Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Vol 12 [8] July 2023 : 237-245

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD

ORIGINAL ARTICLE **OPEN ACCESS**

Sulindac-Loaded Topical Nanoemulgel Formulation and Optimization

Kumawat Jaymala Arun[1*], Anwar Khan[2], Nabani Mahato[3], Joti Devi[4], Sanghavi SaurabhJawahar[5], Chirag Goda[6], Prathibha S[7]

[1]Assistant Professor, Vishwakarma University, School of Pharmacy, Kondwa, Pune- 411048,Maharashtra, India

[2]Assistant Professor and Research Officer, Department of Pharmaceutics, ERA College of Pharmacy, ERA University, Sarfarazganj, Lucknow-226003, Uttar Pradesh, India

[3]Assistant Professor, Netaji Subhas University, Jamshedpur, Bhilai Pahri, EastSinghbhum-831012, Jharkhand, India

[4]Hospital Pharmacist, Agha Khan University Hospitals, Clifton Medical Services, Street11, Block 2, Clifton, Near Indus Valley School of Art and Architecture, Karachi-75600, Pakistan

[5]Assistant Professor, SVPM College of Pharmacy, Malegaon, Baramati, Pune-413115, Maharashtra, India

[6]Assistant Professor, Department of Pharmaceutical Sciences, Pharm.D Program, IbnSina National College, Jeddah-22421, Saudi Arabia

[7]Professor, Department of Botany, JSS College of Arts, Commerce and Science,Mysore-570015, Karnataka, India

[*]Corresponding Author Email: jaymalakumawat@gmail.com

ABSTRACT

To improve its aqueous solubility and permeability and prevent first-pass metabolism, the suggested research aimed to design and optimize a topical nanoemulgel containing Sulindac. Based on individual screening, the components peppermint oil, tween 80, and peg 400 were chosen as the oil phase, co-surfactant, and surfactant, respectively. To choose the ideal ratio of oil and Smix to create the nanoemulsion, pseudo- ternary phase study was used. With the help of the high pressure micro-fluidization process, the nanoemulsion formulations (NEF1-NEF9) were created. The optimization was carried out using a 22 Central Composite Design (CCD), with the dependent variables being particle size and %DR and the independent variables being peppermint oil (X1) and Smix ratio (X2). The ideal formulations included particle sizes ranging from 69.5 nanometers to 297.1 nanometers, zeta potential of -35.19 nanometers to -18.91 nanometers, PDI of 0.147 to 0.666, and in vitro drug release of 76 nanometers to 92.1 nanometers. The improved formulation (NEF1) was added to 1% Carbopol 934 gel base, and 5%weight-per-weight Sulindac nanoemulgel was created and tested. The pH value of the 5% Sulindac nanoemulgel was 5.8 with a pH spreadability of 7.6±0.2 cm. Sulindac nanoemulgel's percent drug release and flux were 97.4±0.21% and 5.291.20µg/cm^2.h respectively. The marketed 5% Sulindac gel (Clinoril) and the optimized 5% Sulindac nanoemulgel were then side-by-side compared. The drug release from the nanoemulgel gel was higher than that of the commercial product by 80.12%, and it remained stable at 4˚C for 90 days.

Keywords: *Sulindac, High pressure microfluidization technique, Central CompositeDesign(CCD), Nanoemulgel*

Received: 04.05.2023 Revised: 16.05.2023 Accepted: 29.07.2023

INTRODUCTION

The proposed research work in all scientific and biomedical areas is formed on nanosize for topical delivery of drugs because of low side effects, high bioavailability etc [1, 2]. Nanoemulsions are known as thermodynamically stable transparent dispersions of oil and aqueous phase stabilized as an interfacial film of surfactant and co-surfactant molecules (Smix) having low particle size in range of 10– 200nm [3-5]. The long-term stability ease of preparation, effective permeation, small dose, improved patient compliance and high-drug solubilization property, make nanoemulsions a promising tool for drug delivery [6, 5]. Nanoemulsion as a delivery system has been used to enhance solubility and permeability. Sulindac belongs

to BCS Class II and is widely used as an ora l formulation to control pain in spondylitis,Rheumatoid arthritis, osteoarthritis. When given orally it undergoes first- pass metabolism, gastric ulcers and bleeding, thus it is preferable to opt for topical route. Natural oils possessing therapeutic activities can be used as oil phase of nanoemulsions which not only acts as nanocarrier but also exerts its therapeutic properties [17]. Nanoemulgel formulation is not only known to support better delivery of lipophilic and poorly soluble drugs but also possesses the properties of thixotropic, non- greasy, effortlessly spreadable, easily be removed, emollient, longer shelf life, bio-friendly, translucent and agreeable appearance. The current research utilizes a high energy microfluidization technique for formulation of nanoemulsion gel. Design of experiment (DOE) used here was based on 2^2Central Composite Design (CCD).

