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Development and Characterization of Nimesulide Loaded Organogel

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ABSTRACT

Organogel is three dimensional network of jelly like phase with macro molecule as major gelator compound and proportionate amount of organic and aqueous phase in them. They are thermodynamically stable in nature of biphasic solubility of drugs, biocompatible nature with skin. Organogel is used as matrix delivery of various drugs through transdermal route. This work had explained about the types of organogels, properties of organogels, parameters influencing in gelatin. Arthritis is a disease of the joint that involves inflammation in joints. The common symptoms of arthritis include pain, swelling, joint stiffness. This study was to resolve conventional dosage form of NSAIDs which increased the risk for serious gastrointestinal complications, when administered through oral route. Topical administration of NSAIDs could deliver to the site of action in rheumatoid disease which would reduce the side effects of the drug. The optimized formulation was characterized for drug content, pH, viscosity, spreadability, melting point, partition coefficient, stability studies etc.

INTRODUCTION

An organogel is a class of gel composed of a liquid organic phase with a three-dimensional cross-linked network structure. Organogel technology was extensively reviewed for human health applications in pharmaceutical purposes. Organogel is a semi-solid material composed of gelling molecules organized in the presence of organic solvent.[1]

Over a decade there has been much developments but still there are many disadvantages in dosage forms like tablets, capsules, parental, rectal, vaginal etc., this is for the development of novel drug delivery system. Novel topical drug delivery systems using lipid based carrier such as lecithin organogel has attained more importance and demands.[2] Topical drug delivery is the method of delivery of drugs through skin layer for local action and for systemic circulation by using different carrier vehicle. Topical dosage form includes creams, pastes, ointments, solutions and gels. They are mainly targeted for pain relief management, anti inflammatory effect, and contraceptive devices and wound healing effects.[3]

As compared to other semi solid topical dosage forms, gels have more important among the other topical formulations because of their properties such as smooth texture, elegant appearance, miscibility with skin layer secretions, transparency, biocompatible, highly penetrable, spreadable, prolong stability and ease of preparations.[4] Semi solid preparation of gel are mainly categorized in organogel and hydrogel based on solvent proportions and they are used in various forms like sustained release, controlled release, extended release, bio adhesive etc.[5]

Organogels are semi-solid systems in which three-dimensional network of gelator molecules are aggregates immobilize an organic liquid continuous phase in a nonpolar solvent. These compounds are cross linked structure either by physical or chemical interactions. They are immobilized in the organic phase within the network. Inflammation and pain in the joints are symptoms of the autoimmune disease (osteoarthritis, rheumatoid arthritis).[6]

Advantages of organogel[7]

1. Ease of administration.
2. Avoids first pass metabolism.
3. Controlled release of drug and longer shelf life for prolonged action used.

4. Good patient compliance.
5. Site specific drug delivery.
6. Avoid systemic adverse effects associated with oral administration of drug.
7. Reduces drug toxicity.
8. More stable than other types of gel.
9. Less greasy and can be easily removed from the skin.
10. Thermodynamically stable.

Disadvantages of organogel[8]

1) Route is not suitable for drugs that is irritate or sensitize the skin.
2) If impurity present than no gelling will occur.
3) Require proper storage condition.
4) When gel stands for long time, it often shrinks naturally and some of its liquid is pressed out.
5) It is most costly and it is not available in large scale.
6) Less stable to high temperature.

Classification of organogels

Classification of gel is based on nature of solvent, gelators and intermolecular interactions.

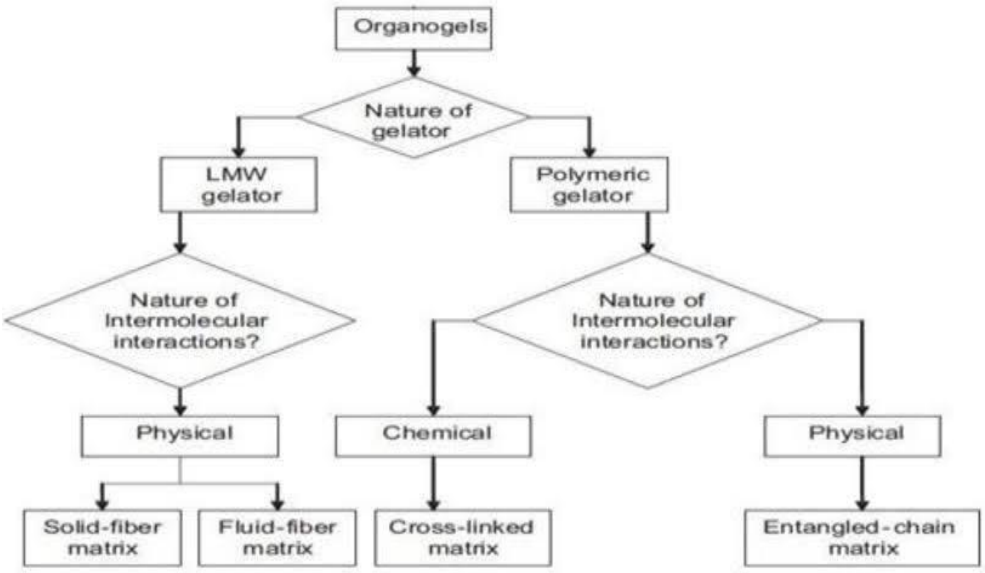

Fig.1: Classification of organogel.[9]

Low molecular weight (LMW) gelator

Polymers immobilize the organic solvent by forming network of crosslinked or entangled chains for chemical and physical gels. The low molecular weight organogelators depends on physical interactions for the formation of aggregates sufficiently long to overlap and induce solvent gelatin. Low molecular weight gelator is high ability of immobilized apolar solvents at small concentration.[10]

Solid-fibre matrix organogel

LMW gelator discovered so far self-assemble into solid networks when added to organic solvents. The variety of such gelators combined with the growing interest in organogel design. The general principle of solid matrix assembly, such as physical interactions and chirality effects, with special emphasis on organogels having current or potential drug delivery applications. Chirality related to the stability of the self assembled fibrillar networks of LMW physical gels.[11]

Fluid-fibre matrix organogel

Fluid fibre gel organic solvents in much the same way as solid fibres: aggetate size increases and structures immobilized the solvent as a result of surface tension. Fluid matrix systems are thermoreversible and can be transparent or opaque. Solid matrix have robust and permanent morphology over gel's lifespan, fluid matrices are transient structures in dynamic remodeling.[12]

