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FORMULATION AND EVALUATION OF TOPICAL GEL FOR TREATMENT OF KNEE JOINTS PAIN BY USING ETORICOXIB DRUG

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Abstract: The present investigation is to develop topical gel of etoricoxib drug with better-permeable, controlled and localized delivery via topical route. Etoricoxib drug was estimated analytical process by reported UV spectrophotometric methods in the dissolution medium (pH Phosphate buffer 6.8) at 233 nm. The calibration curves show excellent linearity of data as evidenced by the values of correlation coefficients that were found to be greater than 0.998. The curves were found to be recti-linear in the concentration range 5 µg / ml to 25 µg / ml for the drug. The estimation procedures for drugs were found to be sensitive, precise and reproducible. Preformulation studies used and drug was found to be light yellow, odorless, The characteristic peaks of blends were shown, there was no interaction between them. The prepared emulgel formulations were examine visually for their feeling after application on skin, color intensity, pH determination, consistency and extrudability determination. The result concluded that ETEG4 was best formulation. This formulation ETEG4 was prepared emulgel Carbopol 940 (2g), PVP, neem oil base. The drug release profile and release kinetics are two important characteristics of the dosage forms, which play an important role for describing dissolution profile of dosage form. The dissolution data was obtained after in-vitro release performance, fitted to mathematical different models. The formulations ETEG1 to ETEG4 showed the values of n> 0.5, followed Fickinan diffusion and supercase II transport mechanism.

Keywords: Topical Gel, Emulgel, Etoricoxib**,** Carbopol 940, Knee Joint Pain, NSAIDs.

Introduction: Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most widely used medications for the management of knee pain in patients with osteoarthritis of the knee. The efficacy of oral NSAIDs, diclofenac in particular, for symptomatic relief of knee osteoarthritis has been well established in the literature. NSAIDs are recommended by several international and national guidelines as the initial oral medication of choice in the treatment of symptomatic osteoarthritis of the knee with moderate-to-severe pain intensity. Several NSAIDs, including oral diclofenac, are available as over-the-counter medications in many countries, so the use of this drug is particularly widespread.

NSAIDs: One of the strong anti0inflammatory drugs, e.g. naproxen, piroxicam, diclofenac, indomethacin or etoricoxib is given in relatively high and quickly repeated doses. They are quite effective in terminating the attack, but may take 12–24 hours, i.e. response is somewhat slower than with colchicine, but they are generally better tolerated; majority of patients prefer them over colchicine. Their strong anti-inflammatory (not uricosuric) action is responsible for the benefit. Naproxen and piroxicam specifically inhibit chemotactic migration of leucocytes into the inflamed joint. After the attack is over, they may be continued at lower doses for 3–4 weeks while drugs to control hyperuricaemia take effect. They are not recommended for long term management due to risk of toxicity. The NSAIDs have also substituted colchicines for covering up the period of initiation

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of therapy (6–8 weeks) with allopurinol or uricosurics in chronic gout (Tripathi, 2013).

In the mid-1980's, Topical -gels have been attainment significance in pharmaceutical topical semisolid dosage forms. Topicalgels are emulsions, may be oil-in-water or water-in-oil type, and gelled by mixing with a gelling agent (Marquardt et al., 1998). It is under major group of semisolid preparation, the use of transparent gels has prolonged widely both in cosmetics and in pharmaceutical preparations (Kullar et al., 2011). The USP defines, gels as semisolid systems containing either suspensions made up of either small inorganic particles, or large organic molecules interpenetrated by a liquid (The United States Pharmacopoeia, 2009). Gel forms cross linked network, inwhich small drug particles captures and provides its release in a controlled manner. As mucoadhesive property of system, it prolongs the contact period of medication over the skin (Alexander et al., 2011; Lachman, 2014).