To the best of author's knowledge, fabrication of a Sulindac-loaded Nanoemulsion involving High-energy micro fluidization method and 2^2 CCD is not reported till date.

MATERIALS AND METHODS

Sulindac was obtained from Hygro Chemicals Pharmatek Pvt. Ltd. India. Peppermint oil, Isopropyl alcohol, Propylene glycol (PG), and PEG-400 purchased from Fischer Scientifics, Mumbai. Castor oil, Olive oil, Soybean oil, isopropyl myristate (IPM), Tween 80and Carbopol- 934 were purchased from R.P Chemicals, Mumbai. Tween 20 was acquired from S.D.Fine Chemicals, Mumbai. All other chemicals and solvents used were of analytical grade.

Screening the Oil Phase

Comparative solubility of drug in oily phase was governed by screening [20]. Excess Sulindac was added to 2ml of each of the oils, surfactants, and co-surfactants in stopper vials with a 5 ml capacity. For 24 hours at 37±1°C, mixtures were put to orbital agitation after vortex mixing. Stable samples were centrifuged at 3000 rpm, the supernatant was then filtered through amembrane filter with a pore size of 45 m, and the filtrates were then diluted in the suitable solvent. Using validated UV spectrophotometric method solubility and concentration was measured at 247 nm.

Screening of Surfactant

Tween 20, 40 and 80 were chosen for the purpose of screening. 15% w/w sol. of the pre-selected surfactants was formulated utilizing distilled water. A 2.5 ml of above solution was taken in eachof the three glass vials. Previously screened oil phase was added to glass vial in drop wise manner with vigorous vortex till the solution becomes cloudy. The surfactant that solubilized greater amount of oil without turning cloudy was selected as surfactant. Surfactants having HLB value >10 (8- 18) are preferred when O/W NE is desirable [21].

Screening of Cosurfactant

The oil and surfactant blend that forms a translucent emulsion in minimum flask inversions was selected for screening. Solubility of Sulindac in different co-surfactants such as Methanol, isopropyl alcohol (IPA), Polyethylene glycol (PEG-400), propylene glycol, glycerol was analyzed. Different weight ratios i.e. 1:0, 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 2:1, 3:1 of surfactant: co-surfactant (Smix) respectively were chosen. After equilibrium is achieved, the mixture was observed visually. The sample clear in appearance was selected as stable Smix ratio for development of Nanoemulsion [3]·

%Transmittance

1ml of the prepared Surfactant and co-surfactant ratios was diluted using double distilled water to 100 times and analyzed using water as blank at 247nm [12].

Selection of Surfactant–Cosurfactant Mass Ratio in the Formulation of Nanoemulsions

The ternary phase study was carried out by using various ratios of surfactant and co-surfactant such as1:1-1:9, 2:1 and 3:1 respectively. These were mixed with the oil in different ratios ranging as oil: Smix ratio of 1:9, 1:8, 1:7, 1:6, 1:5 and 1:4. The pseudo-ternary phase diagram used for selecting the best ratio of Smix and oil.[3] The ability of various surfactant and co- surfactant to emulsify peppermint oil was assessed by %Transmittance and emulsification efficacy.

Drug–Excipients Interaction StudyInfrared spectrophotometry

Infrared study was carried out for plain drug and drug– excipients mixture using Fourier transform IR (FTIR) (Shimadzu FTIR-8400S) based on KBr disc method. The study was carried out with a resolution of 4/cm within the frequency range of 4000-400/cm [22].

Differential scanning calorimeter study

The DSC thermogram of Sulindac was recorded on DSC (DSC-60, Shimadzu, Japan) to detect thermal behaviour of a substance. The samples were heated in aluminium pans over a temperature range of 25–200°C at a rate of 10°C.min-1 in an atmosphere of nitrogen possessing flow rate of 40 ml/min [22].

Design of Experiment and Optimization of Nanoemulsions

The optimization of nanoemulsions was done by 2^2Central Composite Design (CCD) using Sigmatech® softwareto understand the impact of two factors, i.e., oil (X1), surfactant and co- surfactant (S_{mix}) (X2) as they were the critical quality attributes (CQA) affecting final formulation. at two levels [high (+1) and low (−1)] to evaluate their main effects and interaction effects, if any, on the identified critical parameters, i.e., Particle size and % Drug release as discussed in Table 1a and 1b.

