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FORMULATION AND EVALUATION OF NANOEMUGEL TRANSDERMAL DRUG DELIVERY SYSTEM OF INDOMETHASIN AND PIROXICAM

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ABSTRACT

Inflammation is a complex process, which is frequently associated with pain and involves occurrences such as the increase of vascular permeability, increase of protein denaturation, and membrane alteration. It is defensive response that is characterized by redness, pain, heat, and swelling and loss of function in the injured area. The most common causes of inflammation are infections, burns and trauma, and many types of immune reactions. Indomethacin and Piroxicam are a potent nonsteroidal anti-inflammatory drug with broad applications. The drug inhibits prostaglandin synthesis produced by cyclooxygenase enzymes, which are critical mediators of inflammation, fever, and pain. Indomethacin is approved by the US Food and Drug Administration (FDA) to manage acute pain, rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, bursitis, gouty arthritis, and patent ductus arteriosus

Gel formulation provides better application property and stability in comparison to cream and ointment .topical application of drug offers the advantages of delivering the drug directly to the site of action and acting for an extended period of time. The purpose of this study was to formulate and evaluate Indomethacin and Piroxicam topical Nano emugel for the treatment of Inflammation. Topical Nano emugel prolong residence time of drugs, improve bioavailability, and facilitate drug delivery through systemic route With this objective, Indomethacin and Piroxicam Topical Nanoemulgel as a model drug was prepared for the treatment of Inflammation.Nine different formulations of Topical Nano emugel Loaded with Indomethacin and Piroxicam were prepared by dispersion method The formulations were evaluated for physical parameters like: PH, Spread ability, Retention time, viscosity, skin irritancy, Homogeneity, uniformity of weight, drug content, buoyancy time, dissolution, and drug release mechanism. The formulations were optimized on the basis of buoyancy time and in-vitro drug release. The compatibility of the drug, polymers and other excipients were determined by FT- IR Spectroscopy. Results showed that the drug was compatible with polymers and other excipients. The Viscosity (cP) of all formulations was in the range 4560-6230cp. The Spread ability ranged from 19.14-25.43. All formulations are Homogenous with PH of 6-7. Extrudability was found to be in the range of 80-86% The formulation F6 and F9 obtaining Carbopol and Xanthan gum, respectively at the concentration of 40 % showed more than 97 % drug release at the end of 24 hours. All the tablet formulations followed non-Fickian mechanism of drug release. The stability studies were carried out for 3 months and result indicates that the selected formulation were stable throughout study period. The present study shows that oil phase oleic acid, emulsifiers like tween 20 and PEG 400 are suitable to form stable emulsion in the proportion of 3:1 Carbopol and Xanthan gum combination as gelling agent can be used to develop Nano emugel formulation of Indomethacin and Piroxicam

Keywords: Indomethacin, piroxicam, NSAIDS, Nanoemugel, Topical application, Buoyancy time, Carbopol and *Xanthan gum.*

INTRODUCTION

Introduction to Topical Drug Delivery and Nano emulsion-Based Systems

Topical drug delivery is one of the simplest and most convenient methods for administering drugs directly to the site of action through the skin or mucosal surfaces such as ophthalmic, rectal, vaginal, and cutaneous routes. These formulations are widely used in dermatological and cosmetic applications and are available in various forms ranging from solids and semisolids to liquids. The primary objective of topical administration is to produce a localized therapeutic effect; however, certain formulations may also exert systemic effects[1]. Compared to oral drug delivery, topical administration offers several advantages, including avoidance of first-pass metabolism, improved patient acceptance due to its non-invasive nature, ease of application, and the ability to withdraw treatment immediately if adverse effects occur. Additionally, topical systems can provide sustained drug delivery,

resulting in more stable plasma drug concentrations, particularly for drugs with short biological half-lives[2]. Despite these advantages, effective topical drug delivery is often limited by the barrier function of the stratum corneum, which restricts the permeation of most exogenous substances. Consequently, only a limited number of topical formulations are commercially available, emphasizing the need for advanced delivery systems[3].