Gels and emulsions have a major limitation as their inability to delivery of hydrophobic drugs and instability during storage respectively. So to overcome these limitations an emulsion move towards i.e., Topical gel is being used so that a hydrophobic therapeutic moiety is successfully incorporated and advanced unique property of gels (Panwar et al., 2011; More et al., 2016). Topical gel possesses the property of both emulsion and gel it acts shown the dual control release system. Emulgel propose the capability of delivering both hydrophilic and lipophilic drug moieties due to presence of both aqueous and non-aqueous phases. It is suitably applied to the skin due to its non-greasy character in comparison to other topical formulations such as ointments, creams etc. which are very much thick and require excess rubbing (Kumar et al., 2013). To improve emulsion stability and penetration ability it is incorporated into gel (Philippova et al., 2012). Topical gel for dermatological use, because have several favourable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, nonstaining, water-soluble, greater shelf life, bio-friendly, clear & pleasant appearance (Vats et al., 2014).

The present research work aims at preparing Topical gel containing Etoricoxib an analgesic agent. Etoricoxib is a non-steroidal antiinflammatory drug that exhibits anti-inflammatory, analgestic and antipyretic activities. However its use has been associated with a number of gastrointestinal disorders. These potential side effects may be overcome by the topical administration of the drug. In vitro, etoricoxib exhibits a greater selectivity for COX-2 over COX-1 compared with the COX-2 inhinitors rofecoxib, valdecoxib and celecoxib. Etoricoxib binds competitively to COX-2 with 1;1 stoichionetry in a reversible, noncovalent manner. In healthy volunteers, oral etoricoxib is rapidly and completely absorbed. It reaches Cmax after approximately 1 hour and has up to 100% absolute bioavailability. Etoricoxib is indicates in the management of Osteoarthritis, Rheumatoid The major drawback of topical dosage form is dissolution and diffusion of drug in the delivery of hydrophobic drugs, and permeation through stratum corneum is for hydrophilic drugs. Therefore, to are referred as topical gels. The oil-in-water and water-in-oil emulsions are extensively used as vehicles to deliver various hydrophilic as well as hydrophobic drugs to the skin in topical gel formulation. They also have a high ability to dissolve drug and to penetrate skin. Oil-in-water emulsions are mostly useful as water washable drug bases. The present research work aims at preparing topical gel containing etoricoxib an analgesic agent.

Materials & Methods:

Drug Profile

Etoricoxib: Etoricoxib is a new COX-2 selective inhibitor. Current therapeutic indications are: treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, chronic low back pain, acute pain and gout. Like any other COX-2 selective inhibitor, Etoricoxibselectively inhibits isoform 2 of cyclo-oxigenase enzyme (COX-2). This reduces the generation of prostaglandins (PGs) from arachidonic acid.

Physical and chemical property of Etoricoxib
Structure:

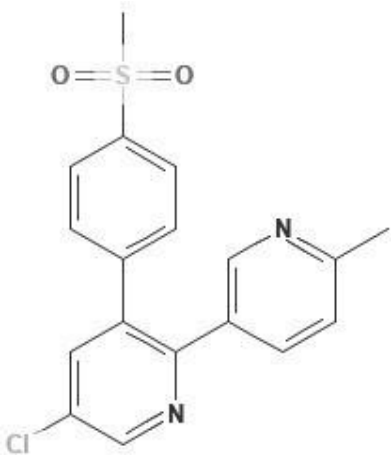

Figure 1: Structure of Etoricoxib

Chemical structure: $C_{18}H_{15}ClN_2O_2S$
IUPAC: 5-chloro-3-(4-methanesulfonylphenyl)-2-(6-methylpyridin-3- yl) pyridine
The CAS Registry number: 202409-33-4
Mol. Wt.: 358.84 g/mol
Description: A white, crystalline powder or small crystals.It is odorless and has a bitter taste
Solubility: Freely soluble in water, in methanol and in methylene chloride
Loss on drying: Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.
Protein binding: 92%
Metabolism: Hepatic, primarily via CYP3A4
Half life: 22 hours
Pharmacodynamics: Etoricoxib is a COX-2 selective inhibitor (approximately 106 times more selective for COX-2 inhibition over COX-1). Currently it is approved in more than 60 countries worldwide but not in the US, where the Food and Drug Administration (FDA) require additional safety and efficacy data for etoricoxib before it will issue approval.
Mechanism of action: Like any other COX-2 selective inhibitor Etoricoxib selectively inhibits isoform 2 of cyclo-oxigenase enzyme (COX-2). This reduces prostaglandins (PGs) generation from arachidonic acid.
Drug indication: For the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, chronic low back pain, acute pain and gout (Tripathi, 2013).
Analytical methods: The drug samples (Etoricoxib) studied for determination of absorption maxima (λmax) in phosphate buffer pH 7.4. The analytical method was validated in terms of preparation of calibration curve etc.
Determination of absorption maxima (λ_{max}): The absorption maxima of drug were determined by scanning drug solution in double beam ultraviolet spectrophotometer between 200 to 400 nm wavelengths. 25 mg of drug was dissolved in 25 ml of various dissolution medium (phosphate buffer pH 6.8) in 50 ml volumetric flask, sonication process was also applied in bath sonicator for 20 min to obtain 1000 µg/ml solution. The resulting solution was labeled as Stock-I. 1 ml of Stock-I solution was diluted up to 100 ml with same buffered solvent separately with the addition of sonication process for 20 min to obtain 10 µg / ml solution. The spectrum of these solutions was run in 200 – 400 nm range in double beam UV spectrophotometer (Shimadzu, UV-1800, A11454500755/UV-1800, Shimadzu Corporation, Kyoto, Japan). [81]
Preparation of calibration curve: 25 mg of drug was dissolved in 25 ml of various dissolution medium (phosphate buffer pH 6.8) in 25 ml volumetric flask with addition of sonication process in bath sonicator for 20 min to obtain 1000 µg/ml solution. The resulting solution was labeled as Stock Solution-I. From the above stock solution-I 10 ml was again diluted with 100 ml of dissolution medium (phosphate buffer pH 6.8) to obtain 100 µg / ml solution. The resulting solution was labeled as Standard Stock Solution-II.
From above standard stock solution-II 1 ml, 2.5 ml, 4.0 ml, 6.5 ml and 8.0 ml aliquots were withdrawn and diluted up to 10 ml with respective solvent (phosphate buffer pH 6.8) in 10 ml volumetric flasks to get concentration of 10 µg / ml, 20 µg / ml, 40 µg / ml, 65 µg / ml and 80 µg / ml respectively. The

absorbance of each solution was measured separately at 233 nm in phosphate buffer pH 6.8 respectively for etoricoxib. The absorbance was measured and standard curve was plotted between absorbance vs. concentration.

Preformulation studies of drug sample: Preformulation studies may carry out to standardize a spectrophotometric method of estimation for ETB and to investigate any possible drug polymer interaction. Melting point determination, Determination of distribution coefficient, Drug polymer interaction was studied by carrying out Fourier Transform Infrared (FTIR) spectral studies etc.

Organoleptic properties: The organoleptic properties of drug was whitish yellow color, slightly pungent odor and slightly sweet taste.

Microscopic examination: Microscopic examination of the plumbagin sample was done to study the nature / texture of the powder. A pinch of drug powder was spread on a glass slide and observed under phase contrast microscope.

Physical Characteristics Density: The drug powder was exactly weighed (M) and poured gently through a glass funnel into graduated cylinder and the volume was noted and bulk density was determined. The tapped density was determined using tapped density apparatus. A bulk and tapped density of etoricoxib is to be 0.312 gm / cm^3 to 0.326 gm / cm^3, respectively.

Particle size: The average particle size (davg) of drug was determined by using a microscope (66172/Olympus, 100 X, Olympus (India) Pvt. Ltd., New Delhi) fitted with ocular micrometer and stage micrometer. The particle size of unmilled drug powder was 41 µm.