Table 1a: Factors with levels for 50ml Nanoemulsion

Levels	Values	Oil (ml)	S_{mix} (ml)
+1	High	3.5	25
-1	Low	2.5	17.5

Table 1b: Selected variables for optimization of formulations

Independent Variables	Dependent Variables
Concentration of oil	Particle size
Concentration of S_{mix}	% drug release

METHOD OF PREPARATION OF NANOEMULSIONS

The current research utilizes a high energy microfluidization method for formulation of nanoemulsion.

Preparation of Coarse Emulsion

The oil, surfactant and co-surfactant (S_{mix}) ratio which were screened previously was selected for formulation of nanoemulsion as shown in Table 2. The oily phase (5-10% w/w oil and 40-60% w/w S_{mix}) was added gradually to aqueous phase containing water at 30˚C under magnetic stirring. The formulated emulsion was then subjected to sonication using the ultrasonic probe sonicator (Mangaldeep tech solutions) for 30 min. to reduce the particle size. The formulated coarse emulsion was then kept in an ice bath to attain the room temperature.

Preparation of Nano emulsion

The coarse emulsions were further introduced into micro fluidizer (LM20, Micro fluidizer) (Figure 1) where high-energy technique breaks emulsions into small droplets with the use of shear, cavitational, and turbulent forces. Each formulation was subjected to 15 cycles at 25000psi where the intensifier applies the force which leads to collision within the particles and also with the walls of micro-channels results in reduction of particle size. With every 1000psi rise in pressure the 1 ˚C temperature raised, soin order to avoid degradation of formulation ice was added to the cooling chamber.

Figure 1: Micro fluidizer used in the formulation of Sulindac-loaded Nano emulsion

Characterization of Nano emulsion

Particle Size, PDI and Zeta Potential

The particle size, polydispersity Index (PDI) and zeta potential of prepared formulation were analyzed by photon correlation spectroscopy utilizing Zeta sizer (Horiba Scientific, Japan). The method was based on the concept of Photon correlation spectroscopy that calculates the light scattering due to Brownian motion of the fragments where 1ml of the sample is observed at 25°Cat a scattering angle of 90°. The samples were suitably diluted with solvent that is not soluble with the sample and placed in quartz/plastic disposable cuvette having two electrodes.

The samples analyzed for particle size and zeta potential analysis in triplicate [24].

Determination of Drug content

For this study, 1ml of sample taken in a 10ml volumetric flask and was diluted with methanol to produce

required drug concentration. It was then centrifuged at 3500 rpm for 30 mins. Supernatant obtained was filtered and the drug content of was analyzed by UV spectrophotometer.[12]

PREPARATION OF SULINDAC NANOEMULGEL

Using a gelling agent i.e. 1% Carbopol 934, 5% w/w Sulindac Nanoemulgel was prepared. The precise quantity was taken into a beaker that contains 60 mL hot distilled water, and allowed to soak overnight. The optimized nano emulsion formulation containing 5% Sulindac was added by stirring continuously for uniform distribution of Sulindac nano emulsion in gel base. Sodium benzoate as preservative is used. To neutralize the dispersion Triethanolamine was added dropwise until a homogenous gel was obtained [25, 26].

Evaluation of Sulindac Nanoemulgel

Homogeneity

It is crucial for patient compliance to evaluate uniformity of semisolid formulation which areapplied topically. Minimum quantity Nanoemulgel was pressed between the index finger and thumb and examined whether homogeneous or non-homogeneous.

Table2: Formulation code and interaction factors in emulsion

Code	Interaction		Drug(g)	Oil Phase (ml)	Smix (ml)	Aq.Phase (ml)	% of Oil	% of Smix	% of Aq. Phase
	A	B							
NEF1	-α	-α	1.25	2.5	17.5	30	5	35	60
NEF2	+α	-α	1.25	3.5	17.5	29	7	35	58
NEF3	-α	+α	1.25	2.5	25	22.5	5	50	45
NEF4	+α	+α	1.25	3.5	25	21.5	7	50	43
NEF5	0	0	1.25	3.0	21.25	25.75	6	42.5	51.5
NEF6	-1	0	1.25	2.0	21.25	26.75	4	42.5	53.5
NEF7	+1	0	1.25	4.0	21.25	24.75	8	42.5	49.5
NEF8	0	-1	1.25	3.0	13.75	33.25	6	27.5	66.5
NEF9	0	+1	1.25	3.0	28.75	18.25	6	57.5	36.5

Spreadability

1g of NEG was spread using 2 horizontal plates (20 cm × 20 cm each) and determined for spreadability by measuring the diameter.