Polymeric gelator

Polymeric gelator behave same to their LMW counter-parts, solidifying organic solvents based on physical interactions. Polymeric gel can vary from linear to hyperbranched or star shaped polymers. Preparation of star shaped alkylated poly glycerol forming polymer micelles in pharmaceutically acceptable apolar solvents such as ethyl oleate.[13]

Physical organogel

It forms three dimensional networks which are held together by non-conventional bonds such as hydrogen bonding, vander waals, electrostatic and coordination interactions. They are thermoreversible, which the system is a solution of polymer in organic liquid, whereas colling the hot solution phase resulting the gel phase.[14]

Chemical organogel

It is formed by entrapment of organic liquid in a chemical crosslinking network structure. The network is maintained by covalent bond: it is more robust and resistant in physical deformations. Chemical organogels have been developed based on copolymers including polymeric organogels based on acrylic acid and sodium allyl sulfonate, polymeric organogels based on acrylic acid and sodium styrene sulfonate and organogel of metalloporphyrin based conjugated microporous polymer.[15]

Types of organogel

- ❖ Lecithin organogel
- ❖ Pluronic lecithin organogel
- ❖ Sorbital monosterate organogel
- ❖ Eudraget organogel

- Fatty acid derived sorbital organogel
- Premium lecithin organogel
- Poly(ethylene) organogel

Lecithin organogel

Lecithin is a phospholipid extracted from various plants and animal tissues apart from egg yolk. Lecithin procured from natural source able to form the gelled structure. Lecithin organogels are jelly like phase consist of a 3-dimensional network of entangled reverse cylindrical micelles which immobilizes the microscopic external organic phase, thus turning a liquid into a gel.

Lecithin organogels have been found to be thermodynamically stable, biocompatible and non-irritant. These properties of the lecithin organogel used as controlled delivery vehicle.[16]

Pluronic lecithin organogel

The difference between pluronic lecithin organogel and lecithin gels , in the presence of pluronic (a hydrophilic polymer) and greater amount of water with the oil. It consist of isopropyl myristate quickly absorb from skin.

It is feels like a cream but is actually a gel. pluronic lecithin organogel is a thermostable, viscoelastic and biocompatible in nature. Pluronic lecithin organogel have also been found to produce minimal skin irritation. It has also been used as a delivery vehicle for both lipophilic and hydrophilic molecules for topical and transdermal applications and reduces side effects.[17]

Sorbital monosterate organogel

Sorbital monosterate is a non-ionic surfactant which is hydrophilic in nature and forms organogel of organic solvents for example isopropyl myristate, olive oil, soybean oil, sunflower oil. Sorbital monosterate is a better vehicle for topical delivery of aceclofenac. It is also used for parenteral drug delivery.

It includes the gelators sorbital monosterate (span60) and sorbital monopalmitate (span40) have ability to immobilize various solvents via isopropyl myristate at low concentration can be converted into gel with organic solvent.[18]

Eudraget organogel

The organogel is a mixture of eudraget and polyhydric alcohols such as glycerol, propylene glycol and liquid polyethylene glycol containing high concentrations of eudraget. These gel is prepared by dissolving the drug in propylene glycol, pouring the resulting solution into eudragit and immediately mixing with pestle, measure the gel consistency and spreading using a penetrometer. Viscosity was found to be increased by increasing concentrations of eudragit and decrease the drug content. The drug content in eudragit must be kept low to maintain gel rigidity. Drug release from eudragit organogel can be increased with increasing temperature. It show high gel rigidity and stability when drug concentration was low.[19]

Fatty acid derived sorbital organogel

Gels prepared by these gelators are thermostable, thermoreversible and opaque at RT for weeks. It forms a physical interaction forming a 3-D network structure. These gelators are hydrophobic non-ionic molecule have surface active properties and have the ability to immobilized various solvent viz isopropyl myristate, vegetable oil and it forms solid fiber matrix. Fatty acid gelators may also be prepared by dissolving the gelators in a water-in-oil emulsion at a higher temperature followed by the decrease of the emulsion temperature. The temperature results in the decrease in the solubility of the gelator with the precipitation and self assembly of the gelators into network of tubules and gets entangled so as to form a gelled structure.[20]

Premium lecithin organogel

The use of premium lecithin organogel as a carrier for drug delivery has been indicated that the gel help in achieving improve bioavailability in the tissue by improving the penetration of the bioactive agents.

This gel has been successfully used for most the bioactive agents like diclofenac and ibuprofen has been considered as vehicle of choice for intradermal drug delivery. This gel do not form pluronic derivative, which results in the avoidance of the skin-irritation highly thermostable and thermoreversible apart from its non-greasy and non-tacky help to improving nature.[21]

Poly [ethylene] organogel

Poly [ethylene] organogel have been extensively used as ointment bases. The formation of gelled structure may be attributed to the physical interactions of the solid fibers formed gelled structure while formed due to the precipitation of the polyethylene molecules, polyethylene is dissolved in mineral oil.

Solid fiber matrix may be formed when a heated mixture of the organogelators in a polar solvent is cooled down than below the solubility limit of organogelators. These results in the precipitation of the organogels as fiber like structure which undergo physical interaction, so as to form a gelled structure.[22]

Applications of Organogel

1. Topical delivery

Lecithin based organogels for topical delivery systems because of its ability to improve the transport rate of the bioactive agents, from its proven long term biocompatibility and low irritability potential. The topical administration of aromatic tetra-amidines loaded lecithin organogels were able to reduce the tumor cell growth with the highly tumorigenic cell line. The methyl nicotinate incorporated within lecithin gel showed almost complete absorption in experimental human models in a short period of time.[23]

a) Ointment

Drug nanoparticles can be water free ointment. The nanocrystalline form leads to an increased solubility of the drug in the topical dosage form for enhancing the diffusion of the drug into the skin.[24]

b) Creams / cosmetics

Skin care products are mainly emulsion based which contain water and oil phase. Some products are also there with only in oil phase but organogel belongs to this group. They are recommended for skin problems this is used for the dermatological cosmetics. skin barrier disorder depend in high dosage of physiological lipids due to a specific group in the organogel. Sorbitan and glyceryl monostearates olegogel with different types of vegetable oils which are biodegradable in lubricating greases. Oils such as rapeseeds and soybean oils yields gels with higher values in the viscoelastic functions.[25]

c) Ophthalmic

Eye drops are mostly use for the ophthalmic drug delivery but drawback of drug is not absorbed to targeted tissue because of immediate dilution by tear flow therefore needed repetitive dose. Suspension does not help in this condition as drug release from it depend on the rate of dissolution of drug particles due to continues change in composition. Therapeutic efficacy can be increase by prolonging the contact period of medicament which can be done by increasing the viscosity. Organic solvent as a continuous phase make them difficult to wash it due to three dimensional network of gel and drug release at steady rate. For delivery of poorly soluble drug in suspensions and ointments are recommended. Suspensions have advantages of prolonged residence time and avoidance of higher tonicity produced by water soluble drugs. The bioavailability of suspensions depends on the dissolution rate of the drug.[26]