Flow properties: The flow properties of drug powder were characterized in terms of carr's index, hausner's ratio and angle of repose. The Carr's index ((IC)) and Hausner's ratio (HR) of drug powders were calculating according to following equation:

- Carr's Index (IC) = ρTapped - ρBulk / ρTapped
- Hausner's ratio (HR) = ρTapped / ρBulk

The angle of repose (θ) was measured by fixed height method. This was calculated by following equation:

- Angle of repose (θ) = tan-1 2 H / D

Where H is the surface area of the free standing height of the powder heap and D is diameter of heap that formed after powder flow from the glass funnel.

Solubility determination: The solubility of drug was determined in various solvents (Water, 0.1 N HCl, phosphate buffer pH 4.5, phosphate buffer 6.8 and phosphate buffer 7.4). Sodium thiosulphate was added to the medium, when phosphate buffer pH 6.8 and phosphate buffer pH 7.4 were used to prevent oxidation. The excess amount of drug etoricoxib was added to 100 ml of medium and stirred continuously overnight at 37±0.5ºC. The solubility value of drug etoricoxib in different medium was determined by above UV-Visible spectrophotometric method.

Partition coefficient: The partition coefficient of drug was determined in n- octanol: phosphate buffer pH 6.8 solution. An accurately weighed (100 mg) amount of drug was added into 25 ml each of an n-octanol and buffer phase in a separating funnel. The mixture was shaken for 24 h until equilibrium reached. Both phases were separated and collected separately, filtered. The amount of drug solubilized in aqueous phase was diluted and determined by UV-Visible spectrophotometric method. The amount of drug in organic phase was calculating by subtracting the amount of drug in aqueous phase from the total drug taken. The partition coefficient of drug was calculated from the ratio between the concentrations of drug in organic and aqueous phase using following equation.

Log P (oct / pH 6.8) = Log (C Oct / C pH 6.8) equilibrium

Drug-excipient compatibility studies: The compatibility i.e. drug-excipient interaction studies are useful for dosage form design. In general, solid-state reactions are slower and more difficult to interpret than reaction in solution, because of a reduced number of molecular constants between drug substances and excipients molecules and the occurance of multiple-phase reactions. For

compatibility studies drug / excipients ratio are choosen and investigated based on the reasonable drug / excipients (1:1 ratio) in the final product.

Table 1: Drug-excipient combinations for compatibility study

Batch no.	Drug-excipient combinations
S1	Pure drug
S2	Drug + all excipients (1:1 ratio)

Preparation of Topical gel: Topical gel with drug in different combinations prepared by the high speed homogenization method. The composition of the formulation was prepared with oil as a carrier, Edetate disodium, glycerin and polysorbate 80 in purified water by high speed homogenization. The various formulations were prepared using varying amount of gelling agent and penetration enhancers. The preparation of emulsion was same in all the formulations. The gel phase in the formulations was prepared by dispersing Carbopol 940 in distilled water with constant stirring at a moderate speed using mechanical shaker, then the pH was adjusted to 6–6.5. The oil phase of the emulsion was prepared by dissolving span 20 in castor oil. The aqueous phase was prepared by dissolving tween 20 in distilled water and required weighed quantity of drug was dissolved in ethanol. Now all prepared both solutions were mixed with the aqueous phase. Both the oily and aqueous phases were separately heated to 70– 80°C, then the oily phase was added to the aqueous phase with continuous stirring until it got cooled to room temperature. The obtained emulsion was mixed with the gel base in 1:1 ratio with gentle stirring to obtain the emulgel. The composition of different formulations has been discussed in Table 2.