$S = M \times L.T^{-1}$

Where;

S represents spreadability in g/s,M represents mass in gms

L represents length of gel spreadT represents time (seconds)

pH Measurement

50mg gel put in 10 mL of dis. water, using a pH meter (Systronics Digital– 335). It was done thrice to calculate the mean± SD.

Viscosity Measurement

As it is understandable that flow property of nanoemulgel is enhanced by lowering viscosity. The viscosity of gel was tested using viscometer (Brookfield DVE) by spindleS-64 rotated fora10-s runtime at a speed of 12 rpm at 37°C. [27]

SEM of Nanoemulsion gel

Scanning electron microscopy (SEM) was done to know the shape and size of Sulindac loaded nano emulsion gel. After the samples have been washed, dehydrated and dried using suitable protocol then samples are placed on holder that can be put into scanning electron microscope.

Drug Content determination

The 1 g of gel was calculated for Sulindac content by placing on a volumetric apparatus (100 mL) and making up the volume with 7.4 pH buffer which was then agitated (2 hrs), filtered and samples were analyzed using UV Spectroscopy at 247nm.

In-Vitro diffusion testing

It was performed using Franz diffusion cell using dialysis membrane-60mm. Dialysis membrane was drenched in dis. water for 24 hours. Franz diffusion cell contain two compartments i.e., upper being donor and lower being receptor compartment. The receptor compartment was filled with 7.4 pH and donor compartment contain 5ml of nanoemulgel formulation on dialysis membrane having 2 cm^2exposure are at receptor medium. The device was subjected to magnetic stirring at 600 rpm for 8 hours, and samples were removed at specific intervals of 1 hour and replaced with an equal volume of buffer. Samples were

thoroughly neutralized with buffer before being examined at 247 nm with an UV spectrophotometer.
The slope of the linear line of the cumulative amount of medication penetrated per unit area(g/cm^2) vs time (h) plot was used to calculate steady state flux (Jss).
Permeability coefficient (Kp) =Jss/Co,where,
Co=initial Sulindac concentration.

Stability Studies

In lacquered aluminum collapsible tubes maintained at three different temperatures (4°C, 25°C, and 40°C) stability investigations on the Optimized Sulindac NEG were conducted for three months as per International Conference on Harmonization (ICH). Samples were evaluated for physical appearance, pH and drug content.

RESULTS AND DISCUSSION

Solubility studies Components screening

The potential of nano emulsion to keep the drug insolubilized form is significantly affected by the solubility of Sulindac in the oil phase. Pharmaceutically admissible oil, surfactant and co- surfactant were chosen to develop nanoemulgel for topical application of Sulindac. The surfactant used in this preparation is known to enhance skin permeation which could further be improved by the addition of co-surfactant which also aids in increasing the extent of nano emulsification.
Formulation of stable nanoemulsion requires the drug in its dissolved state. This is because it will assist in enhancing the topical efficacy by increasing permeation of drug across the skin attributed to the higher concentration gradient. Co- surfactants plays a crucial role in yielding uniform NE systems at low surfactant concentration.
The criteria for selection of surfactants and co-surfactants were based on ease of micellization of the oil with minimal number of flask inversions, i.e., minimum input of energy for mixing with maximum transparency estimated by % transmittance. Tween 80 revealed the highest % Transmittance.
The larger the nanoemulsifying region in the phase diagram greater is the nano emulsification efficiency of the chosen cosurfactant. Among various cosurfactants like Isopropyl alcohol, PEG 400, glycerol and propylene glycol screened for formulation of nano-emulgel system, PEG 400 revealed highest %transmittance, thus the highest nano emulsification efficiency in phase diagram for selected oil and surfactant system. Phase diagram study revealed that tween 80 and PEG 400 in ratio 1:2 gave maximum nano emulsification with selected oil phase for developing Sulindac- loaded NE.