Role of Nanotechnology in Topical Drug Delivery: Nanotechnology has emerged as a revolutionary approach in the field of drug delivery to overcome the limitations associated with conventional dosage forms. It involves the design and development of materials at the Nano scale that exhibit novel physicochemical properties. Nanotechnology-based delivery systems include nanoparticles, Nano capsules, Nano spheres, Nano suspensions, Nano sponges, Nano crystals, dendrimers, carbon nanotubes, and Nano emulsions. These Nano systems enhance drug solubility, stability, permeability, and bioavailability while minimizing side effects. In topical applications, nanocarriers improve drug penetration through the skin barrier and allow controlled and targeted drug release. Among various nanocarriers, nanoemulsions have gained significant attention due to their high solubilization capacity and excellent stability[4,].

Nano emulsion-Based Topical Drug Delivery Systems: Nanoemulsions are isotropic, thermodynamically stable systems composed of oil, surfactant, co-surfactant (Smix), and water, with droplet sizes typically ranging from 10 to 200 nm. The Nano sized droplets provide a large interfacial area, which enhances drug transport across biological membranes. Nanoemulsions are particularly effective for improving the solubility and bioavailability of lipophilic drugs. Major advantages of nanoemulsions include high drug loading capacity, improved absorption and permeability, low viscosity, transparent or translucent appearance, and enhanced physical stability. They can carry both hydrophilic and lipophilic drugs and protect drug molecules from hydrolysis and oxidation. Nanoemulsions also overcome stability issues associated with conventional macro emulsions, such as creaming, flocculation, coalescence, and sedimentation. Nanoemulsions can be administered via multiple routes, including topical, oral, and intravenous delivery, and can be incorporated into various dosage forms such as creams, gels, foams, liquids, and sprays. The use of Generally Recognized as Safe (GRAS) surfactants approved by regulatory agencies further supports their suitability for pharmaceutical applications[5].

Ingredients Used in Nano emulsion Formulation

Nanoemulsions consist of four primary components:

Oils: Oils solubilize lipophilic drugs and enhance drug transport through the stratum corneum and lymphatic system. The selection of oil significantly influences drug loading, release, and skin permeation characteristics.

Surfactants: Surfactants possess both hydrophilic and lipophilic regions and reduce interfacial tension between immiscible phases. They are classified as anionic, cationic, non-ionic, or zwitterion and play a crucial role in stabilizing nanoemulsions.

Co-surfactants: Co-surfactants further reduce interfacial tension and increase interfacial fluidity, facilitating the formation of stable nanoemulsions. They improve system entropy and enhance emulsification efficiency.

Additives: Additives such as antioxidants, preservatives, tonicity modifiers, stabilizers, and pH-adjusting agents are incorporated to improve shelf life, stability, and patient safety[6].

Techniques for Preparation of Nanoemulsions

Nanoemulsions can be prepared using either high-energy or low-energy emulsification techniques. High-energy methods include high-speed stirring, ultrasonic emulsification, high-pressure homogenization, micro fluidization, and membrane emulsification. These methods rely on mechanical energy to reduce droplet size. Low-energy methods include phase inversion temperature, emulsion inversion point, and spontaneous emulsification, which utilize changes in system composition or temperature to form nanoemulsions. Gels as Topical Drug

Delivery Systems: Gels are homogeneous, semisolid systems consisting of a liquid phase immobilized within a three-dimensional polymeric network formed by physical or chemical cross-linking. They are easy to manufacture, aesthetically appealing, and suitable for drug delivery via dermal, oral, buccal, nasal, and ophthalmic routes.