2. Targeted drug delivery

Organogel are suitable for targeting particular organs because of their surface properties. It is easy to alter in vivo behavior by changing the stabilizer. The drug can be taken by the mononuclear phagocytic system which allows specific delivery. This can be used for targeting antifungal or anti-mycobacterium drugs to macrophages if the pathogens persist intracellularly. It can be improved the drug targeting to macrophages which were leishmania infected.[27]

3. Bioavailability enhancement

The poor oral bioavailability of the drug may be poor solubility or poor stability in the gastrointestinal tract. Organogel resolve the problem of poor bioavailability by solving the problem of poor solubility and poor permeability across the membrane. Bioavailability of poorly soluble oleanolic acid and hepatoprotective agent was improved. The therapeutic effect was significantly enhanced which indicate the higher bioavailability.[28]

4. Rectal drug delivery system

Organogels containing eudragit have been designed for rectal delivery of drugs. The drugs used are salicylates and ketoprofen. In vitro evaluation of the drug by using rotation disc method after a initial burst of drug release the drug follows apparent first order kinetics. The drug release has found to be dependent on the concentration of eudragit.[29]

5. In vaccines

The micro emulsion based organogels are used as a vehicle for delivery of hydrophilic vaccines. These systems offer various advantages like the slow release of antigen from the organogel system which produces a depot effect. This is basically useful where a short depot effect is effective eg. immunoadjuvants where a short depot action is through to be effective in enhancing the immune response. The vaccine has been found to be trapped in these niosomes which themselves are located within the surfactant network. The gel could be prepared by the addition of a hot aqueous noisome suspension containing the antigen to the organic solution, a vesicle in water in oil emulsion is formed. Organogel based formulation hold a good potential as carriers for vaccines.[30]

6. Bio-adhesive

Bio-adhesive of pharmaceutical interest are mucoadhesive this implies that the substrate for adhesion. Many of the alternate routes of administration like buccal, ophthalmic, nasal and vaginal lend themselves bio-adhesives because of the presence of the mucosal tissue.[31]

7. In suppositories

Suppositories are used in the formulation of some suppositories example- glycerin suppositories, ketorolac tromethamine suppositories and ketoprofen suppositories.[32]

8. Gelatin gels

Gelatin gels are employed in the preparation of hard and soft capsules that may be used to mask the unpleasant taste of solids and liquids.[33]

9. Microbiological media

Gelation gels are used as a solid media for the culture of microorganisms. The diffusion of antibiotics, vitamins and enzymes through the culture media is used in the microbiological assays. Such diffusion produces zones of either retarded or enhanced growth on seeded agar plates depending on the activity of the diffusion.[34]

10. Oral delivery

Improved bioavailability can be explained by the adhesiveness of the drug nanoparticles to the mucosa for increased saturation solubility leading to an increased concentration gradient

between gastrointestinal tract lumen and increased dissolution velocity of drug. The use of organogels for oral delivery of bioactive agents, that cyclosporine showed improved activity when the same was delivered orally to sorbital monoleate based organogel formulation. For the development of organogels with soyabean oil as an apolar phase. Non-steroidal anti-inflammatory drug was incorporated within the gelled structure. In vivo studies in rats showed that the organogels may be used a controlled delivery vehicle for oral delivery.[35]

11. Organogels as iontophoretic transdermal drug delivery system

Drug delivery extensively enhance by intophoresis mainly topical delivery of large hydrophilic species as proteins and peptides having poor penetration during passive condition. Problem aeries in case during use of solution, this problem overcome by drug loaded gels and hydrogels have been used as drug reservoir for iontophorosis but major drawback is the microbial contamination. Which leads to breakdown of gel structure and pH change. This problem can be avoided by use of organogels as the existence of organic solvent as the continuous phase by inhibit the microbial growth.[36]

12. Parenteral delivery

Sorbital monosterate organogel have a very short half-life at the injection site. For administration by the parentral route the drug must be solubilized and particle size below 5µm to avoid capillary blockage. Parentral delivery include salt formation, solubilization using cosolvents, complexation with cyclodextrin and currently liposomes. The diffusion of water molecule within the gelled structure which results in the subsequent disruption of the networked structure due to the emulsification of the gel surface. The development of a sorbital monosterate based organogels which has shown sustained delivery of a model antigen and serum albumin after intra-muscular administration. The results indicated the use of the formulation as depot l-alanine injectable in situ forming organogels may be used for the delivery of macromolecular bioactive agents. Organogels may be used for sustained delivery of bioactive agents after the same is being administered within the body. These gels are thermoreversible in nature. Experimental results indicates the organogels system which injected subcutaneously in rats release the bioactive agents for a period of 14-25 days with degradation of the gelled structure. Organogel were thermosensitive in nature which allowed release of the bioactive agent.[37]

Factors affecting organogel[38]

1. Organic solvent

Organic solvent is further divide into two parts:

a. Polar solvent

The polar solvent introduces into spherical lecithin micelles may be associated with an increase in cross sectional area of the lecithin polar region in which the solvent is arranged.

b. Non-aqueous solvent

A non-aqueous solvent is not particularly limited as long as it replaces water of the bacterial cellulose hydrogel completely without destroying the shape. Example dimethyl ether.

2. Salt addition

Salt may be attract part of water for hydration of the polymer allowing more formation of hydration of the polymer allowing more formation of intermolecular secondary bond this is called as salting out.

3. Phase transition temperature

It gives an insight into nature of microstructures that form the gelling cross linking network. For example a narrow PTT range is indicative of homogenous microstructures. For determination of PTT hot stage microscopy and differential scanning calorimetry is accurate and sensitive techniques.

4. Temperature

Depends on the chemistry of the polymer used and its mechanism of interaction. If the temperature is reduced once the gel is in the solution and degree of hydration is reduced. The cross linking often cannot be liquefied by dilution and changes temperature.