Table 3: Solubility of Sulindac in Oils at 25°C (Mean ± S.D., n=3)

Oils	Solubility(mg/ml)
Peppermint oil	48.28±0.077
Soybean oil	30.33±0.55
Olive Oil	25.95±1.65
IPM	30.06±0.92
Castor oil	34.93±0.006

Table 4: Solubility of Sulindac in surfactants and co-surfactants (Mean ± S.D, n=3)

Surfactant/Co-surfactant	Solubility(mg/ml)
Tween 80	41.48±0.95
Tween 20	35.8±3.54
PEG-400	28.59±2.14
Propylene glycol	23.24±1.97
IPA	23.27±0.89
Glycerol	22.96±1.45

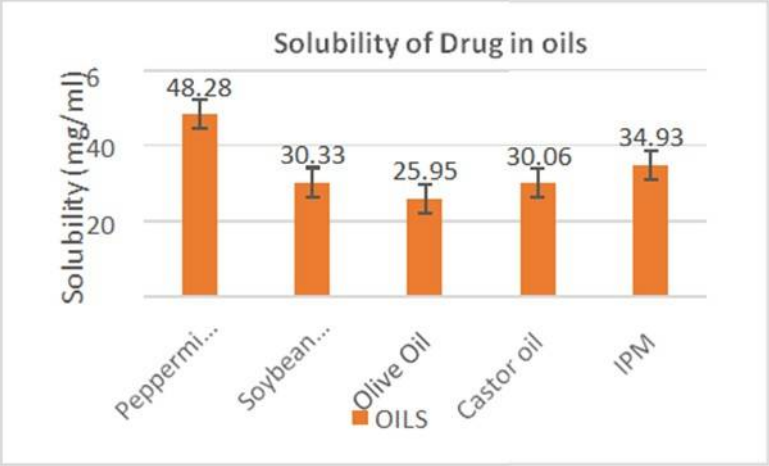

Figure 2: Solubility of Sulindac in Different Oil

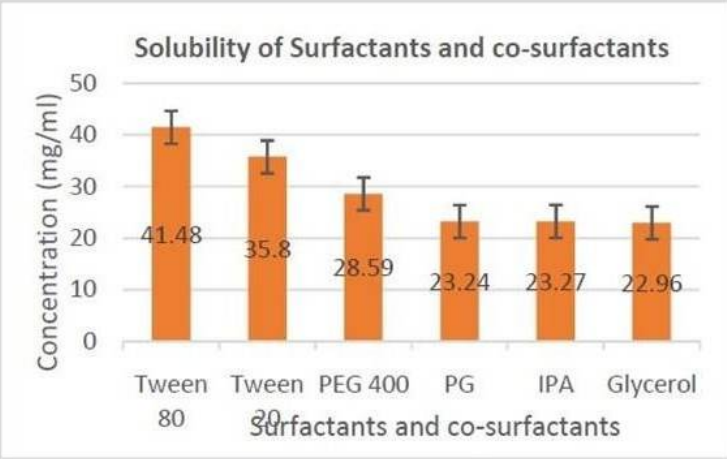

Figure 3: Solubility of drug in surfactants and cosurfactants

The maximum solubility among all selected oils was observed in peppermint oil (38.28±5.77mg/ml). Among all selected surfactants and co-surfactants, Sulindac was highly solubility in Tween 80 (41.48±0.055 mg/ml), a medium-length alkyl chain and PEG-400 (71.29±0.975 mg/ml) having an HLB value of 15 and 12.8 respectively. Therefore, peppermint oil as oil phase, Tween 80 as surfactant and PEG-400 as co-surfactant were chosen as best suitable for formulation of nano emulsion system.