Gels can be classified based on colloidal phases, nature of solvent, rheological properties, and physical nature. Based on solvent type, gels are categorized as hydrogels (water-based), organ gels (non-aqueous), and xerogels (low solvent content). Rheologically, gels exhibit non-Newtonian behaviour and may be plastic, pseudoplastic, or thixotropic. Based on physical nature, gels may be elastic or rigid.

Emulgel: A Novel Topical Drug Delivery System. Emulgel is an advanced topical formulation that combines the advantages of both emulsions and gels. It is particularly useful for delivering hydrophobic drugs that are difficult to incorporate into conventional gel systems. In emulgels, the drug is entrapped in the internal phase of an emulsion, which is then incorporated into a gel base, providing controlled drug release and enhanced skin penetration. Emulgels offer improved stability, patient compliance, non-greasy texture, and better drug bioavailability compared to traditional topical dosage forms such as creams and ointments. Due to these benefits, emulgels represent a promising and rapidly developing area in topical drug delivery research. [7]

MATERIALS AND METHODS

CHEMICALS AND REAGENTS

The following materials that were either AR/LR grade or the best possible grade available were used as supplied by the manufacturer without further purification or investigation. Piroxicam , Indomethacin ,Xanthan gum ,PEG 400 ,Tween 20 ,Oleic acid ,Carbopol 940 Ethanol.

Preformulation Studies

Preformulation study is one of the important prerequisites in development of any drug delivery system. It gives the information needed to define the nature of the drug substance and provide a frame work for the drug combination with pharmaceutical excipients in the dosage form.

Hence, Preformulation studies on the obtained sample of drug for identification including colour tests, solubility analysis, melting point determination and compatibility studies were performed. [8]

Identification: The obtained sample was examined by infrared absorption spectral analysis.

Solubility Analysis: Preformulation solubility analysis was done, which include the selection of suitable solvent, to dissolve the respective drug as well as various excipients used for the fabrication of Nanoemugels

Melting point determination: Melting point determination of the obtained sample was done because it is a good first indication of purity of the sample, since the presence of relatively small amount of impurity can be detected by a lowering as well as widening in the melting point range

Preparation of Reagents & Solutions

a) Preparation of Stock Solution

Accurately weighed 100 mg of Indomethacin and Piroxicam was dissolved in 10ml of methanol in a 100ml of volumetric flask and make up the volume with pH 6.8 buffer solution.10ml of this solution was taken in a 100ml of volumetric flask and make up the volume with pH 6.8 buffer solutions to get working stock solution having concentration 100 µg/ml.

b) Analytical Methods

The UV Spectrophotometric analytical method was developed for Indomethacin and Piroxicam using a UV double beam Spectrophotometer (UV 1700, Shimadzu, Japan). Indomethacin and Piroxicam prepared as above was scanned for absorbance in UV double beam spectrophotometer between range 200 to 400 nm, against distilled water as blank. It was found that the solution showed absorbance maxima of 233 and 262 nm.

Standard Calibration Curve for Indomethacin and Piroxicam

From this stock solution aliquots 1ml,2ml,3ml,4ml and 5ml were pipette out into a series of 50ml volumetric flasks and make up to mark with pH 6.8 buffer solution in order to get a concentration within the Beer's range from 2-14µg/ml.

The absorbance of the resulting solution was then measured at 262 and 233 nm using UV spectrometer against respective parent solvent as a blank. The standard curve was obtained by plotting absorbance v/s. concentration in µg/ml.

Compatibility study using FT-IR

The infrared spectroscopy of the pure drug sample was carried out to identify the drug. Infrared spectroscopy was conducted using a Thermo Nicolet FTIR and the spectrum was recorded in the region of 4000 to 400 cm-1. The procedure consisted of dispersing a sample (drug and drug-excipient mixture, 1:1 ratio) in KBr (200-400 mg) and compressing into discs by applying a pressure of 5 tons for 5 min in a hydraulic press. All spectra were collected as an average of three scans at a resolution of 2 cm-1. The interaction between drug-excipients was observed from IR-Spectral studies by

Observing any shift in peaks of drug in the spectrum of physical mixture of drug.