Table 2: A various composition of different Topical gel formulations

Ingredient	ETEG1	ETEG 2	ETEG 3	ETEG 4
Etoricoxib (mg)	100	100	100	100
Carbopol 934 (g)	0.5	1	1.5	2
Neem oil (ml)	7.5	7.5	7.5	7.5
Tween 20 (ml)	0.5	0.5	0.5	0.5
Span 20 (ml)	1	1	1	1
Polyvinyl pyrrolidone (mg)	50	50	50	50
Ethanol (ml)	2.5	2.5	2.5	2.5
Water (ml)	q.s	q.s	q.s	q.s

Characterization of Topical Gel: The preparing systems was evaluated with various parameters such as Organoleptic Evaluation, physical Evaluation of gel, determination of pH, spread ability, tube Extrude ability, viscosity, in Vitro Diffusion Studies, skin irritation study, drug release kinetic data analysis: The release data was fitted to following mathematical models.

Physical examination: The prepared Topical gel formulations were inspected visually for their color, appearance and consistency. The prepared emulgel formulations were inspected visually for their Feeling after application on skin, color intensity, pH determination, consistency and extrudability determination. The gels were tested for homogeneity by visual inspection prior to the gels being filled into containers. They were also tested for their appearance and presence of any aggregates.

Globule size and polydispersity index (PDI): GS and PDI were determination by mean droplet size and polydispersity index of the emulsions was determined by Dynamic Light Scattering (DLS) technique. The Topical gel was evaluated for globule size and polydispersity index.

Viscosity Determination: The viscosity of the formulated batches was determined by using a cone and plate viscometer with spindle 7 with Brook field viscometer. The assembly was connected to a thermostatically controlled circulating water bath maintained at 25°C. The sufficient quantity of gel base was filled in wide mouth jar separately and it should sufficiently allow dipping the spindle. Spindle was allowed to move freely into the emulgel and the reading was noted with RPM of the spindle was adjusted to 2.5 RPM. The viscosities of the formulations were recorded.

Spreadability: Spreadability was determined by an apparatus mimicking the extensometer which was suitably modified in the laboratory and used for the study. This apparatus is made of a wooden block affixed with a pulley on one end. The principle involved in this spreadability method is 'slip' and

'drag', following which the spreadability characteristics of nanoemulsion gels were measured. A ground glass slide is fixed onto the wooden block, while another upper glass slide having the same dimensions as that of the fixed ground slide is provided with a hook and placed on the ground slide. 2 g of Topical gel were placed in between the glass slides and a weight of 1 kg was applied on the upper slide for 5 min to form a uniform film of the formulation between the slides. Excess of the formulation was scrapped off from the edges. The top plate was then subjected to a fixed weight of 100 g with the help of string attached to the hook and the time (in seconds) required by the top slide to cover a distance of 7 cm was noted. A shorter interval indicates better spreadability. Spreading coefficient is determined by using the formula (Bhanu et al., 2011): S + m * l / t where, S = Spreadability,

m = Weight tied to upper slide, l = Length of glass slides, t = Time taken to separate the slides completely from each other.

Drug content determination: One gram each of Topical gel was taken and dissolved in methanol and sonicated for 1 h respectively. The resulting solutions were filtered with 0.45 µm filter to obtain clear solutions. The drug content was analyzed using a UV spectrophotometer method at 350 nm.