Selection of suitable ratios of components for Formulation of Nano emulsion

Figure 4: Components screening for formulation development

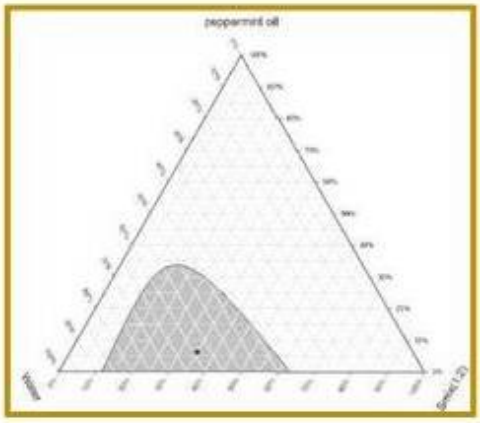

Figure 5: Pseudo ternary plot showing area of NE

Nano emulsions zone is represented by Pseudo ternary phase diagram study using Ternary plot software. Peppermint oil, Tween 80 and PEG-400 as the oil phase, surfactant and cosurfactant were selected. The ternary phase study was carried out by using ratios of surfactant and cosurfactant such as 1:1-1:9, 2:1 and 3:1 respectively. These were mixed with the oil in ratios ranging as oil: S_{mix} ratio of 1:9, 1:8, 1:7, 1:6, 1:5 and 1:4. The ability of various surfactant and co-surfactant to emulsify peppermintoil was assessed by % Transmittance and emulsificationefficacy. The ratio 1:7 and 1:5 of oil and S_{mix} was found to produce stable nano emulsions for almost all the S_{mix}. The S_{mix} ratio 1:2 showed the highest area of nano emulsions as obtained from Figure 4.13. It was concluded that a high amount of S_{mix} is required for stabilizing the nano emulsions. Thus, from the study it was concluded that 5-10% oil, 40-50% of S_{mix} were suitable to form nano emulsions in various combination. The optimization of the combination was done by using 2^2 Central Composite Design.

Formulation And Optimization Of Sulindac Loaded Nanoemulsion

Nanoemulsion formulations (NEF1-NEF9) prepared using probe sonicator and High pressure homogenizer (Microfluidizer) in composition as mentioned in Table 2.After characterization of prepared formulations the formulations were optimized using 22 CCD which gives a total of 9 formulation values including midpoint value. The independent variables selected for optimization were Peppermint oil (X1) and Smix ratio (X2) and the dependent variables were Particle size and
%Drug release.

The formulations NEF1-NEF9 were found to be transparent to translucent in appearance andevaluated for particle size, zeta potential and Invitro drug release.

Characterisation of Prepared Sulindac NanoemulsionParticle size

The size ranged from (69.5±0.9nm) to (297.1±1.1nm) the data obtained through particle size analysis, It was deemed that all prepared Sulindac nano emulsions have a particle size less than 300 nm, and as such are effective for topical administration. Although all formulations were within the range, NEF1 and NEF particle size i.e.69.5±0.9nm and respectively.

Zeta potential

Almost all formulations were found to be stable owing to their zeta potential, most stable NEF1(- 35.19± 0.02) to least stable NEF7(-18.91±0.27).

Polydispersity Index

PDI of almost all formulations was found to be within the limit i.e.<0.5, indicating the uniformity of formulations, except NEF7 which exceeded the limit. The nonuniformity in formulation NEF7 owes to greater particle size of the formulation.

%Drug content

It was deemed that formulations NEF1 and NEF6 showed greater drug content among allformulations i.e.98.14±0.09% and 95.61±0.19%.

In-Vitro Diffusion Studies

These were performed for 8 hours using dialysis membrane and samples were examined using UV copy (double beam) at 247nm. Highest % CDR after 8 hours was found to be from formulations NEF6 i.e. 92.02% followed by NEF1 and NEF5 i.e. 91.76% and 89.45% respectively.

Sulindac, belonging to the category of NSAIDs was selected for formulating Topical Nanoemulgel.Solubility

studies have been conducted using various oils, surfactants and co- surfactants. Maximum solubility was observed using Peppermint oil (48.28±0.077) as oil phase, Tween80 (41.48±0.95) as surfactant and PEG-400 (28.59±2.14) as co-surfactant. Based on the %transmittance value (i.e. 88.5%) 1:2 ratio of Smix was selected. Pseudo ternary phase diagram gave greater region of Nano emulsion in 1:7 ratios of oil and Smix respectively. Sulindac loaded nano emulsion was formulated using High pressure Micro fluidization technique.

Optimization was carried out using 2^2 CCD which gives a total nine formulation i.e. NEF1- NEF9. Formulation NEF1(5% oil, 35% S mix and 60 % Aqueous phase was found to be optimized formula having particle size of 69.5nm, Drug release of 91.76%, Coefficient value 89.023. From the results of particle size, it was found that all prepared Sulindac nano particle size in (69.5±0.9nm)to(297.1±1.1). Although all formulations were within the range, NEF1 and NEF6 showed least particle size i.e.69.5±0.9nm and 65.81±0.8nm respectively.

Almost all formulations were found to be stable owing to their zeta potential, most stable NEF1 (- 35.19± 0.02) to least stable NEF7 (-18.91±0.27). PDI of almost all formulations was found to be within the limit i.e.<0.5, indicating the uniformity of formulations. The formulations NEF1 and NEF6 showed greater drug content i.e.98.14±0.09% and 95.61±0.19%. Diffusion testing of all formulations were performed and Highest %CDR after 8 hours was found to be from formulations NEF6 i.e. 92.02% followed by NEF1 and NEF5 i.e. 91.76% and 89.45% respectively.

A 5% Sulindac nanoemulgel was formulated by 1% Carbopol 934 (gelling agent).The concentration of Sulindac in the prepared nanoemulgel was 5%w/w.