5. Functional group of solvent

Depends on the polymer used and its mechanism of interaction.

Example 1-octanol, n-alkens

6. Surfactants

Gel characteristicscan be varied by adjusting the concentration of the ingredients. Example polyethylene that function as a surfactant.

7. Physicochemical properties

- **Charge**

The charged groups on a polymer favors mucoadhesion, polyanions particularly polycarboxylates are preferred to polycations.

- **Solubility**

Mucoadhesive swell on contact with moisture and increasing the mobility of the polymer molecules at the interface and exposing more sites for bond formation.

- **Molecular weight**

Low molecular weight polymers which require a high concentration to build up viscosity and to set to gel possibly. It changes in entangled and interaction after the polymer.

Uses of Organogels[39,40]

I. For rheumatoid arthritis

Rheumatoid arthritis is a chronic disorder in which no known cure is formed. In the last decades, a shift in strategy toward the earlier institution of disease modifying drugs and the availability of medications have greatly improved and the outcomes that can be expected by most patients.

II. For osteoarthritis

Seventy percent of individuals older than 65 have radiographic signs of osteoarthritis and large percent have symptoms. The chronic nature of the disease and the high incidence of medication show side effects in the elderly, an understanding of the risks and benefits of non-steroidal anti-inflammatory druds in the treating osteoarthritis is crucial.

III. For the treatment of skin aging

Skin aging is an unavoidable aspect of human life in which premature skin aging can result from environmental pollutants and ultraviolet radiation exposure. Skin aging like lines, wrinkles, spots and pigmentation. Lecithin organogel is an effective vehicle for topical delivery of many bioactive agents which is used in aging treatment. Lecithin organogel can form a resistant to microbial growth, heat stable, optically transparent and micellar system. Lecithin organogel act as a penetration enhancer which can be expored as a carrier for anti-aging agents.

IV. Help in achievement of constant blood levels with lower dosage form of drug by continuous drug input. It is commonly used dosage form and it is used for avoided various side effects which may be shown in another dosage form.

V. The main advantage of topical delivery is to avoid first pass metabolism and avoidance of the risks and varied conditions of absorption like presence of enzyme, pH change, gastric emptying time and reduces frequency of drug dosing are another advantage of topical preparations.

VI. Clinicians faced problems with conventional dosage form for local delivery of drug so to avoid the risk of local delivery with topical preparations.

VII. It is used for acute gout treatment.

VIII. It is used for mild to moderate pain due to inflammation and tissue injury.

IX. This preparation are made for the localized effects at the site of their application by virtue of drug penetration into the layer of skin or mucous membrane with low concentration of active drugs in the blood stream for minimize side effects.

Preparation of Nimesulide loaded Organogel

Process: Accurate quantity of nimesulide is weigh and propyl paraben is dissolved in oil. Tween 80 and PEG 400 are mixed thoroughly in the proportion of 3:1 ratio to obtain the surfactant cosurfactant mixture (S_{mix}) which is used as gelator. Specified amount of the S_{mix} is added to the clove oil containing propyl paraben, nimesulide is added to the mixture of oil. Above mixture is stirred on magnetic stirrer for 20min. Subsequently, water containing methyl paraben is added drop-by-drop to the gelator solution with constant stirring on

magnetic stirrer. Carbopol 934 used as gelling phase added into microemulsion phase. Thus, organogel is obtained spontaneously on stirring the mixture. Depending on the composition of the gelator solution- water mixture, the system either formed gelled structure. The final concentration of nimesulide in organogel is maintained at 2%(w/w).[41]

F-2

F-3

Fig.2: Formulation of organogel F-2, F-3.

Other various methods

- **Hydration method**

Gel may be prepared by directly hydrating the inorganic chemical, which may produce dispersed phase of the dispersion. Than addition of water vehicle and other agents as

propylene glycol, propyl gallate and hydroxyl propyl cellulose used to enhance gel formation.[42]

- **Solid fibre method**

Solid fibre mechanism characterized by heating-cooling process of the solution containing the organic phase and organogelator. Organogelator molecules precipitate out as fibrils it forming a three dimensional fibrillar network structure that holds the organic phase.[43]

Table 1: Formulation of organogel

Sr. no	Formulation code	Drug (Nimesulide)	Clove oil	Methyl paraben	Carbopol 943	Water
1	F_1	4	1	0.03	1.0	20
2	F_2	5	2	0.04	1.0	20
3	F_3	6	2	0.04	1.5	20
4	F_4	7	2.5	0.04	1.5	20

Table 2: Formulation of molar ratio

Sr.No	Formulation code	Molar ratio (w/w)	Tween 80 (surfactant)	PEG 400 (cosurfactant)
1	F_1	3:2	4	2
2	F_2	3:1	3	1
3	F_3	3:2	3	2
4	F_4	3:1	3	1

Pre-formulation study

Pre-formulation studies are the leading phase in the development of dosage form that can be well defined as investigation of physical and chemical properties of drug substance alone and when combines with excipients. These physicochemical studies shown focus on properties of new compound that can affect the drug development and performance of an effective dosage form. A thorough understanding of physicochemical properties of a drug is essential which will ultimately provide a rationale formulation design.[44]

Goals of pre-formulation are:

- ❖ To determine the necessary physicochemical parameters of new drug substances.
- ❖ To determine the kinetic rate profile.
- ❖ To establish the physical characteristics.
- ❖ To determine the compatibility with common excipient.

Therefore, pre-formulation studies are compulsory to establish the identity a physicochemical parameter of selected drug combination.[45]

- ➢ Solubility study
- ➢ Melting point determination
- ➢ Organoleptic properties
- ➢ Partition coefficient determination
- ➢ UV spectrum of drug

- **Solubility study**

The quantitative solubility study, excess amount of drug is taken in cleaned test tubes containing 5 ml of different solvents (methanol, ethanol, acetone, chloroform, water) and test tubes are tightly closed. These test tubes are shaked while placed in water bath shaker for 24hrs at room temperature. After 24hrs the sample is centrifuged for 15minutes. At 15,000rpm by placed in cooling centrifuge, then suitably diluted and determined spectrophotometrically.[46]

- **Melting point determination**

The melting point was determined by using capillary fusion method. A small amount of drug was in capillary, thermometer was placed in melting point apparatus. Then the temperature at which drug crystals started melting and turning into liquid was noted down.[47]

- **Organoleptic properties**

The organoleptic properties are the study of general appearance like colour, odour, taste were performed by visual observations.

