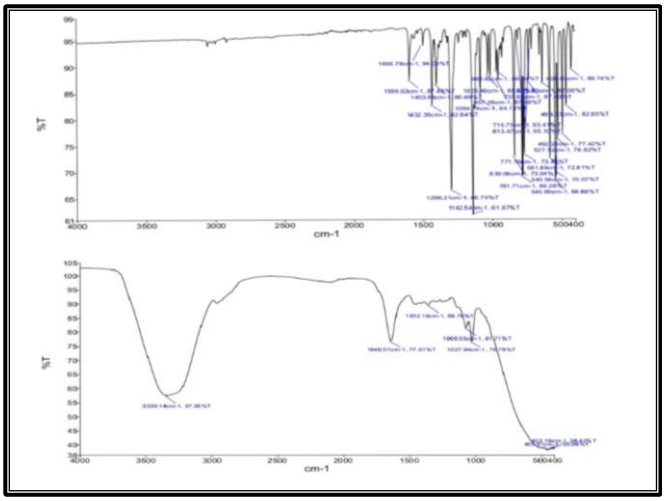

Figure 2: FTIR of API and API with excipients

The FTIR spectrum of Etoricoxib showed characteristic peaks at 781.71 cm^{-1} indicating C-Cl stretching, 1432.39 cm^{-1} indicating C-CH_3 stretching, 1599.03 cm^{-1} indicating N=C stretching, 1082.79 cm^{-1} indicating S=O stretching. The obtained spectrum confirms the purity of the drug.

The FTIR spectrum of Etoricoxib with excipients showed characteristic peaks at 771.19 cm^{-1} indicating C-Cl stretching, 1432.39 cm^{-1} indicating C-CH_3 stretching, 1640.57 cm^{-1} indicating N=C stretching, 1069.55 cm^{-1} indicating S=O stretching. The obtained FTIR spectrum of the drug with excipients confirms that there are no specific interactions between the drug and excipients.

Physical Appearance

The formulated Etoricoxib nanogels showed a clear appearance and all the formulations were found to be homogenous and free of aggregates. The result of the physical appearance test was shown in table 3.

pH

The pH of prepared nanogels varied between 6.59 to 7.01 which is ideally near the pH of the skin to avoid any irritation. Hence it can be concluded that nanogels are non-irritant to the skin and the pH values were shown in table 3.

Viscosity determination

The formulation is an oil in water emulsion; hence the viscosity was low resulting in rapid release of complete drug in 6hrs. It is seen that among all the formulations F4 showed higher viscosity compared to other formulations. That values were ranging between 6659cp to 8799cp. The viscosity of the formulations were shown in table 3.

Spreadability

The spreadability of various formulations of nanogels was measured and the diameter of the formulations was ranging between 8.6 g.cm/s to 10.2 g.cm/s. The spreadability values of all the formulations were given in table 3.

Extrudability

The extrudability studies for Etoricoxib nanogels were done using collapsible tubes. The formulations showed good extrudability. The measurement of the extrudability of each formulation shows the triplicate and the average value is presented in table 3.

Drug content

The estimation of drug content in Etoricoxib nanogel formulations was done by dissolving 1gm of prepared nanogel in pH 7.4 phosphate buffer and analyzed by using UV-visible Spectrophotometer (PG instruments limited) at 235 nm. The drug content of formulations is given in table 3.

Table 3: Evaluation parameters of Nanogels

Nanogels	Physical appearance	pH	Viscosity at 10 rpm	Spreadability (g.cm/s)	Extrudability (g)	% Drug content
F1	Clear and homogenous	6.59±0.15	7879	10.1	277±0.5	87.75%
F2	Clear and homogenous	6.60±0.13	8799	8.6	400±0.3	79.24%
F3	Clear and homogenous	7.01±0.09	6659	9.16	204±0.6	76.79%
F4	Clear and homogenous	6.68±0.19	7799	10.2	277±0.6	97.93%

Selection of dissolution medium

Solubility studies:

As the drug is poorly water soluble, solubility studies were conducted in various buffers and pH 7.4 phosphate buffer saline with 1% SLS (60:40) was selected as the dissolution medium as the drug is highly soluble in it and showed absorbance of 4.61.