The SEM images deemed that the NE droplets were globular shaped and represent a typical appearance of oil-in-water NE. The results corroborate with the results of globule size analysis showing that globules are present in nanometric range, varying from 51 to 120 nm.

Sulindac NE gel showed Spreadability values is 76±0.22 cm, pH value is 5.8±0.63, drug content found to be 98.2±0.41% and viscosity of Sulindac Nanoemulgel is found to 16254±0.74 cps. Stability studies showed that Sulindac NEG was found to be stable at 4˚C compared to the temperatures.

CONCLUSION

The studies demonstrated Peppermint oil as a novel, efficient and economic excipient in dispersed system for nanoemulsions delivery technology. A blend of surfactant and cosurfactant

i.e. Tween 80 and PEG-400 in 1:2 ratio, enhanced the stability of nanoemulsions. Pseudo ternary phase diagram gave greater region of Nano emulsion in 1:7 ratio of oil and Smix respectively. Sulindac-loaded nano emulsion was formulated using High pressure Micro fluidization technique. Optimization was carried out using 2^2 CCD which gives a total of nine formulations

i.e. NEF1- NEF9 among which NEF1(5% oil, 35% S mix and 60 % Aqueous phase) was found to be optimized formula having particle size of 69.5nm, Drug release of 91.76%, Coefficient value

89.023. The SEM images showed globular shaped NE droplets and represent a typical appearance of oil in water NE. The various studies performed such as viscosity, drug release, and correlation with the formulation variable gave the best optimized formulation. It was noticed that the optimized formulation NEF1 had a close similarity with the NEF6 formulation therefore;it was subjected to various physical evaluations and stability testing. The optimized formulation was further incorporated into 5% Carbopol gel and was subjected to the in-vitro diffusion studies which confirmed the greater %CDR i.e. 97.4 ±0.11. Thus, from the various data analysis it was concluded that developed nanoemulgel had a great potential for effective topical drug delivery.

REFERENCES

1. Trakatelli M, Ulrich C, del Marmol V, Euvrard S, Stockfleth E and Abeni D: (2007). Epidemiology of nonmelanoma skin cancer (NMSC) in Europe: accurate and comparabledata are needed for effective public health monitoring and interventions. Br J Dermatol 156 (Suppl 3): 1-7.
2. Kim RH and Armstrong AW: (2012). Nonmelanoma skin cancer. Dermatol Clin 30: 125-139.
3. Rogers HW, Weinstock MA, Harris AR, et al: (2010). Incidence estimate of nonmelanoma skincancer in the United States, 2006. Arch Dermatol 146: 283-287.
4. Baron JA, Cole BF, Sandler RS, et al: (2003). A randomized trial of aspirin to prevent colorectal adenomas. N Engl J Med 348: 891-899.
5. Gravitz L: (2011). Chemoprevention: First line of defence. Nature 471: S5-S7.
6. Elmets CA, Viner JL, Pentland AP, et al: (2010). Chemoprevention of nonmelanoma skin cancerwith celecoxib: a randomized, double-blind, placebo-controlled trial. J Natl Cancer Inst 102: 1835-1844.
7. Cuzick J, Otto F, Baron JA, et al: (2009). Aspirin and non-steroidal anti-inflammatory drugs for cancer prevention: an international consensus statement. Lancet Oncol 10: 501-507.