Formulation Development of Indomethacin and Piroxicam Nano Emugel: Formulation of Indomethacin and Piroxicam Nano Emulsion[9]

Indomethacin and Piroxicam was added to the mixture of tween 20, PEG 400, and oleic acid ratios (table 3) taken from the pseudo ternary phase diagram. The water was then added drop wise to the above solution and stirred at room temperature

Formulation of Indomethacin and Piroxicam Nano emulgel[10]

A measured amount of Xanthan gum was added to distilled water and mixed it properly using a magnetic stirrer. The stirring was carried out uniformly and the gel was placed in the refrigerator for 24 h. The formulation (F1-F9) was prepared using S3 Nano emulsion containing a Smix ratio of 3:1 given in table 4

Evaluation of Nanoparticles

Transmission electron microscopes

The size and shape of nanoemulgel were examined by transmission electron microscope (TEM) (Philips CM 10, Philips electron optics, Eindhoven, The Netherlands) with the image software. The drug loaded emulsion was spread on firmware-coated copper grids and absorbed after complete air drying.

Particle size analysis

The particle size of the formulated nanoemulgel was measured using the dynamic light spectroscopy by using Zeta seizer (ZS 90, Malvern Instrument Ltd, and UK). The prepared nanoemugel was diluted with deionized water (1:1000) and measured for the particle size scattering method or photon correlation.

Measurement of zeta potential

Zeta potential for nanoemulgel was estimated using Zeta sizer (ZS 90, Malvern Instrument Inc., UK) by using an electrophoretic light scattering method. The formulated sample was placed in zeta cells and results were analysed. The average of three measurements with Standard Deviation (±SD) was reported. [11, 12, 13]

Evaluation of indomethacin and piroxicam topical Nano Emugel

Physical examination

The prepared gels were inspected visually for their colour, homogeneity, consistency, spread ability and phase separation

Homogeneity.

All developed gels were tested for homogeneity by visual inspection after the gels have been set in the container. They were tested for their appearance and presence of any aggregates.

Grittiness

All the formulations were evaluated microscopically for the presence of particles if any no appreciable particulate matter was seen under light microscope. Hence obviously the gel preparation fulfils the requirement of freedom from particular matter and from grittiness as desired for any topical preparation. [14, 15]

Extrudability study

A good gel extrude optimally from the gel with slight pressure applied. The extrudability of formulations from aluminium collapsible tubes was determined using universal tube filling machine. Aluminium collapsible tubes filled with 10g gels were held between two clamps. A tube was compressed and extrudability of the formulation was determined in terms of weight in grams required to extrude a 0.5 cm. ribbon of gel in 10 seconds.[16]

Measurement of pH

The pH of Nano emugel formulations was determined by using digital pH meter. One gram of gel was dissolved in 100ml of distilled water and stored for two hours. The measurement of pH of each formulation was done in triplicate and average values were calculated.

Drug content

A 100 mg of Nano emugel was taken and dissolved in 50ml of phosphate buffer pH 7.4 The volumetric flask were kept for 2 hours and shaken well in a shaker to mix it properly. The solution was passed through the filter paper and filtered. The drug content was measured spectrophotometrically at 208 nm against corresponding gel concentration as blanks.

Viscosity study

The measurement of viscosity of the prepared gel was done with a Brookfield Viscometer. The gels were rotated at 20and 30 rpm using spindle no. 64. At each speed, the corresponding dial reading was noted.