In-vitro permeation studies: In-vitro permeation studies of the developed gels were carried out using excised pork ear skin. The pig ears were collected from the local slaughter house in phosphate buffered saline. Hair was shaved off using a scapel, subcutaneous/ underlying tissue was scrapped off and the skin was cut into small pieces. Skin with irregularities or tears was excluded from the study. Skin samples were stored at -20 0C until further use. Franz diffusion cells (diffusion area of 3.8 cm2) were utilized for performing permeation studies of the formulations (Topical gel) and M.C. Pork ear skin was chosen the tissue of choice for evaluation of permeation due to its anatomical similarity to human skin (Barot et al., 2012; Barbero and Frasch 2009). Phosphate buffer (pH 6.8) (75 ml) was filled into the receptor chamber and maintained under constant stirring with a magnetic stirrer at 100 rpm (Salunkhe et al. 2013). Pork skin was fixed between the donor and receptor compartments of the cell with the stratum corneum positioned towards the donor compartment and allowed to equilibrate for 30 min. The buffer media was maintained at a temperature of 37 ± 0.5 0C. Formulations 100mg containing Topical gel was applied onto the pork skin surface. Sample withdrawal of 1 ml was made from each cell at regular time intervals of 0, 2, 4, 6, 8 upto 24 h and replaced with equal volume of buffer media (Zhu et al., 2009). The amount of etoricoxib was determined in permeation samples using UV spectrophotometric studies at 350 nm. At the end of permeation studies, the percentage drug retained on the skin was determined by washing the skin three to four times with methanol. The solution was filtered through 0.45 micron-filter and was analyzed for the drug content using UV spectrophotometric method. For estimation of the drug retained in the skin, the skin was cut into small pieces and homogenized in methanol. The resultant dispersion was sonicated for 10 min followed by vortexing for 15 min. The samples were centrifuged at 6,000 rpm for 15 min, supernatant was filtered through 0.45 micron-filter and analyzed for their drug content.

Results and Discussion: Etoricoxib drug was estimated analytical process by reported UV spectrophotometric methods. The reported UV spectrophotometric methods were slightly modified and optimized according to the existing laboratory conditions. The drugs were estimated in the dissolution medium (pH Phosphate buffer 6.8). The calibration curves in the dissolution medium i.e. phosphate buffer pH 6.8 prepared with drug solutions of known concentrations. The absorbance of each solution was measured separately at 233 nm for phosphate buffer pH 6.8. The absorbance was measured and standard curve was plotted between absorbance vs. concentration. The result of linearity is as shown in . The calibration curves show excellent linearity of data as evidenced by the values of correlation coefficients that were found to be greater than 0.998. The curves were found to be

recti-linear in the concentration range 5 µg / ml to 25 µg / ml for the drug.

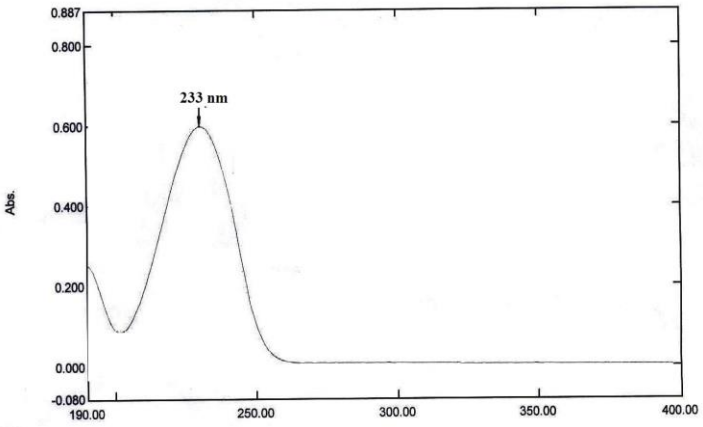

Figure 2: Absorption maxima (λ-max) of etoricoxib (10 µg) in phosphate buffer pH 6.8 solution

Preformulation studies used for the development of dosage forms of model drug substances. Etoricoxib was found to be light yellow, odorless, bitter taste in nature.

Table 3: Organoleptic characteristics of etoricoxib

Properties	Etoricoxib
Color	Whitish yellow
Odor	Slightly pungent
Taste	Slightly sweet

Microscopic examination of drug was crystalline in nature. A bulk and tapped density of etoricoxib is to be 0.412 gm / cm3 to 0.426 gm / cm3, respectively. The particle size of unmilled etoricoxib powder was 113 µm. The milled drug powder exhibited showed excellent flow properties. The result is given in Table 6.3.