***In-vitro* diffusion studies of Etoricoxib nanogel**

The *in-vitro* diffusion studies were done using a Franz diffusion cell with the aid of a magnetic stirrer. The *in-vitro* diffusion studies showed that formulation F4 showed

higher drug release of 103.8±0.76% in 6 hours. % drug release of formulations in pH 7.4 phosphate saline buffer with 1% SLS are given in table 14. The % drug release of nanogels was shown in figure 3:

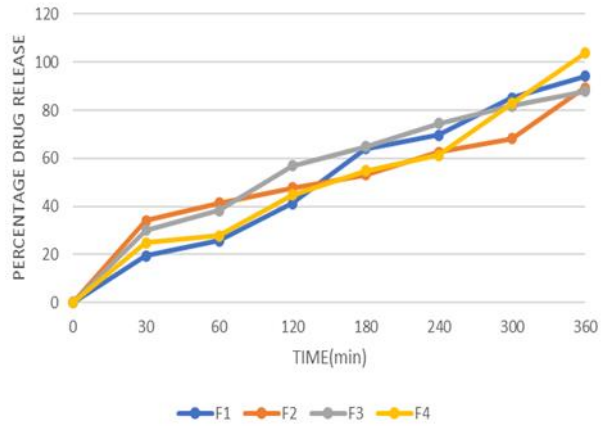

Figure 3: Percentage drug release graph of nanogels

Particle size and Polydispersity index:

The mean particle size of the Etoricoxib nanogel formulation F4 was determined using Malvein master sizer. The Particle size was found to be 211.2 nm and the Polydispersity index was found to be 0.481 which indicates a midrange of polydispersity. The zeta potential of the Etoricoxib nanogels was determined using a Zetasizer. Etoricoxib nanogel had a zeta potential value of -43.5mV, which is a measure of the net charge of emulsion. It was concluded that the nanogel formulation containing emulsion showed good stability. The negative sign of zeta potential indicates that the particles have a negative charge.

***In-vivo* studies:**

The *In-vivo* animal studies were done for optimized Etoricoixb nanogel using healthy male albino Wister rats. The procedure was followed as per the protocol which is approved by the IAEC. The percentage decrease in paw edema was compared between the conventional group and the test group. Paw volume in control, test and conventional groups is shown in table 4 and percentage inhibition of paw edema was higher in nanogel when compared to conventional gel and the percent inhibition graph was shown in figure 4. At a 1 hour interval as the drug concentration is higher at the site of action the percent inhibition is higher and when compared to conventional drug the p-value was found to be < 0.0001. At 2hr, 4hr, 6hr, and 12hr intervals as the drug concentration decrease the % inhibition decreased with time. The p-value was found to be <0.05.

Table 4: Paw Volume after induction

	0 min	1 hour	2 hours	3 hours	6 hours	12 hours
Conventional gel	13.3±0.18	11.93±0.212[b]	9.58±0.196[a]	7.81±0.167[a]	5.28±0.166 [a]	3.28±0.150 [a]
Etoricoxib nanogel (test)	13.46±0.16	10.15±0.172	9.05±0.147	7.28±0.177	4.71±0.195	2.71 ±0.22
Control	13.65±0.076	13.3±0.164	13.93±0.076	14.23±0.088	14.16±0.125	14.4 ±0.182

a = P < 0.05, b = P < 0.0001; Data are expressed as Mean ± SEM

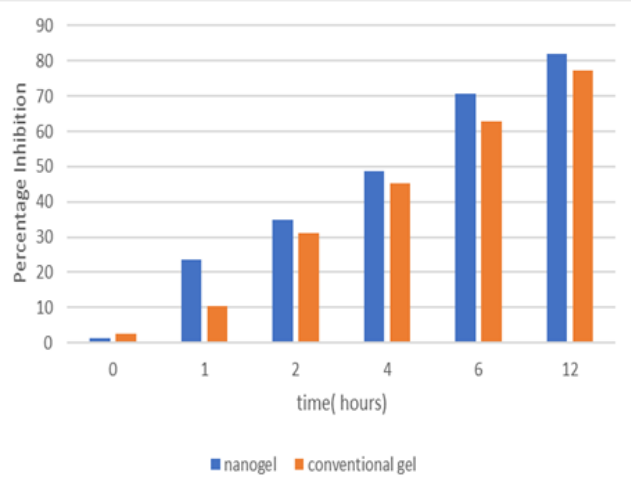

Figure 4: Comparison of the Percentage decrease in Paw edema between conventional and test group