In-vitro diffusion studies

The in vitro diffusion studies of prepared gel were carried out in Franz diffusion cell using through a cellophanemembrane.100 ml of phosphate buffer was used as receptor compartment, and then 500 mg of gel containing mg of was spread uniformly on the membrane. The donor compartment was kept in contact with a receptor compartment and the temperature was maintained at 37±0.50. The solution on the receptor side were stirred by externally driven Teflon coated magnetic bars at predetermined time intervals, pipette out 5ml of solution from the receptor compartment and immediately replaced with the fresh 5ml phosphate buffer. The drug concentration on the receptor fluid was determined spectrophotometrically against appropriate blank. The experiment was carried out in triplicate.

Stability Study.

For the evaluation of stability study, maintaining the formulations at an ambient condition over a period of three months on temperature 40°C.

Spread ability

It indicates the extent of area to which gel readily spreads on application to skin or affected part. The therapeutic potency of a formulation also depends upon its spreading value. Spread ability is expressed in terms of time in seconds taken by two slides to slip off from gel which is placed in between the slides under the direction of certain load. Lesser the time taken for the separation of two slides, better the spread ability. It is calculated by using the formula:

S = M. L / T where,

M = wt. tied to upper slide

RESULTS AND DISCUSSION

Determination of absorption maximum (λ max)

The λ max of the Indomethacin and Piroxicam was found to be 262 and 233nm and combined 208nm in pH 6.8 phosphate buffers.

Calibration curve of Indomethacin and Piroxicam

The absorbance was measured in a UV spectrophotometer at 262 and 233nm in pH

6.8 Phosphate buffer. The linear plot between concentrations versus absorbance showed that Beer-Lambert's law was obeyed in concentration range of 50-250 µg/ml in pH 6.8 phosphate buffer (figure 25). The methods have shown good reproducibility. Correlation coefficient (r2) values were found to be 0.9993 in pH 6.8 phosphate buffer, which indicate linearity. The data of calibration curve of Indomethacin and Piroxicam is reported in table 5.

Melting Point Determination

Melting point of pure drug Indomethacin and Piroxicam was found to be 200.0ºC and it is within the range specified in the official limits

(243-246 °C), which complied with official standards, indicating purity of the drug sample.

Drug-excipient compatibility studies

Studies of drug-excipient compatibility represent an important phase in the pre formulation stage of the development of all dosage forms. The potential physical and chemical interactions between drugs and excipients can affect the chemical, physical, therapeutically properties and stability of the dosage form. Fourier transformed infrared (FTIR) spectroscopy was selected for checking of drug-excipient compatibility

Fourier transformed infrared (FTIR) spectroscopy

Because the frequency of vibrations within a chemical structure is very sensitive to how the atoms are arranged and how the atoms interact with neigh boring functional groups, not only can FTIR provide a detailed fingerprint of pharmaceutical substances of different physical forms, but also it can detect changes in hydrogen-bonding pattern of amorphous materials.

Infra-red spectrum of drug Indomethacin, Piroxicam and polymers were recorded over KBr disc method and obtained spectra were shown in the figure 26-29. In pure drug Indomethacin and Piroxicam, the characteristic absorption band at 3365.43cm−1was due to the stretching vibration of

N-H group. The absorption band at 3074.93 was due to the Ar-CH group, C-C symmetric band at 1707.78cm -1, and (C-N) stretching vibration at810.37cm-1. This further confirms the purity of Indomethacin and Piroxicam. All the characteristic peaks of Indomethacin and Piroxicam were present in the spectrum of drug and excipients mixture, indicating compatibility between drug and polymer. Hence, IR spectrum confirmed that there was no significant change in the chemical integrity of the drug. Results of all the IR-spectra were tabulated in table 7

Table:1 Formulation of Indomethacin and Piroxicam Nanoemulsion

Formulation Code	**Smix***	**Oleic acid (Smix)**	**Tween20:PEG400**	**Water**
S1	1:1	15	45	40
S2	1:2	15	45	45
S3	1:3	10	40	50