Table 4: Flow properties of drug (n = 3)

Drug	Type of powder	Carr's index (%)[a]	Hausner'sratio [a]	Angle ofrepose θ [a]
Etoricoxib	Unmilled	12.38±0.018	1.12±0.014	26.4±0.121
	Milled	9.06±0.016	1.03±0.007	18.9±0.093

a; all values are in mean ± Standard deviation

The prepared emulgel formulations were examined visually for their feeling after application on skin, color intensity, pH determination, consistency and extrudability determination. The emulgels were tested for homogeneity by visual inspection prior to the gels being filled into containers. The Formulation ETEG4 was best formulations among all the prepared formulations. The consistency of ETEG4 was excellent and the result is shown in Table 6.7. The globule size and polydispersity index (pdi) (Figure 6.5 – 6.8), viscosity, spreadability and drug content of prepared formulations also examined. All the result is shown in Table 6.7 and the result concluded that ETEG4 was best formulation. This formulation ETEG4 was prepared emulgel Carbopol 940 (2g), PVP, castor oil base.

Conclusion: Oral route is the majority ideal route close to patient execution; though, oral administration is additional prone to hepatic first pass metabolism required higher dose of drug. Topical drug administration is a localized drug delivery system everywhere in the body during ophthalmic, vaginal, rectal and skin as topical routes. Skin is one of the most readily available organs on human body for topical management and is the major route of topical drug delivery system. Emulsion as a dispersed system, which consists of small droplets and well distributed in to immiscible vehicle. Topical gel ensures tolerable localization and dispersion of the drug by passable percutaneous absorption within the skin to enhance its local efficacy and/or through the skin to the circulation to polish its systemic effect.

References

1. Alberti I, Kalia YN, Naik A, Bonny J, Guy RH, "Effect of ethanol and isopropyl myristate on the availability of topical terbinafine in human stratum corneum in vivo," Int J Pharm, 2001, 219, 11–19.

2. Alexander A, Tripathi DK, Verma TS, Maurya J, Patel S, "Mechanism responsible for Mucoadhesionof Mucoadhesive Drug Delivery System: A review," Int. J. Appl. Biol. Pharm. Technol, 2011, 2.
3. Arora R, Khan R, Ojha A, Upadhyaya K, Chopra H (2017) Emulgel: A Novel Approach for Hydrophobic Drugs, International Journal of Pharmacy and Biological Sciences, 2017, 7, 3, 43 – 60.
4. Arora R, Khan R, Ojha A, Upadhyaya K, Chopra H, "Emulgel: a novel approach for hydrophobic drugs," International Journal of Pharmacy and Biological Sciences, 2017, 7, 3, 43 – 60.
5. Arora R, Khan R, Ojha A, Upadhyaya K, Chopra H, "Emulgel: A Novel Approach for Hydrophobic Drugs," International Journal of Pharmacy and Biological Sciences, 2017, 7, 3, 43 – 60.
6. Bakshi P, Jiang Y, Nakata T, Akaki J, Matsuoka N, Banga AK, "Formulation Development and Characterization of Nanoemulsion-Based Formulation for Topical Delivery of Heparinoid,: Journal of Pharmaceutical Sciences, 2018, 30, 1-8.
7. Barradas TN, Senna JP, Cardos SA, Holanda e Silva GD, Elias Mansur CR, "Formulation characterization and in vitro drug release of hydrogel- thickened nanoemulsions for topical delivery of 8- methoxypsoralen," Materials Science & Engineering, 2018, S0928-4931, 17, 34962-7.
8. Barradas TN, Senna JP, Cardoso SA, Holanda ESilva K, Elias Mansur CR, "Formulation Characterization and In Vitro Drug Release Of Hydrogel- Thickened Nanoemulsions For Topical Delivery Of 8-Methoxypsoralen," Materials Science & Engineering (Article in press), 2018.
9. Calder Lorena, Llaurad Elisabet, Companys Judit, Pla-Paga Laura, Boqu Noem, Acute Effects of Turmeric Extracts on Knee Joint Pain: A Pilot, Randomized Controlled Trial. Journal of Medicinal Food, 2020,1-20.
10. Cameron M, Chrubasik S, "Topical herbal therapies for treating osteoarthritis," Cochrane Database Syst Rev., 2013, 5, CD010538.
11. Carolyn EH, Renee L, Bennett, Ishik C and Williams HB, "Activities of fluconazole and ketoconazole against ketoconazole susceptible and resistant candida albicans," Antimicrobial and chemotherapy, 1988, 23, 209-212.
12. Cevc G, Vierl U, "Nanotechnology and the transdermal route: a state of the art review and critical appraisal," J Control Release, 2008, 141, 3, 277– 299.
13. Chellapa P, Mohamed AT, Keleb EI, Elmahgoubi A, Eid AM, Issa YS, Elmarzugi N, "Nanoemulsion and Nanoemulgel as a Topical Formulation," IOSR Journal of Pharmacy, 2015, 5, 10, 43-47.
14. Chen H, Khemtong C, Yang X, Chang X, Gao J, "Nanonization strategies for poorly water soluble drugs," Drug Discov Today, 2011, 16, 7–8, 354– 360.
15. Chojnicka A, Sala G, Cornelus G, "The interaction between oil droplets and gel matrix affect the lubrication properties of sheared emulsion filled gels," Food hydrocolloids, 2009, 23, 1038-1046.
16. Choudhurya H, Gorainb B, Pandeya M, Chatterjeea LA, Senguptac P, Dasb A, Molugulua N, Kesharwani P, "Recent update on nanoemulgel as topical drug delivery system," Journal of Pharmaceutical Sciences, (Article in press), 2017.
17. Dawson AL, Dellavalle RP, Elston DM, "Infectious skin diseases: a review and needs assessment," Dermatol Clin, 2012, 30, 141–151.
18. De Faro Silva R, Barreto AS, Trindade GDGG, Lima CM, Araújo AAS, Menezes IRA, Candido EAF, Santana ÉTN, Silva-Júnior WM, Quintans
19. JSS, Coutinho HDM, Kim B, Quintans-Júnior LJ. Enhancement of the functionality of women with knee osteoarthritis by a gel formulation with Caryocar coriaceum Wittm ("Pequi") nanoencapsulated pulp fixed oil. Biomed Pharmacother. 2022, 150:112938.

