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FORMULATION AND EVALUATION OF TOPICAL NANOEMULGEL LOADED WITH SULFASALAZINE FOR RHEUMATOID ARTHRITIS

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic inflammatory condition that primarily impacts the joints, causing pain, swelling, and potential loss of function. Conventional treatment strategies often involve the systemic use of antiinflammatory drugs, which are associated with significant side effects. To address this, targeted drug delivery systems, particularly topical formulations, offer a more localized approach with reduced systemic exposure. This study aimed to develop and evaluate a sulfasalazine-loaded nanoemulgel for the effective topical management of rheumatoid arthritis. Method: Preformulation studies were conducted to assess the physicochemical compatibility between sulfasalazine and selected excipients (Arachis oil, Tween 80, Span 80). Nanoemulsions were prepared using ultrasonication method. Carbopol 934p was used as gelling agent. The optimized nanoemulsion was incorporated into a Carbopol-based gel to create the nanoemulgel. The prepared nanoemulgel was evaluated for various parameters including particle size, zeta potential, pH, viscosity, drug content, and spreadability. In vitro release studies were conducted using a Franz diffusion cell to assess the sustained release of sulfasalazine. **Result:** The nanoemulgel constituting Smix ratio 1:2 and 32% arachis oil was optimized formulation. The prepared nanoemulgel was yellow translucent in nature having a particle size of 210.8nm with PDI 0.33 drug content and drug release of optimized formulation were found to be 87.5 and 68.5 respectively. pH, viscosity, spreadability were found to be optimum. The stability data showed that the prepared nanoemulgel was stable for 3 month at various temperature. **Conclusion:** Sulfasalazine loaded nanoemulgel has been successfully formulated for topical delivery for the management of rheumatoid arthritis.

KEYWORD:- Sulfasalazine, Nanoemulgel, Rheumatoid Arthritis, Topical Delivery, Arachis Oil.

INTRODUCTION

Rheumatoid arthritis (RA) is a long-term autoimmune condition that leads to joint inflammation, pain, and progressive damage, severely impacting the quality of life of individuals affected by the disease. Sulfasalazine, a commonly used disease-modifying antirheumatic drug (DMARD), is effective in managing RA symptoms by reducing inflammation and halting joint deterioration. However, oral administration of sulfasalazine is often associated with systemic side effects, including gastrointestinal issues, liver toxicity, and hematological complications, which can limit its use and patient adherence to treatment.

To overcome these limitations, the development of a topical delivery system using sulfasalazine- loaded nanoemulgel presents a promising alternative. Nanoemulgels, which combine the benefits of nanoemulsions and gel formulations, offer an efficient method for localized drug delivery, enhancing skin penetration and providing targeted effects at the site of inflammation. By applying sulfasalazine topically in a nanoemulgel form, it is possible to achieve higher drug concentrations at the affected joints, potentially improving therapeutic outcomes while minimizing the systemic side effects associated with oral administration.

The formulation and evaluation of this nanoemulgel involve careful selection of excipients, optimizing drug entrapment, ensuring appropriate particle size, and conducting thorough stability and drug release testing. These factors are essential in determining the safety, efficacy, and performance of the final product. This research focuses on developing and evaluating a sulfasalazine-loaded nanoemulgel to enhance the treatment of rheumatoid arthritis while reducing systemic exposure and associated adverse effects.

MATERIALS AND METHODS

Sulfasalazine was obtained from Yarrow Chem. Products

Ltd, Mumbai; All other chemicals and reagents used were of analytical grade.

1. Preformulation study

a. Description of drug: It is the initial evaluation during pre-formulation studies which assess the state, nature, color and odor of the substance.

b. Determination of solubility: Aqueous solubility is an important physicochemical property of the drug substance which determines the systemic absorption as well as the therapeutic efficacy. Here, the quantity of the solvent required to dissolve one gram of pure drug substance was noted and categorized. Solubility of drug was determined by taking little quantity of drug (1-2mg) in the test tube and added the 5ml of solvent (water, ethanol, Diethyl ether, 0.1N HCl, chloroform) shake vigorously and kept for sometime. note the solubility of drug in different solvents.

c. Determination of λmax of Sulfasalazine: The λmax of the drug was determined for identification of the drug as the λ max is distinct for each drug. Take 5ml of methanol in volumetric flask of 10ml. add 10mg of Sulfasalazine in it. And add quantity sufficient buffer medium to prepare stock solution containing 1mg/ml sulfasalazine. Then a sample was taken from the stock solution and scanned from 200-400nm by UV Visible spectrophotometer to determine the λmax.