Colour: Small quantity of drug is placed in butter paper and observed in well illuminated place.

Odour: Small quantity of drug is smelled to identify the odour.

Taste: Very less quantity of drug is tasted to identify the taste.[48]

Partition coefficient of drug

Partition coefficient is measure of a drug lipophilicity and an indication of drug ability to cross cell membranes. It is defined as the ratio of unionized drug distributed between the organic and aqueous phase of equilibrium. Partition coefficient provides a means of characterizing the lipophilic and hydrophilic nature of the drug. Drug having values of P much greater than 1 are classified as lipophilic, whereas those with values much less than 1 are indicative of a hydrophilic drug. The partition coefficient is determined using an oil phase of n-octanol and water. In the case n-octanol and water.

Shake flask method

Partition coefficient study is determined by using shake flask method. Excess amount of the drug dissolved in 5ml of two solvents which is n-octanol and water together 1:1 and placed for 24hrs. After 24hrs, the two layers are separated and centrifuge for 15 mins at 15,000 rpm. The absorbance is found in UV spectrophotometer at the respective λmax after appropriate dilution.[49]

- **Determination of absorption maxima of drug by UV spectrophotometer**

Absorption maxima (λ_{max}) of drug was determined by UV Spectrophotometer. Stock solution containing nimesulide was prepared by dissolving 50mg drug in 25 ml of methanol. It was then sonicated for 10min and the final volume of solution was made up to 50 ml in a 50 ml standard flask to obtain a concentration of 1mg/ml. Then we pipette out 5ml from stock solution and volume make up to 50ml into a standard flask and the volume were made upto the mark using methanol. The resulting solution had a concentration of 100 µg/ml, the (1^o) primary stock solution preparerd. An appropriate dilution was scanned for determine λ max from 200-400 nm through UV spectrophotometer.[50]

Preparation of calibration curve of nimesulide in methanol

The stock solution was prepared by dissolving 50mg drug in 50ml of methanol. The primary stock solution was prepared by pipette out 5ml from stock solution and make volume up to 50ml (100µg/ml). Make dilutions in the range of 0.5µg/ml to 5µg/ml were prepared from stock solution. Dilutions were scanned for determining λ max from 200-400nm through UV Spectrophotometer.[51]

Characterization of Organogel[52-62]

Spreadability test

A sample of 0.5g of each formula was pressed between two slides and left for about 10 minutes where no more spreading was expected. Diameters of spreaded circles were measured in cm and were taken as comparative values for spreadability.

Skin irritation

Skin irritation study was performed in each group of four rats. The hairs was removed from the back of the rat with the help of hair removing cream and an area of $4cm^2$ was marked on both the sides. After 24h of depilation, the formulations were applied (100mg/rat) once a day for a week and sight was covered with cotton bandage. The rat was observed for sign and symptoms of any sensitivity and reaction that may occur and were classified as: no reaction, slight reaction, patchy erythema, moderate but patchy erythema, moderate erythema and severe erythema with or without edema.

Physical appearance

Colour

The colour of the gel formulations was checked out against white background.

Consistency

The consistency was checked by applying on the skin.

Greasiness

The greasiness was assessed by the application on to the skin.

Odour

The odour of the gels was checked by mixing the gel in water and taking the smell.

Homogeneity

Homogeneity was tested by visual inspection after allowing them to set in a container, they were evaluated for their appearance and presence of aggregates.

Grittiness

The formulations were evaluated microscopically under 40x magnifications for the presence of any particulate matter or aggregates.

FTIR spectroscopy of organogel

Fourier transform spectroscopy of organogel was performed for identification of that compound. FTIR spectroscopy of organogel was done. Various peaks in FTIR Spectrum were interpreted for identification of different group in the structure of organogel. FTIR spectroscopy can also be used to investigate any physicochemical interactions between different compounds.

Percentage drug content

To ensure uniform formulation of the gel. drug content of the gels was determined by dissolving an accurately weighed quantity of the gel (about 1 gm) added in 5ml organogel of different concentration (1%, 1.5%, 2.0%) and diluted in 25ml methanol, sonicate for 10 mins and fill it into Eppendorf, centrifuged for 15 mins. After that 1ml supernant layer taken and makeup volume upto 10ml with methanol. Then further diluted and analyzed under UV spectrophotometry analysis for nimesulide at 226nm. Drug content was determined from the standard curve of nimesulide.

***In vitro* determination**

- **Brookfield viscometer**

Viscosity of all the formulations was determined using brookfield viscometer. Viscosity was determined using the spindle rotating at 10rpm at 25^{o}C.

- **pH determination**

The pH of all the gel formulations was determined by using digital pH which was calibrated before measurements using standard buffer solution of pH 7 and pH 4. After calibration the electrode was dipped in an aqueous solution of gel (1g in 20ml water) at 25^{o}C which directly gives the pH of the gel formulation.

***In vitro* permeation studies**

In vitro permeation studies were performed by using franz diffusion cells for studying the dissolution release of various formulation of gel through a dialysis membrane with an effective diffusion area of 1.77 cm^2 and receptor volume of 20ml. 1g of gel sample was taken in dialysis menbrane. The diffusion studies carried out at 37 ± 1^{o}C using 250ml of phosphate buffer (pH 7.4) as the dissolution medium. The standard dialysis membrane (soaked in 20% ethanol for 24hrs before use) was fixed to one end of the cylinder with the aid of an adhesive to result in the permeation cell. One gram of gel was taken in the cell and the phosphate buffer 7.4 filled in the donor compartment was taken at various interval of time (0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24hr) and assayed for nimesulide organogel at 295nm. The volume withdrawn at each time was replaced with drug free phosphate buffer and amount of nimesulide released at various intervals at time was calculated and plotted against time.

Drug release kinetic studies

In this study, raw data obtained from in vitro release studies was analysed, where in data was fitted to different equations and kinetic models to calculate the percent drug release and release kinetics of nimesulide loaded organogel. The kinetic models used were a zero-order equation, first order, Higuchi model and korsmeyer peppas equation.

Stability study

The 10gm organogel is placed at different temperature and identify its stability after a regular interval of time (monthly for 6 months).

RESULTS AND DISCUSSION

Pre-formulation studies

Pre-formulation studies are an integral part of the entire drug development process. The study of the physical and chemical properties of the drug previous compounding process. These

pre-formulation surveys may merely confirm that there are no substantial barriers to the compound's development. These studies are indispensable protocol for the development of effective, suitable and stable dosage form. The obtained drug samples are recognized by various analytical techniques such as organoleptic properties, melting point, solubility etc.