Note: Smix represents the ratio of surfactant to co-surfactant

Table No 2: Composition of Indomethacin and Piroxicam loaded Nano emulgel

Formulation (%)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Itraconazole	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Miconazole	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Carbopol 934	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Tween20:PEG400 (Smix)	38.7	38.4	38.8	34.5	35.2	36.4	35.6	35.8	38
Oleic acid	15	15	15	15	15	15	15	15	15
Water	31.8	31.6	31.7	35.5	34.8	33.9	34.4	34.2	32
Benzyl alcohol	1	1.5	1	1.5	1.5	1.2	1.5	1.5	1.5

Figure No 1: Formulation of Nano emugel

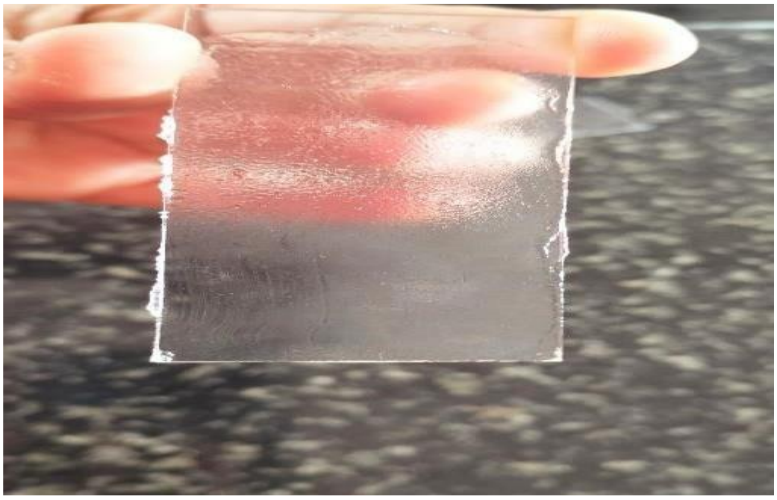

Figure No 2: Indomethacin and Piroxicam loaded Nano emulgel Gel

Table 3: Pre-formulation studies[17-20]

Preformulation parameters	Indomethacin	Indomethacin Piroxicam
Melting point	>149ºc	>160ºc
max	262nm	233nm
Solubility	Moderately soluble in Water, freely soluble in alcohol	Soluble in Water, freely soluble in alcohol
pH	6.5	6.5-7.5

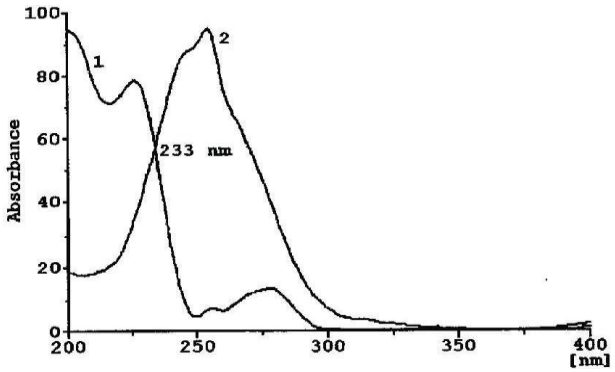

Figure No 3: UV spectrum of Indomethacin and Piroxicam in pH 6.

Table 4: Optical characteristic and statistical data of the proposed method

Parameters	Values
	pH 6.8 phosphate buffer
λmax (nm)	233, 262nm
Beer's law limit (µg /ml)	50-250
Slope (b)	0.0034
Intercept (a)	0.0115
Regression equation; (y= a+bx)	y = 0.0034x - 0.0115
Correlation coefficient (r2)	0.9993