d. Determination of the calibration curve using pH 6.8 Phosphate buffer: Preparation of calibration curve of Sulfasalazine in pH 6.8 phosphate buffer

i. Preparation of phosphate buffer pH 6.8: Placed 50mL of 0.2 M solution of potassium dihydrogen phosphate in 200 mL volumetric flask, and added 22.4 mL of 0.2 M sodium hydroxide followed by addition of distilled water to makeup volume.

ii. Calibration plot of Sulfasalazine in phosphate buffer pH 6.8.from the above standard stock solution 0.2,0.4,0.6,0.8,1.0ml was taken into 100ml volumetric flask and individually made upto 100ml using phosphate buffer to prepare 2-10µg/ml.

iii. All prepared solutions then analyzed Spectrophotometrically at 359nm and The calibration curve was plotted against absorbance vs concentration

e. Determination of melting point: The melting point of the pure drug sulfasalazine was determined by capillary tube method using digital melting point apparatus and the temperature at which the drug melted was noted as melting point.

f. Identification of drug: The identification of pure drug sample was carried out using FT- IR spectroscopy. The spectrum of sample obtained by FT- IR spectroscopy was compared with that of reference spectrum of Sulfasalazine in IP 2022.

g. Drug – Excipient compatibility study: For any successful formulation, it is very important that the drug and the excipients are compatible. Degradation of drug may occur due to the addition of the excipients. The compatibility between drug and various excipients were evaluated by ATR- IR spectroscopy by peak matching method. The obtained spectrum was compared with the individual reference spectrum of pure Sulfasalazine and excipients. The physical mixture of equal proportions of Sulfasalazine and carbopol 934p was prepared by trituration and blending in a mortar and pestle.

2. Formulation of sulfasalazine loaded nanoemulgel

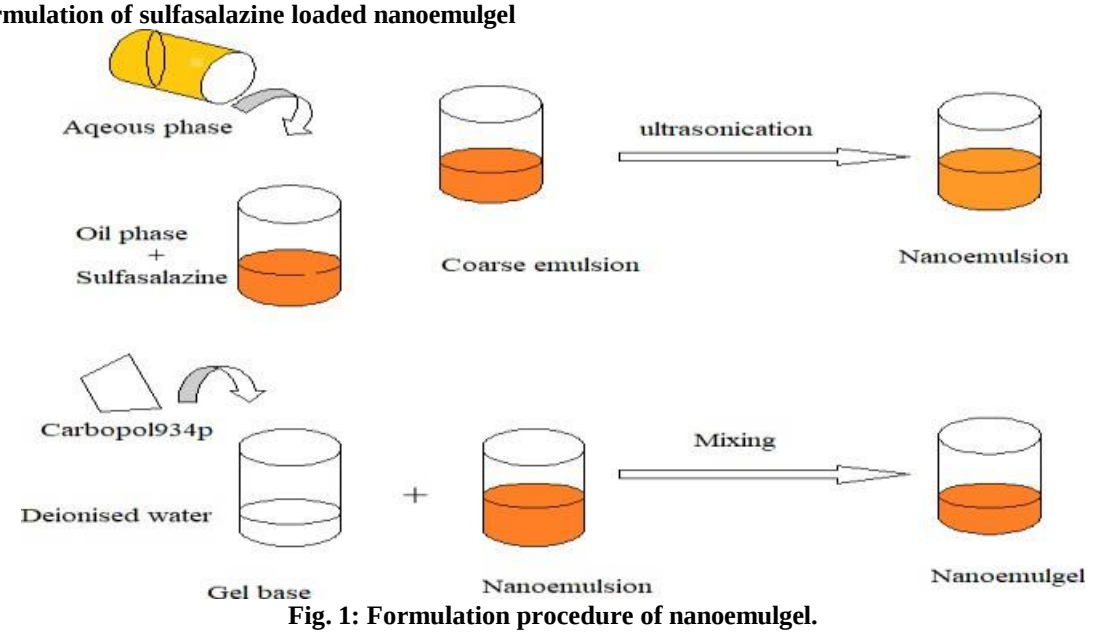


Fig. 1: Formulation procedure of nanoemulgel.