Organoleptic properties of drug: As shown below

Description	**Crystalline**
Odour	Odourless
Colour	Pale yellow
Taste	Bitter
Texture	Smooth
Form	Powder

Melting point

The melting point of drug was found to be range 143-145^{o}C and hence drug sample was free from any type of impurities.

Solubility studies

The spontaneous interaction of two or more substances to form a homogenous molecular dispersion is called solubility. The evaluation of the solubility the following procedure is followed. The excess quantity of drug was added in each solvent (5ml) in separate test tubes. These test tubes were kept in water bath shaker at 50rpm for 24 hrs at room temperature. After 24 hrs each sample was centrifuge at 15000rpm for 15 mins, then sample was suitably diluted and analyzed for the drug content using UV spectrophotometer. The observed solubility profile of the drug is shown in figure 3.

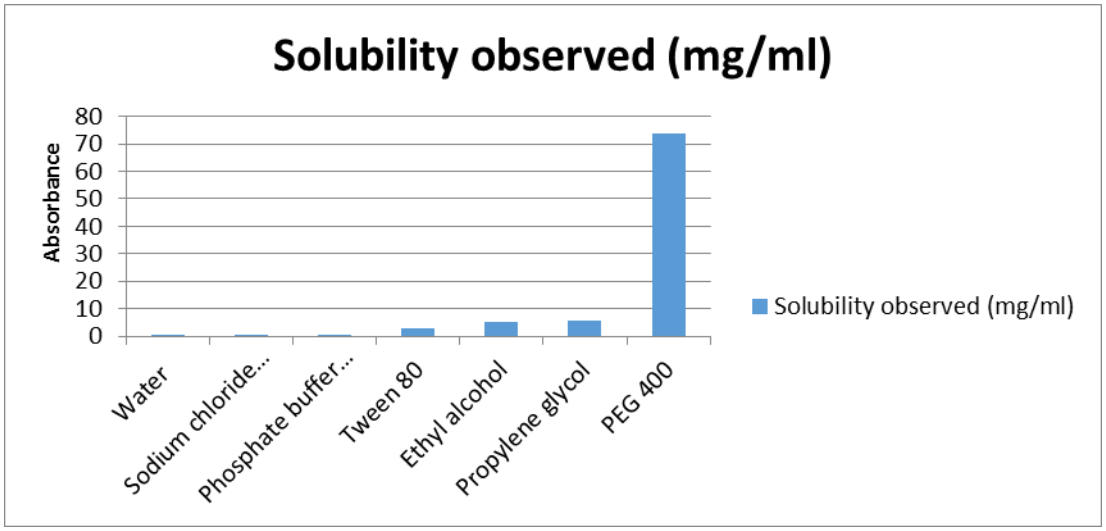

Fig. No.3: Solubility profile of nimesulide in different solvents

Discussion: The drug nimesulide was more soluble in PEG 400 < Propylene glycol < ethyl alcohol < Tween 80 < phosphate buffer 7.4 < 0.15M HCL < water.

Partition coefficient determination

The determination of partition coefficient study was performed by using shake flask method. The determination of partition coefficient study was performed by using shake flask method.

Discussion: The partition coefficient of nimesulide in n-octanol: water was found to be 1.80±0.07. This indicates that the nimesulide drug is lipophilic in nature.

Determination absorption maxima by UV Spectroscopy of nimesulide

UV spectroscopy is mainly used for quantitative analysis and serves as a useful auxiliary tool for structural elucidation of various drugs to obtain specific information on the chromophoric part of the molecules in solution, when it exposed to light in the ultraviolet region of the spectrum absorbing light of particular wavelength depending on the type of electronic transition associated with the absorption. The ultraviolet spectrum is recorded as a plot of absorbance versus wavelength.

A double beam ultraviolet visible spectrophotometer was used for quantitative analysis of the drug. A 100 µg/ml solution of nimesulide in methanol was scanned in the range of 200-400nm. The result of UV spectrum of nimesulide is shown in figure 4.

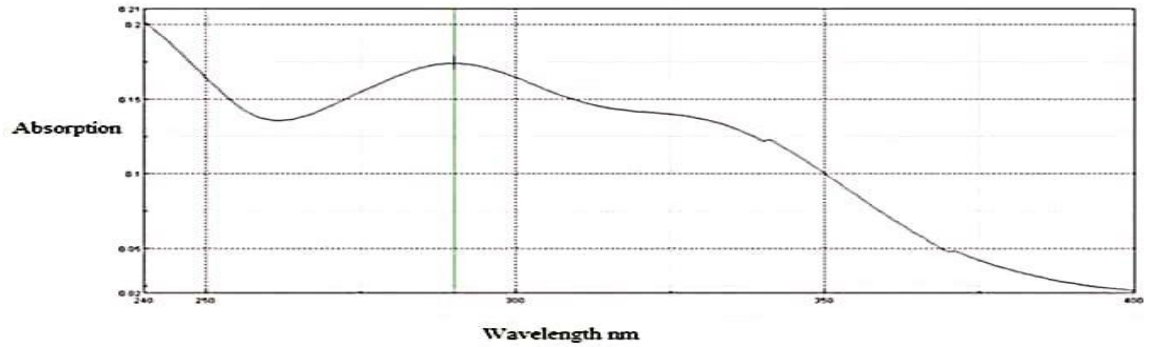

Fig.no.4 UV spectrum of nimesulide in methanol

Discussion: The maximum wavelength of nimesulide was observed at 295 nm.

Preparation of calibration curve of nimesulide in methanol

The stock solution of nimesulide was prepared in methanol. This solution was diluted with methanol to obtain suitable dilutions and analyzed spectrophotometrically at 295 nm. The results obtained are shown below in table 3 and graphically shown in figure 5. The calibration curve of nimesulide as shown in graph indicated the regression equation Y = 0.0296x + 0.0193 and R^2 = 0.9977, which shows good linearity shown below.

Parameter linearity range 5-25, slope 0.0296, intercept 0.0193, correlation coefficient 0.9977.