20. Fang W, Yang F, Li W, Hu Q, Chen W, Yang M, Chen J, Qiu L. Dexamethasone microspheres and celecoxib microcrystals loaded into injectable gels for enhanced knee osteoarthritis therapy. Int J Pharm. 2022 Jun 25;622:121802.
21. Forster TH, Jackwerth B, Pitterman W, Rybinski W, Schmitt M, "Properties of emulsions," Cosmet. and Toile, 1997, 1, 1-6.
22. Gondaliya DP and Pundarikakshudu K, "Studies on preparation, characterization and Transdermal permeation of nimesulide from aqueous and emulgel," Indian drugs, 2002, 39, 465-473.
23. Gu¨ngo¨r S, Sedef Erdal M, Aksu, "New Formulation Strategies in Topical Antifungal Therapy," J Cosmet Dermatol Sci Appl, 2013, 03, 56–65.
24. Guido S, Fred V, Martien A, Cohen S, George A, "Oil droplet release from emulsion filled gels in relation to sensory perception," Food hydrocolloids, 2007, 21, 977-985.
25. Gungor S, Erdal MS, Aksu B, "New Formulation Strategies in Topical Antifungal Therapy, Journal of Cosmetics," Dermatological Sciences and Applications, 2013, 3, 56-65.
26. Harshan H, Krishnapillai M, "Emulgel: An advance technique for penetration ofhydrophobic drugs," World Journal of Pharmacy and Pharmaceutical Sciences, 2016, 5, 3, 343-358.
27. Hideaki T and Yuya K, "Preparation of poly (N-isopropylacrylamide) emulsion gels and their drug release behaviours," Coll. and surf. B: Bioinformatics, 2008, 67, 92-98.