I. Preparation of sulfasalazine loaded nanoemulsion

a. Construction of pseudoternary phase diagram

Pseudo ternary phase diagrams are used to determine the nanoemulsion region and it was constructed using Aqeous titration method. The effect of various surfactant cosurfactant ratio on nanoemulsion formulation can be studied using peudoternary diagram. The three components (oil, surfactant and cosurfactant) of a system are plotted on the three corners of the triangle and the diagram helps to get the concentration range of these components. The phase diagrams were constructed by ternary plot exploiting spontaneous-emulsification method. After each addition of water, sample was vortex very well and visually observes for appearance of any turbidity or other phase behaviour. Area of nanoemulsion region obtained after the construction of phase diagram was calculated by calibration plot method.

Surfactant was mixed with cosurfactants (Smix) in ratio 1:1,1:2,1:3,3:1 and 2:1. Then part of each Smix has been combined with oil in ratio of 9:1,8:2,7:3, 6:4,5:5,4:6, 3:7,2:8,1:9 and vortexed for 5min, a transparent homogenous mixture of oil Smix component had been prepared. Then titration of the mixture was carried out by slowly adding distilled water and constantly viewed the clarity of the solution, end point was noted when turbidity appeared. Then percentage of formulation component was calculated and constructed the pseudoternary phase diagram.

b. Procedure for the preperation of nanoemulsion

The nanoemulsion is prepared by high energy method, ultrasonication. The rough emulsion is converted into desirable nano-sized emulsion droplets using a sonicator probe. High- intensity sound waves having a frequency of even more than 20 kHz are generated by the piezoelectric sonicator probe. which has the ability to shatter the rough emulsion into nano- sized droplets (5-500nm). Different types of probes with varying dimensions are available for reduction in size up to recommended values. The sonication input intensity, time, and the probe type affect the droplet scale. Sulfasalazine is taken in a glass beaker, oil phase(Arachis oil) is added to it andstirred with a magnetic stirrer for 15min and sonicated for 30min. Then span 80 is inserted to the above solution and stirred for 15min. A preheated aqeous phase containing distilled water and tween 80 homogenised using probe sonicator for 30min. With continous stirring on a magnetic stirrer water phase is added to oil phase and emulsion is sonicated for 90min.

II. Procedure for the preparation of sulfasalazine nanoemulgel

Nanoemulgel containg Sulfasalazine were prepared using carbopol 934p, triethanolamine and deionized water.

a. Preparation of gel base

The required amount of carbopol 934p for 1%w/v were taken and dispersed in water for 24 h for complete and uniform swelling. Triethanolamine was added to neutralise the pH to around skin pH.

b. Preparation of nanoemulgel

The optimized Nano emulsion is mixed with the prepared gel base by incorporation method.

III. Characterization of sulfasalazine loaded nanoemulsion

A. Entrapment efficiency
B. Drug content
C. Particle size, Polydispersity index and Zeta potential
D. Shape and Surface Morphology Studies

A. Entrapment efficiency

Entrapment efficiency was determined through centrifugation. It was done by assessing the unentrapped drug in the aqeous phase, withdrawn by centrifugation at 5000rpm for 20min and filtered the supernatant, further dilutions were made and analyzed using UV spectrophotometer at λmax 359nm. % Entrapment efficiency calculated by using the following equation:69

$$\%EE = \frac{Total\ drug\ added - Drug\ in\ the\ supernatant}{Total\ drug\ added} \times 100$$

B. Drug content

The drug content of prepared Sulfasalazine loaded nanoemulsion was determined using UV-spectrophotometer. About 2ml of Sulfasalazine loaded nanoemulsion was incorporated into the centrifuge tube. Centrifugation at 5000rpm for 30min was done. The supernatant was collected and absorbance measured at λmax of 359nm using UV spectrophotometer. To extract entrapped drug in Sulfasalazine loaded nanoemulsion, 1ml of methanol and sediment was subjected to vortexing for 5min, mixture then diluted with phosphate buffer of pH 6.8 again absorbance calculated at λmax of 359nm by using UV spectrophotometer. Drug contents of supernatant and sediment were added to get the total drug content of the nanoemulsion.

Drug content= ***Drug in supernatant + Drug in the sediment***

C. Particle size, Polydispersity index and Zeta potential

Particle size, Polydispersity index and Zeta potential were measured by dynamic laser scattering or photon correlation spectroscopy using a Malvern Zeta sizer Nano ZS (Malvern Instruments, Malvern, UK). 2ml of the Nanoemulsion vortexed and/ or sonicated for few a minutes at 25º C and a scattering angle of 90º. To determine the zeta potential, nanoemulsion was taken in disposable zeta cells and measured by Malvern zeta sizer. Each sample was measured in triplicate. The zeta potential of nanoparticles is commonly used to characterize the surface charge property of nanoparticles.