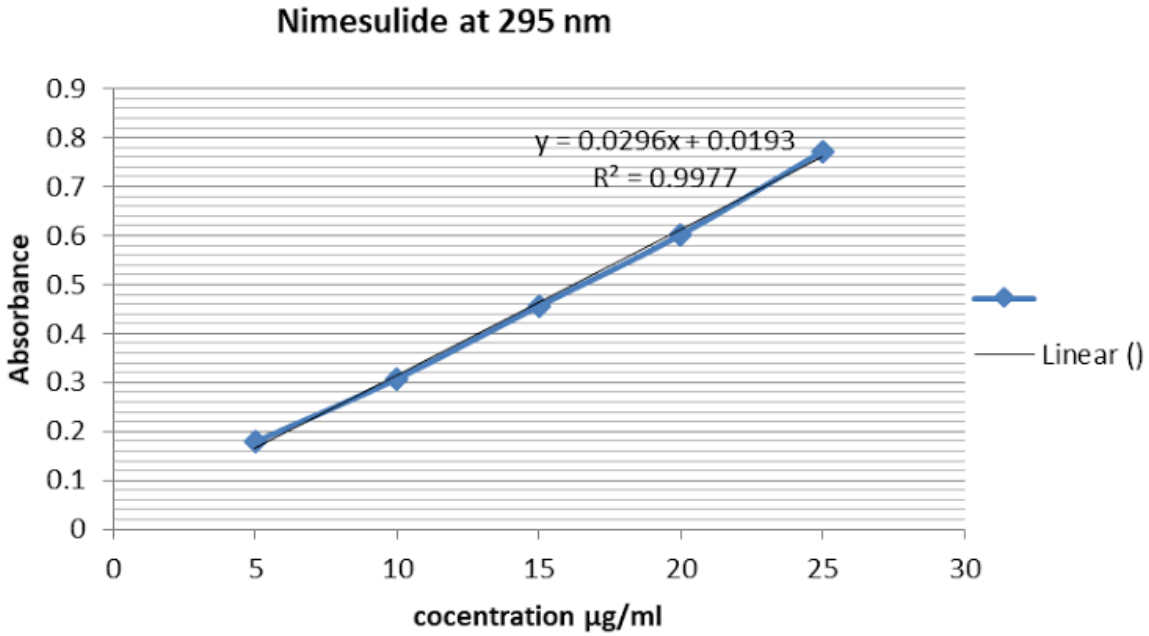

Fig.no. 5 Calibration curve of nimesulide in methanol.

Table.no. 3 Calibration curve data of nimesulide in methanol

Sr. No	Concentration (µg/ml)	Absorbance	Statistical data
1	5	0.180± 0.002	R2 value = 0.9977
2	10	0.300 ±0.001	
3	15	0.459 ±0.004	Regression equation
4	20	0.600 ±0.012	
5	25	0.775 ±0.0015	y = 0.0296x + 0.0193

*All values are average of three determination (n=3).

Characterization of nimesulide loaded Organogel

1 Physical appearance of Organogel

Description	Crystalline
Colour	Creamish
Appearance of gel	Clear
Greasiness	Less greasiness
Consistency	Soft
Homogenity	Smooth
Grittiness	No grittiness
Odour	Characteristic

2. Skin irritation study

Absence of skin irritation in organogel formulation is acceptable. There were no erythema, no edema or reddening of skin. All organogel formulations were found free from any sign of irritation.

3. FTIR of organogel

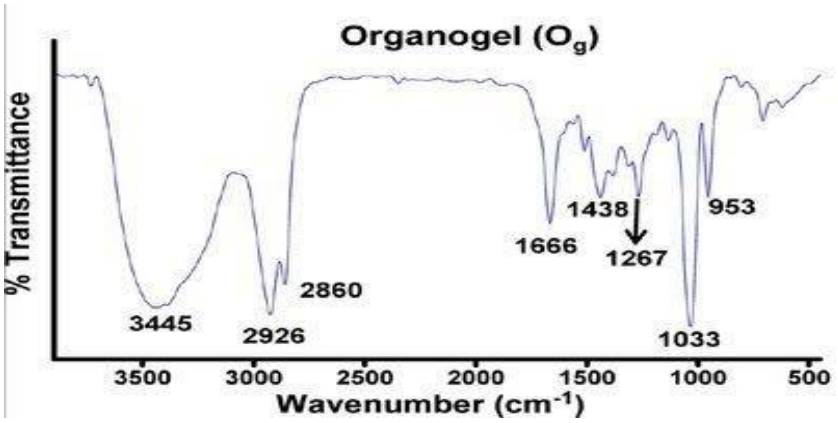

Fig.no. 6 FTIR spectrum of organogel

Table 3: Interpretation of FTIR spectrum of organogel

Experimental (cm^{-1})	Theoretical (cm^{-1})	Functional group	Vibration
3445	3537-3429	N-H	Symmetric stretching
2860	2900-2700	C-H	Asymmetric stretching
1666	1894-1643	C=O	Stretching
1267	1340-1250	C-N	Stretching
953	950-900	O-H	In-plane blend

Discussion: The FTIR interpretation of organogel were shown in table 3 and figure 6. The FTIR absorption peaks of organogel at 3445 (N-H Symmetric Stretching), 2860 (C-H Asymmetric Stretching), 1666 (C=O stretching), 1267 (C-N stretching), 953 (O-H in-plane blend) were all observed in spectra of carbopol 934. The observed FTIR spectrum confirmed and identified the presence of functional groups and purity of organogel.

4. Percentage drug content of organogel

Discussion: The drug content of the nimesulide loaded organogel was found to be for F_1, F_2, F_3, F_4 is 95.92, 98.29, 96.79, 97.21%.

Table 4: Mean of viscosity, pH and drug content of formulations

Formulation code	Viscosity (in cps)	pH (mean ± Sd)	% drug content (mean ± Sd)
F1	2738±4.82	5.60±0.67	95.92±0.201
F2	2872±8.34	5.58±0.27	98.29±1.440
F3	2936±10.95	5.61±0.59	96.79±1.115
F4	2989±1.93	5.59±1.81	97.21±0.310

*All values are average of three determination (n=3).

5. *In vitro* determination

Brookfield viscometer

Fig. no.7: Brookfield viscometer viscosity of organogel

Discussion: The viscosity of organogel formulations was found in the range from 2738cps to 2989cps. The proportion increase in the viscosity with polymer concentration increase, it can be attributed to the incidence of more cross linking in polymer with increase in polymer concentration.

pH detection of organogel

Discussion: The formulations were found in the range of 5.58-5.61 which is the normal range of skin pH. Therefore, organogel formulations are nonirritant to the skin.

6. *In vitro* Permeation studies

Table 5: *In vitro* release profile of pure drug and drug containing organogel with different concentration (1%, 1.5%) of gelling agent.