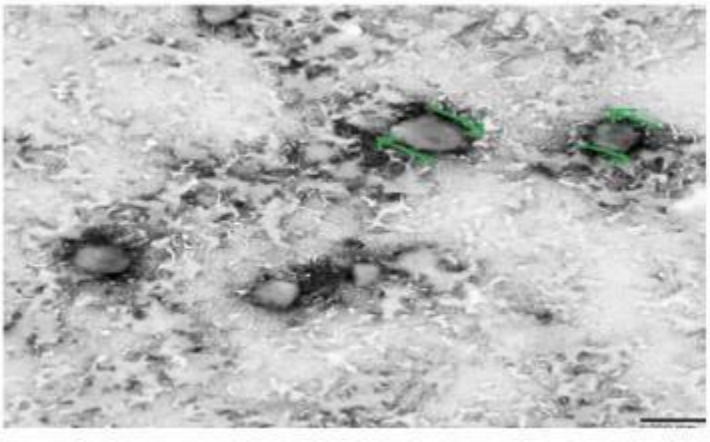

Figure No 4: TEM image of Indomethacin and Piroxicam loaded nanoemulgel

Table 5: Physical evaluation of various gel formulations

Formulation Code	Appearance	Viscosity(cP)	Spread ability	pH	Homogeneity
F1	Light yellow	4560	25.43	6.3	Homogeneous
F2	Light Blue	5260	22.56	6.2	Homogeneous
F3	Light Blue	4230	19.34	6.6	Homogeneous
F4	Light Blue	5670	22.65	6.8	Homogeneous
F5	Light Blue	4980	19.14	7	Homogeneous
F6	Light Blue	6230	19.65	6.9	Homogeneous
F7	Light Blue	4500	21.35	6.2	Homogeneous
F8	Light Blue	5190	22.45	6.5	Homogeneous
F9	Light Blue	4560	20.68	6.6	Homogeneous

Table 6: Extrudability study of various gel formulations

Formulation Code	Weight of Formulation	Weight of gel extruded	Extradibility amount (%)	Grade
F1	15.2	13.1	86.18	Good
F2	15.26	12.50	83.65	Good
F3	15.46	13.5	81.5	Good
F4	15.78	12.8	85.4	Good
F5	15.90	13	85.27	Good
F6	15.75	13.4	86.25	Good
F7	15.15	13.40	89.5	Good

F8	15.3	12.50	85.2	Good
F9	15.40	12.60	85.15	Good

Table 7: Drug content uniformity and percentage drug content (200µg/6cm2)

Formulation code	Drug content in mg mean SD	% of Drug content mean SD
F1	190±1.04881	95.0±0.70616
F2	195±1.04881	97.5±0.70616
F3	198±1.04881	99.0±0.70616
F4	195±1.04881	97.5±0.70616
F5	189±1.04881	94.5±0.70616
F6	195±1.04881	97.5±0.70616
F7	200±1.04881	100±0.70616
F8	197±1.04881	98.5±0.70616
F9	200±1.04881	100±0.70616

Table 8: Results of stability studies for formulation F9

Storage period	Stored at25ºC/60% RH Formulation F9		Stored at 40ºC/75% RH Formulation F9	
	% Drug content	% CDR	% Drug content	% CDR
Initial	99.10±0.023	97.12±0.29	99.10±0.023	97.12±0.29
1 month	98.48±0.053	97.10±0.40	98.06±0.072	97.05±0.53
2 month	98.15±0.078	97.06±0.46	97.44±0.042	96.88±0.30
3 month	97.72±0.024	96.01±0.51	97.15±0.040	96.70±0.91

Evaluation of Nanoemulsion

Transmission electron microscope (TEM)

TEM was implied for evaluating particle shape and size of nanoemulgel. The TEM results of optimized formulation F8 revealed that the particle size of nanoemulgel was found to be 195.1 nm, the same when compared with the particle analyser , with the uniform shape of particles

Particle size analysis

The particle size of the formulation was found to be 195.1 nm and the polydispersity index (PDI) was found to be 0.326 as shown in fig. 19. As per the thumb rule, the PDI value was found to be monodisperse and ensures stability

Measurement of zeta potential

The zeta potential of the prepared formulation was–0.278 mV, which was within the limit, and indicates thermodynamic stability as shown in fig. 20