D. Scanning electron microscopy

Nanoemulgel morphology was studied using scanning

electron microscopy. The globules' three dimensional image is provided via SEM. The samples are inspected at various magnifications and an appropriate accelerating voltage, typically 20 kV. SEM is used to acquire the functional study of the surface morphology of the dispersion phase in the formulation. To automatically analyse the form and surface morphology, image analysis tools might be used.

IV. Characterization of sulfasalazine loaded nanoemulgel

A. Physical appearance

The formulated nanoemulgel was visually examined for color, homogeneity, stability and consistency.

B. pH measurement

Using a pH metre, the prepared gellified emulsion's 1% aqueous solution pH values are determined (Digital pH metre). The pH of nanoemulgel is dependent on the intended use, such as on the skin or another mucous membrane. Human skin pH is estimated to range between 4.5 to 6.

C. Viscosity

The viscosity of the prepared nanoemulgel was measured using a Brookfield viscometer, (LVDVE Brookfield Engineering Laboratories) at room temperature. A cone and plate viscometer with spindle 52 coupled to a thermostatically controlled circulating water bath, the viscosity of the various emulgel compositions is assessed at 25°C.

D. Spreadability

The spreadability of the topical preparation will influence the therapeutic efficacy of the produced formulation. Spreadability refers to how easily a gel covers the application site on the skin and the affected area. The spreadability of nanoemulgels is assessed using two different glass slides (7.5x2.5cm). the first slide was attached with a wooden frame. On the top of the first slide 1g of nanoemulgel was placed, and second glass slide placed over first glass slide. Furthermore 100g weight was applied over second glass top. Due to overweight, air between the sandwiched nanoemulgel was removed. Spreadability was measured as the time (sec) required for a moving slide to cover a predetermined distance of 6.5 cm. The spreadability can be calculated using following formula:69

$$S = \frac{M \times L}{T}$$

Where,
S- Spreadability
M- weight attached to upper slide L-Length of glass slides
T- Separation time of slides.

E. In vitro drug release

Drug diffusion investigations were conducted using the modified Franz diffusion cell. Nanoemulgel (1 g) was equally placed to the outer surface of the dialysis membrane, which was positioned between the donor and receptor compartment. A magnetic stirrer was used to stir the receptor chamber. Phosphate buffer 6.8 was used as a dissolution medium, and the cell's temperature was maintained at 37ºC. Sample (5.0 mL) was removed at appropriate intervals and replaced with an equivalent quantity of a fresh dissolution medium. Samples were analyzed at 359nm by using UV-visible spectrophotometer. To determine the overall amount of medication released at each time interval, cumulative adjustments are done. As a function of time, the total amount of medication released through the cellophane membrane is calculated.

F. Drug kinetics

The obtained permeation data were fitted to zero order, first order, Higuchi- Crowell and Korsmeyer -Peppas equations to understand the rate of drug release from the prepared formulations. The correlation coefficient values were calculated and used to find the fitness of the data.

G. Short term stability studies final formulation

Formulation was kept for Stability studies at 400C/75%RH for 1 month and dissolution studies, pH and drug in vitro drug release was carried out. Results for pH of stability batches and results in in vitro drug release are compared.

RESULTS AND DISCUSSION

1. Preformulation studies

a. Description of drug

Table 1: Physical description of drug.

Sl. No.	Parameter	Obtained result	Reference
1	State	Solid	Solid
2	Colour	Brownish yellow	Bright yellow or brownish yellow
3	Odour	Odourless	Odourless
4	Nature	Crystalline	Crystalline

The color, odor and the nature of the API was same as that mentioned in the IP.

b. Determination of solubility

Table 2: Solubility of Sulfasalazine in various solvents.

Sl No	Solvent	Obtained result
1	Water	Practically insoluble
2	Ethanol	Very slightly soluble
3	Diethyl ether	Practically insoluble
4	Chloroform	Practically insoluble
5	0.1N NaOH	Completely soluble

c. Determination of λmax of Sulfasalazine

The λmax of sulfasalazine was found to be 359 nm in phosphate buffer pH 6.8 and was used for further spectrophotometric evaluations.