Time	% drug release (mean) of pure drug	% drug release (mean) of F-2	% drug release (mean) of F-3
0	0	0	0
0.25	0.531±0.008	2.73±0.001	2.73±0.001
0.5	0.942±0.001	19.176±0.016	18.661±0.016
1	1.274±0.003	27.109±0.016	24.723±0.016
2	2.192±0.009	35.063±0.162	28.514±0.486
3	2.755±0.004	40.114±0.162	34.127±5.109
4	3.674±0.058	48.908±0.324	42.453±0.162
6	5.330±0.070	57.234±0.162	46.663±0.162
8	7.042±0.016	63.97±0.162	51.341±0.324
10	9.004±0.016	75.196±0.162	57.141±8.702
12	10.242±0.032	77.441±0.162	62.38±0.162
24	13.207±0.084	80.248±0.162	68.18±0.162

*All values are average of three determination (n=3).

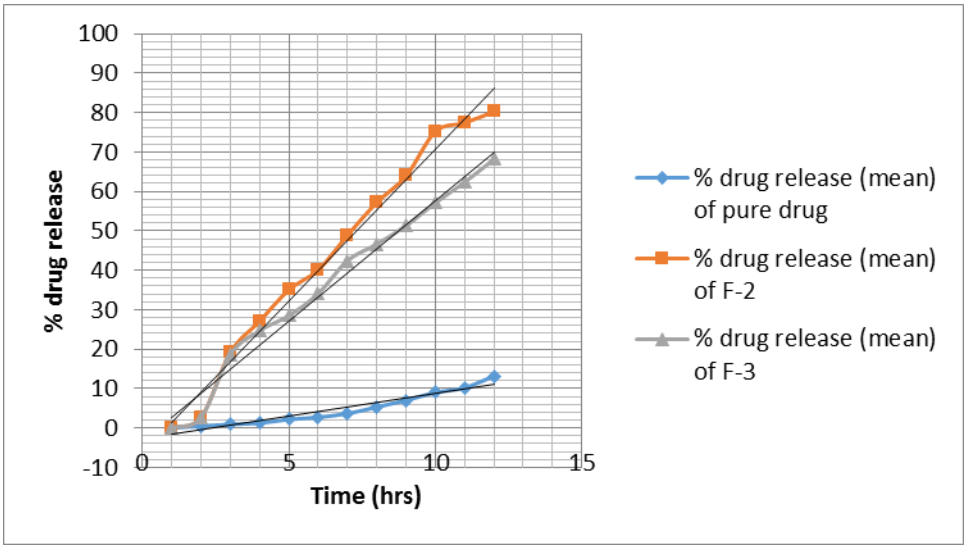

Fig.No. 8: Comparative drug release profile

Discussion: *In vitro* permeation studies were used to find the amount of drug being released into system at a period. Formulation containing different concentration of gelling agent (Carbopol-934) organogel showed good characteristic fast drug release in comparison to pure nimesulide organogel. In the case of F-2 (1%), F-3 (1.5%) formulation, about 80.248±0.162, 68.18±0.162 of the drug was released in the medium within 24hrs apart from it, in vitro release of pure drug showed 13.207±0.084 drug release within 24 hours. In vitro release within 24hrs. The F-2 showed best result.

7. *In vitro* release kinetics

In-vitro drug release kinetic study data of our best formulation F-2 was given below.

Table 6: Kinetic equation parameter of formulation F2

Formulation	Zero order		First order		Higuchi		Peppas	
	R^2	K_0	R^2	K_0	R^2	K_0	R^2	K_0
F-2	0.966	1.4663	0.5384	0.0476	0.9619	12.2944	0.934	1.0306

Discussion: The interpretation of data was based on the value of the resulting regression coefficients. The calculated regression coefficients for zero order, first order Higuchi model and korsmeyer peppas model were shown in table 6 it was found that the in vitro release of F-2 was best explained by Higuchi models as the plot showed in highest linearity. The value of R^2 found to be 0.9619 highest for the Higuchi models for sustained release.

2. Stability studies

Stability study of formulation were examined over 6 month period by storing samples at three different temperatures and relative humidity for drug content. Data of the formulation has been reported in table 7.

Table 7: Stability studies of drug content of F-2 nimesulide loaded organogel

Temperature	**5ºC ± 2ºC**	**25ºC ± 5ºC**	**40ºC ± 5ºC**
Time period	**Drug content**	**Drug content**	**Drug content**
Beginning	95.98±0.24	95.98±0.24	95.98±0.24
30 days	95.48±0.13	95.19±0.43	94.52±1.51
60 days	95.22±1.21	94.47±0.62	93.29±0.96
90 days	94.67±0.42	93.98±0.15	92.65±1.63
120 days	93.85±0.00	93.82±0.00	92.67±0.01
150 days	92.77±0.01	92.70±0.01	92.21±0.00
180 days	92.53±0.00	92.49±0.00	91.79±0.04

*All values are average of three determination (n=3).

Stability test was performed with the formulation F-2 at different temperature 5ºC±2ºC / 92.53±0.00, 25ºC±5ºC / 92.49±0.00, 40ºC±5ºC / 91.79±0.04. General appearance and organoleptic properties of organogel did not change significantly in 6 months during stability studies.

CONCLUSION

Optimized formulation of organogel was chosen for preparation of topical gel. Prepared nimesulide loaded organogel was clear, presented good homogeneity and the range of pH was found normal. The drug release from nimesulide loaded organogel was significantly prolonged by using the gelling system due to the addition of the polymer carbopol 934. Drug release profile conclude that the mechanism of drug release from organogel was non-fickian and it follows Higuchi matrix.

On physicochemical evaluation, melting point of nimesulide was found to be 143-145ºC. The drug nimesulide was more soluble in order PEG 400 < Propylene glycol < ethyl alcohol < Tween 80 < phosphate buffer 7.4 < 0.15M HCL < water. The partition coefficient of nimesulide in n-octanol: water was found to be 1.80±0.07 this indicated that the drug was lipophilic in nature. Optimized formulation in vitro drug release was studied in phosphate buffer pH 7.4 using Franz-type diffusion cells. The rate and mechanism of drug release, in vitro data was fitted to zero order, first order, Higuchi and korsmeyer peppas model. The

results showed that the drug release of F-2 formulation followed Higuchi matrix order which describes that the nimesulide follows.

Thus, it could be concluded from the result obtained that the organogel formulation developed of nimesulide possessed better skin permeation potential.

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