8. Nie T, Wong CC, Alston N, Aro P, (Constantinides PP and Rigas B: (2011). Phospho-ibuprofen (MDC- 917) incorporated in nanocarriers: anti-cancer activity in vitro and in vivo. Br J Pharmacol: Dec. 5, 20-34(Epub ahead of print).
9. Wong CC, Cheng KW, Xie G, et al: (2012). Carboxylesterases 1 and 2 hydrolyze phospho- NSAIDs: relevance to their pharmacological activity. J Pharmacol Exp Ther 340: 422- 432.
10. Mattheolabakis G, Nie T, Constantinides PP and Rigas B: (2011). Sterically stabilized liposomes incorporating the novel anticancer agent phospho-ibuprofen (MDC-917): preparation, characterization, and in vitro/in vivo evaluation. Pharm Res: Nov 10, 90-94.
11. Huang L, Mackenzie GG, Sun Y, et al: (2011). Chemotherapeutic properties of phospho- nonsteroidal anti-inflammatory drugs, a new class of anticancer compounds. Cancer Res 71: 76177627.
12. Xie G, Nie T, Mackenzie G, et al: (2012). The metabolism and pharmacokinetics of phospho- sulindac (OXT-328) and the effect of difluoromethylornithine. Br J Pharmacol 165: 2152-2166.
13. Sun Y, Huang L, Mackenzie GG and Rigas B: (2011). Oxidative stress mediates through apoptosis the anticancer effect of phosphononsteroidal anti-inflammatory drugs: implications for the role of oxidative stress in the action of anticancer agents. J Pharmacol Exp Ther 338: 775-783.
14. Mackenzie GG, Ouyang N, Xie G, et al: (2011). Phospho-sulindac (OXT-328) combined with difluoromethylornithine prevents colon cancer in mice. Cancer Prev Res (Phila) 4: 1052- 1060.
15. Xie G, Sun Y, Nie T, et al: (2011). Phospho-ibuprofen (MDC-917) is a novel agent against colon cancer: efficacy, metabolism, and pharmacokinetics in mouse models. J Pharmacol Exp Ther 337: 876-886.
16. Huang L, Mackenzie G, Ouyang N, et al: (2011). The novel phosphonon-steroidal anti- inflammatory drugs, OXT-328, MDC-22 and MDC-917, inhibit adjuvant-induced arthritis in rats. Br J Pharmacol 162: 1521-1533.
17. Huang L, Zhu C, Sun Y, et al: (2010). Phospho-sulindac (OXT-922) inhibits the growth of human colon cancer cell lines: a redox/ polyamine-dependent effect. Carcinogenesis 31: 1982-1990.
18. Mackenzie GG, Sun Y, Huang L, et al: (2010). Phospho-sulindac (OXT328), a novel sulindac derivative, is safe and effective in colon cancer prevention in mice. Gastroenterology 139: 1320-1332.
19. Kozoni V, Tsioulias G, Shiff S and Rigas B: (2000). The effect of lithocholic acid on proliferation and apoptosis during the early stages of colon carcinogenesis: differential effect on apoptosis in the presence of a colon carcinogen. Carcinogenesis 21: 999-1005.
20. Ahmed S, Imai T, Yoshigae Y and Otagiri M: (1997). Stereospecific activity and nature of metabolizing esterases for propranolol prodrug in hairless mouse skin, liver and plasma. Life Sci 61: 1879-1887.
21. Akarsu S, Aktan S, Atahan A, Koc P and Ozkan S: (2011). Comparison of topical 3% diclofenac sodium gel and 5% imiquimod cream for the treatment of actinic keratoses. Clin Exp Dermatol 36: 479-484.
22. McCarberg BH and Argoff CE: (2011). Topical diclofenac epolamine patch 1.3% for treatment of acute pain caused by soft tissue injury. Int J Clin Pract 64: 1546-1553.
23. Fuller P and Roth S: (2011). Diclofenac sodium topical solution with dimethyl sulfoxide, a viable alternative to oral nonsteroidal anti-inflammatories in osteoarthritis: review of currentevidence. J Multidiscip Healthc 4: 223-231.
24. Huang L, Mackenzie G, Ouyang N, Sun Y, Xie G, Johnson F, et al. (2011). The novel phospho- nonsteroidal anti-inflammatory drugs, OXT-328, MDC-22 and MDC-917, inhibit adjuvant- induced arthritis in rats. Br J Pharmacol. ; 162:1521–33.
25. Ray WA, Stein CM, Daugherty JR, Hall K, Arbogast PG, Griffin MR. (2002). COX-2 selective nonsteroidal anti-inflammatory drugs and risk of serious coronary heart disease. Lancet. 360:1071–3.
26. Mackenzie GG, Sun Y, Huang L, Xie G, Ouyang N, Gupta RC, et al. (2010). Phospho-sulindac (OXT- 328), a novel sulindac derivative, is safe and effective in colon cancer prevention in mice. Gastroenterology. 139:1320–32.
27. Wong CC, Cheng KW, Xie G, Zhou D, Zhu CH, Constantinides PP, et al. (2012). Carboxylesterases 1 and 2 hydrolyze phosphononsteroidal anti-inflammatory drugs: relevance to their pharmacological activity. J Pharmacol Exp Ther. ; 340:422–32.

CITATION OF THIS ARTICLE

Kumawat Jaymala Arun, Anwar Khan, Nabani Mahato, Joti Devi, Sanghavi Saurabh Jawahar, Chirag Goda, Prathibha S. Sulindac-Loaded Topical Nanoemulgel Formulation and Optimization. Bull. Env.Pharmacol. Life Sci.,Vol 12(8) July 2023: 237-245