d. Determination of the calibration curve using pH 6.8 Phosphate buffer

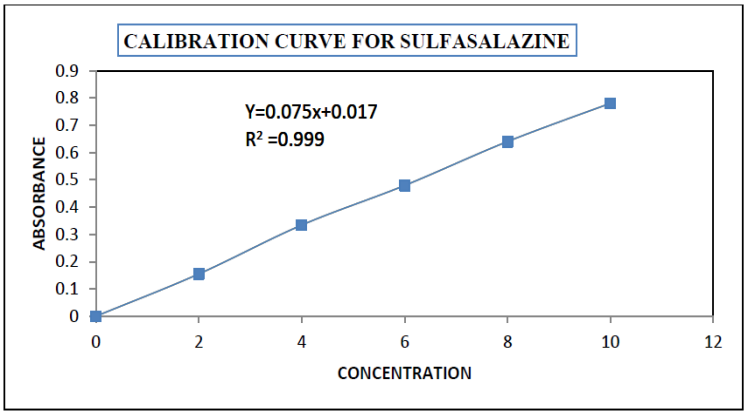


Fig. 2: Calibration curve of Sulfasalazine in pH 6.8 phosphate buffer.

Table 3: Summary of analytical parameters.

Sl. No	Parameters	Results
1	Wavelength (nm)	359nm
2	Slope	0.075
3	Regression coefficient(R^2)	0.999
4	Regression equation	0.075x + 0.017

The calibration curve of sulfasalazine in pH 6.8 phosphate buffer was plotted using different concentrations of the drug (2, 4, 6,8,10 µg/ml) and by measuring absorbance at 359 nm. The plot of concentration V/s absorbance graph (Fig:26) showed a linear relationship with an R^2 value of 0.99. Hence Beer-Lambert's law was obeyed.

e. Determination of melting point

The melting point was determined by the capillary method the and result was found to be 240.33 °C (Table 10). The determined melting point was found to be within the range of the reference melting point. This confirmed the identity of the drug sample.

f. Identification of drug

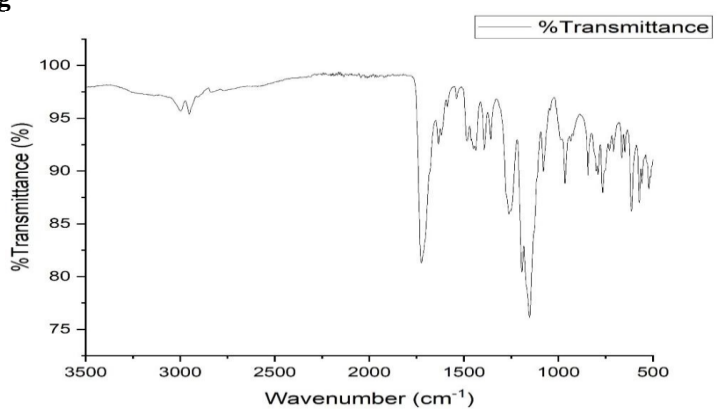


Fig. 3: FT-IR spectrum of Sulfasalazine.

Sulfasalazine was identified by FT-IR spectroscopy and the FT-IR spectrum of Sulfasalazine was compared with that of standard spectrum. The sample spectrum showed all the characteristic peak in the relevant region. So, the given sample of drug was identified as Sulfasalazine.

g. Drug- excipient combatibility test

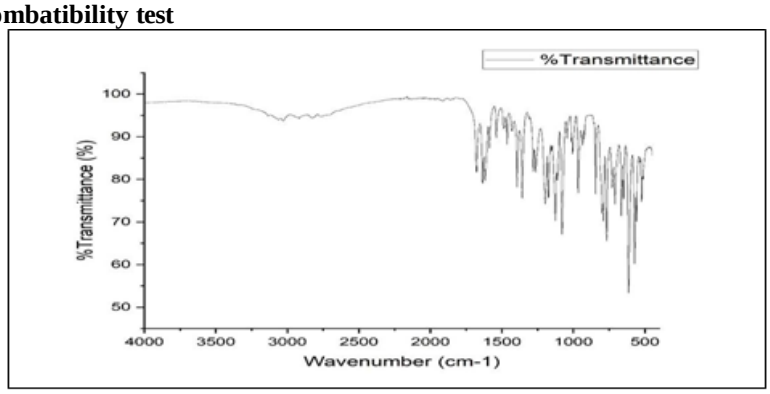


Fig. 4: FT-IR Spectrum of Sulfasalazine +Arachis oil+ Tween 80+ Span 80.

The spectrum obtained from the physical mixture of Sulfasalazine, Arachis oil, Tween 80, Span 80 and Carbopol934p was compared with that of pure drug. All the major peaks present in the spectrum of pure drug were observed in the spectrum of physical mixture of drug and polymer without change in the position. This study indicated the absence of any chemical interaction between the drug Sulfasalazine and the polymers and thus confirming that the drug is compatible with the polymer used in the present investigation.