Evaluation of Nano emugel

F7-F9 STABILITY STUDIES

Short term stability study was conducted for optimized formulation for the period of three months. Optimized formulation was selected based on *in-vitro* drug release study. Based on the results of *in-vitro* drug release study, formulation F3 and F7 were considered as optimized formulation as it prolonged the drug release for 24 hours. Stability study was performed for three month at two different storage conditions i.e. 25ºC/60% RH and 40ºC/75% RH. The selected formulation was evaluated for physical appearance, drug content and *in-vitro* drug release. The results showed that there was no significant change in physical appearance, drug content and drug release profile throughout the study period. Three months of stability studies revealed that; there was no any significant degradation of the drug. Thus prepared formulation was physically and chemically stable throughout its stability period. The result of stability studies were tabulated in table 13 and 14.

CONCLUSION

Inflammation is a complex process, which is frequently associated with pain and involves occurrences such as the increase of vascular permeability, increase of protein denaturation, and membrane alteration. It is defensive response that is characterized by redness, pain, heat, and swelling and loss of function in the injured area. The most common causes of inflammation are infections, burns and trauma, and many types of immune reactions.

Indomethacin and Piroxicam is a potent non-steroidal anti-inflammatory drug with broad applications. The drug inhibits prostaglandin synthesis produced by cyclooxygenase enzymes, which are critical mediators of inflammation, fever, and pain. Indomethacin is approved by the US Food and Drug Administration (FDA) to manage acute pain, rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, bursitis, gouty arthritis, and patent ductus arteriosus The current endeavor aims to create Indomethacin and Piroxicam Nano emugel for topical use. First, Nano emulsion was prepared by using S mix blend of tween 20; PEG 400 in different proportion from which S3 blend is selected (3;1) later Nano emugel were created utilizing a dispersion method with a variable Carbopol, xanthan gum The study has demonstrated various aspects and from the results gathered led to the following conclusions.

The preformulating parameters i.e. melting point, and solubility of the drug were evaluated. The results found to be satisfactory, and all the values obtained comply within pharmacopoeia standards. FTIR studies revealed that there was no chemical interaction between drug and other excipients. The Indomethacin and Piroxicam were formulated into nano emugel formulations were evaluated for different parameters such as homogeneity, pH, spread ability, and viscosity. The values obtained were found to be satisfactory and complies with standard range. All formulation batches showed acceptable results.

Results of rheological study showed all the formulation followed the non- Newtonian flow (shear thinning) as the shear rate increase viscosity of all formulation decreases which are required character for any topical gel. All the formulations were subjected to in-vitro drug release studies in 6.8 pH buffer for 18 hours. The results revealed that Indomethacin and Piroxicam gel formulations sustained the drug release for the prolonged period of time.

The release data was fitted to various mathematical models such as Higuchi, Korsmeyerpeppas, zero order and first order to evaluate the kinetics of drug release. The drug release showed peppas release. Among all batches, formulation F6 and F9 containing Carbopol Tween 20;PEG 400 and Xanthan Gum respectively showed sustained the drug release behavior over a period of 24 hours. Stability studies were carried for three months at 25ºC/60%RH and 40ºC/75%RH. Results showed that the tablets formulations were physio chemically stable throughout the study period.

From the above experimental data it can be concluded that the topical delivery of Indomethacin and Piroxicam gel formulations were successfully prepared by dispersion method Thus, Indomethacin and Piroxicam formulation can be used in future for treatment of Inflammatory disorders as combined therapy with improved bioavailability.

Future Scope of the Study: The work can be extended to the in-vivo studies to conclude in-vitro and in- vivo correlation. Work can be extended to the in-vivo buoyancy studies in humans. The formulation of Indomethacin and Piroxicam system can be tried with different grades of Carbopol, Tween 20: Peg 400 and Xanthan gum

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