The optimized formulation showed a statistically significant decrease in paw volume. Etoricoxib nanogel showed 81.8% inhibition in paw edema at 12 hours whereas conventional gel exhibited inhibition of 77.2% at 12 hours.

CONCLUSION

The nanogel of Etoricoxib was successfully prepared and showed complete drug release in 6 hrs. *In-vivo* animal studies showed that the Etoricoxib nanogel could inhibit the edema effectively. It was concluded that Etoricoxib nanogel is an ideal and effective formulation.

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REFERENCES

1. Hemant KS Yadav, Noor Anwar AI Halabi, and Ghufran Ayman Alsalloum. Nanogels as Novel Drug Delivery System, Journal of Pharmacy and Pharmaceutical Research, 2017;1(1:5):18-23. doi:13751754.
2. Farhana Sultana, Manirujjaman, Md. Imran-UI-Haque, Mohammad Arafat, Sanjida Shamin. An Overview of Nanogel Drug Delivery System, Journal of

Applied Pharmaceutical Science, 2013;3(8): S95-S105. doi: 10.7324/JAPS.2013.38.S15.

3. Vania Rachael Fonseca, Prashan Jivaji, Bhide, Madhusudan Purushottam Joshi. Formulation, development, and evaluation of Etoricoxib nanosize microemulsion based gel for topical drug delivery, Indian Journal of Pharmaceutical Education and Research, 2019;53(4):60-65. doi: 10.5530/ijper.53.4s.152.
4. Swati Talele, Preetam Nikam, Braja Ghosh, Chaitali Deore, Ashwini Jaybhave, Anil Jadhav. A Research Article on Nanogel as Topical Promising drug Delivery for Diclofenac sodium, Indian Journal of Pharmaceutical Education and Research, 2017;51(4S):80-86. doi: 10.5530/ijper.51.4s.86.
5. Phatak Atul A, Chaudhari Praveen D. Development and evaluation of nanogel as a carrier for transdermal delivery of Aceclofenac, Asian journal of pharmaceutical technology, 2012;2(4):125-132.
6. Chopade swapnil, Khabade Sheeba, Patil Ajit and Powar Sayali. Formulation development and evaluation of anti-inflammatory potential of topical Tenoxicam nanogel on animal model. International Journal of Recent Scientific Research, 2018;9(12): 29951-29957. doi: http://dx.doi.org/10.24327/ijrsr.2018.0912.2967.
7. Inamdar Yashadri, Rane Bhushan, Jain Ashish. Preparation and Evaluation of Beta Sitosterol Nanogel: A Carrier Design for Targeted drug Delivery system, Asian Journal of Pharmaceutical Research and Development, 2018;6(3):81-87. doi: https://doi.org/10.22270/ajprd.v6i3.390.
8. Anasuya Patil, Pranoti kontamwar.Formulation and Evaluation of Antifungal nanogel for topical drug delivery system. Asian Journal of Pharmaceutical and Clinical Research, 2021;14(10):127-134. doi: 10.22159/ajpcr.2021.v14i10.42436.
9. Muniraj S N, Yogananda R, Nagaraja T S, Bharathi D R. Preparation and Characterization of Nanogel Drug Delivey System Containing Clotrimazole an anti-fungal drug. Indo American Journal of Pharmaceutical Research, 2020;10(7):24-31. doi: 10.528/zenodo.3970394.
10. Mohammed Layth Hamzah. Formulation and Evaluation of Flurbiprofen nanogel. Research journal of pharmacy and technology, 2020;13(11):5183-5188. doi: 10.5958/0974-360X.2020.00906.3.

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