Formulation of Sulfasalazine Loaded Nanoemulgel

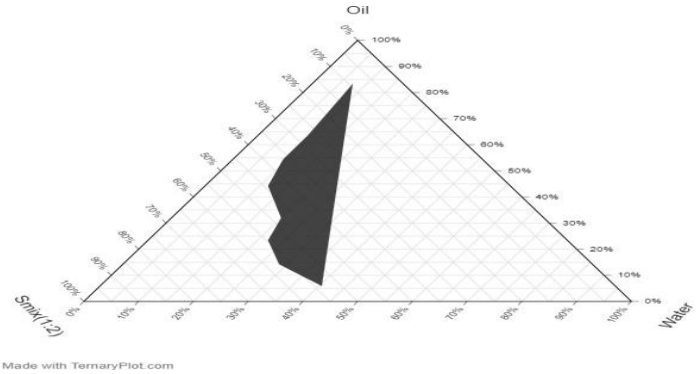
I. Preparation of sulfasalazine loaded nanoemulsion

a. Construction of pseudoternary phase diagram

Phase behavior of different components ((Oil phase, Smix phase and aqueous phase) of nanoemulsion was determined by phase diagram study. The phase diagrams were constructed by ternary plot exploiting spontaneous-emulsification method.

Fig. 5: Aqeous titration Method and End point Pseudoternary phase diagrams of different ratio.

A nanoemulsion region were observed for ternary system (oil, surfactant and water) in phase diagram study. Formulation design of Sulfasalazine nanoemulsion was carried out by constructing the phase diagram exploiting spontaneous-emulsification method in different Smix ratio(1:1,1:2,1:3,2:1,3:1) and different oil, Smix raio (1:9,2:8,3:7,4:6,5:5,6:4,7:3,8:2,9:1). Smix ratio 1:2 showed the highest region of nanoemulsion.



Smix ratio 1: 2

a. Procedure for the preperation of nanoemulsion

The nanoemulsion loaded with Sulfasalazine was prepared by probe sonicator by using surfactants tween 80 and co surfactant Span 80, with varying Smix ratios 1:1, 1:2, 1:3, 2:1, 3:1. F1-F9 Nanoemulsions were prepared using probe sonicator. The prepared nanoemulsion were subjected to evaluation parameters like entrapment efficiency, drug content, particle size determination, and zeta potential.

Fig. 6: Prepared Nanoemulsion and Method.

I. Preparation of sulfasalazine nanoemulgel

Nanoemulgel containg Sulfasalazine were prepared using Nanoemulsion, carbopol 934p, triethanolamine and deionized water.

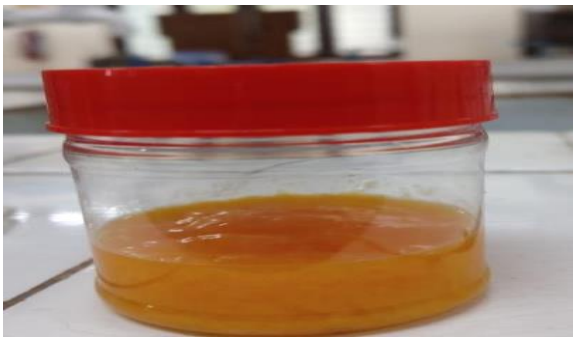


Fig. 7: Sulfasalazine loaded nanoemulgel.

I. Characterization of Sulfasalazine loaded nanoemulsion

A. Entrapment efficiency

Table 4: Entrapment efficiency.

Formulation code	Entrapment efficiency (%)
F1	68.99
F2	70.12
F3	69.98
F4	76.75
F5	74.33
F6	71.90
F7	72.45
F8	67.22
F9	65.99

The entrapment efficiency of the formulations was in the range of 65.99-76.75%. When concentration of polymer is increased, the entrapment efficiency of the nanoemulgel increased Formulation F4 was found to have highest entrapment efficiency.

B. Drug content

Table 5: Drug content of sulfasalazine loaded nanoemulsion.

Formulation code	Drug content (%)
F1	76.1
F2	79.8
F3	77.4
F4	87.5

F5	85.2
F6	81.9
F7	83.7
F8	74.5
F9	72.4

The drug content of the formulation was in the range of 72.4-87.5 %. F4 formulation shows best drug content among all 9 formulation.

C. Particle size, Polydispersity Index and Zeta potential

The particle size distribution of the best nanoemulsion formulation (F4) showed a mean particle size of 210.8 nm and a poly dispersity index of 0.33 (Fig 34). The low value of poly dispersity index indicates the narrow variation in the size range of nanoparticles.

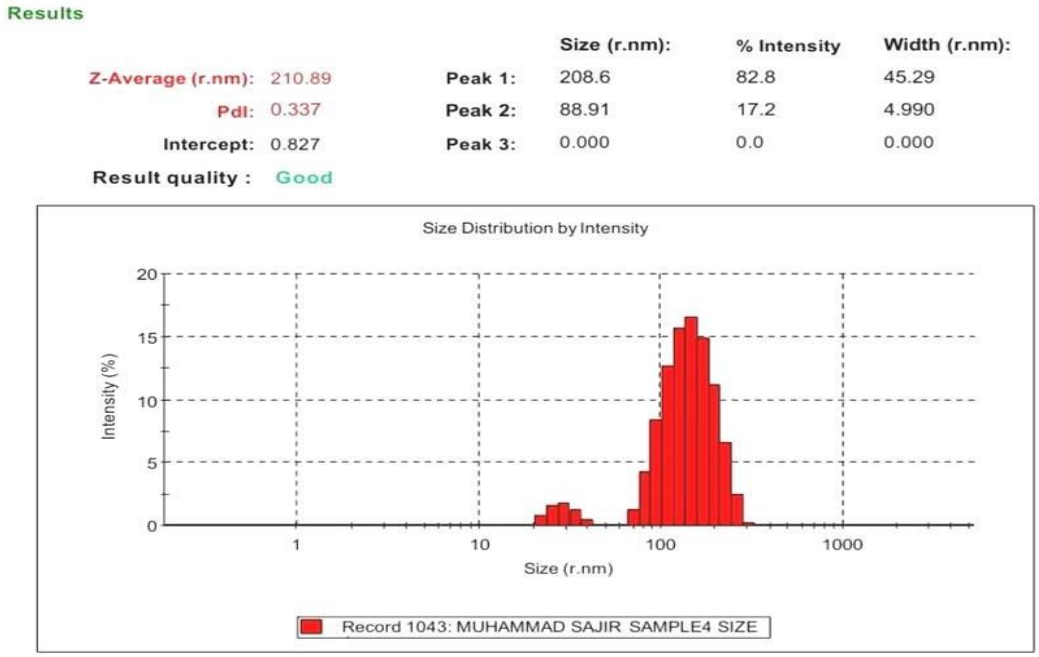


Fig. 7: Particle size analysis of Sulfasalazine nanoemulsion(F4).

The particle size distribution of the best nanoemulsion formulation (F4) showed a mean particle size of 210.8 nm and a poly dispersity index of 0.3 (Fig 34). The low PDI indicates that the formulation show uniform particle size distribution. The small particle size indicates the stable emulsion.

D. Shape and Surface morphology studies

The SEM images of F4 formulation showed that the nanoemulsion had a smooth and spherical structure, indicating successful formulation. Some degree of particle aggregation visible, this could be due to deformation during drying or actual aggregation in the emusion, confirming effective encapsulation and stability of sulfasalazine within nanoemulsion.

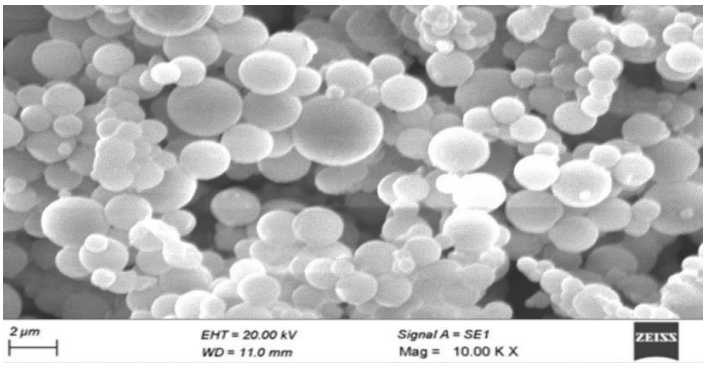


Fig. 8: SEM of Sulfasalazine Nanoemulsion (F4).

II. Characterization of Sulfasalazine loaded nanoemulgel

A. Physical appearance

All the formulations F1-F9 are Yellow to orange in colour, shiny and with out aggregates.

Fig. 9: Nanoemulgel formulation.

All the Sulfasalazine loaded nanoemulgels are same in color and clear without any aggregates, particles and fibers indicating excellent homogeneity of all formulations. Hence, was no physical interaction of the drug with excipients.

B. pH measurement

Table 6: pH of the formulations.

Formulation code	pH
F1	6.1
F2	6.0
F3	5.9
F4	6.3
F5	6.1
F6	5.7
F7	6.2
F8	6.4
F9	5.8

The pH of the formulations was found to be higher in F8 and F4 formulations. This shows that the pH value is within the range near to that of skin pH. This is quite important for topical formulations because increase on the pH value may cause skin irritation.

C. Viscosity

Table 7: Viscosity of the formulations.

Formulation code	Viscosity (CPS)
F1	1340.8
F2	1785.6
F3	2068.2
F4	2215.4
F5	2320.6
F6	2980.7
F7	3506.8
F8	3750.7
F9	3800.6

F4 to F6 shows moderate viscosity formulations that likely provide a good balance between stability, controlled release, and ease of application. For topical applications, the ease of spreading on the skin is influenced by viscosity. F9 may be more difficult to spread evenly, while those with moderate viscosity F4 offer a balance between ease of application and retention on the skin.

D. Spreadability

Table 8: Spreadability of the formulations.

Formulation code	Spreadability g cm/sec
F1	6.2
F2	5.2
F3	4.8
F4	6.4
F5	6.1
F6	5.9
F7	4.3
F8	5.1
F9	4.7

The spreadability of the formulations was found to be in the range of 4.3-6.4. Spreadability is an important factor to be considered in the formulation of gel. If the prepared gel is more viscous. Then the spreadability will be very less and the prepared gel is less or moderately viscous, the spreadbility of the product will be more, this is inversely proportional to each other. F4 has the highest spreadability value (6.4 g·cm/sec), indicating that this formulation is the easiest to spread.

E. Invitro drug release

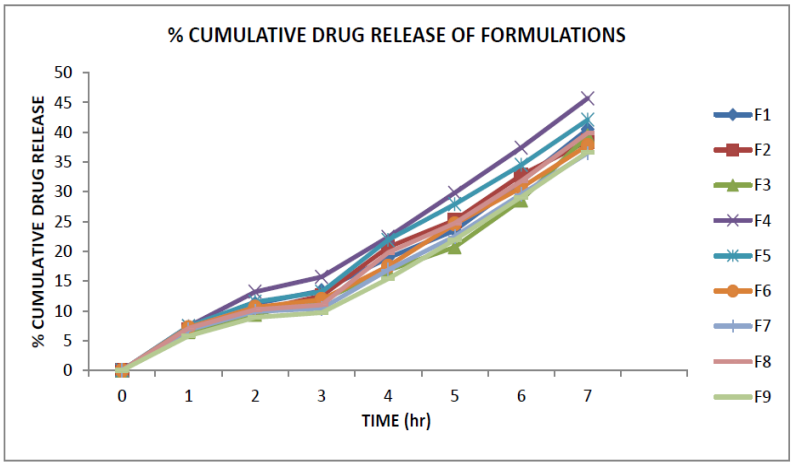


Fig. 10: % Cumulative drug release of sulfasalazine loaded nanoemulgels.

The NE formulation was subjected to in vitro release studies. The result obtained in in vitro release studies were plotted as percent cumulative drug release vs time. F4 shows the highest cumulative release (68.5%), indicating a fast and extensive drug release over the entire 8-hour period.

From the above evaluation parameters F4 has shown lower particle size, higher entrapment efficiency and higher invitro drug release rates. So, F4 formulation is considered as the best from the preliminary trial datas.

F. Drug release kinetics

Regression coefficient (R^2) obtained for first order kinetics and zero order kinetics was 0.800 and 0.986 respectively. The results indicate that the drug release follows nearing zero order kinetics. The coefficients obtained from Higuchi model was 0.986, indicating diffusion played a predominant role in the drug release procedure and drug diffusivity is constant. The in-vitro data as log percentage cumulative drug release versus time was fitted to korsmeyer equation, in order to understand the mechanism by which drug was released from formulation. Slope obtained from Korsmeyer-Peppas equation was the 'n' value and found to be 0.194 indicating that the formulation follows fickian transport mechanism.

G. Short term stability studies of final formulation

The NE formulation was subjected to in vitro release studies. The result obtained in in vitro release studies were plotted as percent cumulative drug release vs time. F4 shows the highest cumulative release (68.5%), indicating a fast and extensive drug release over the entire 8-hour period. From the above evaluation parameters F4 has shown lower particle size, higher entrapment efficiency and higher invitro drug release rates. So, F4 formulation is considered as the best from the preliminary trial datas.

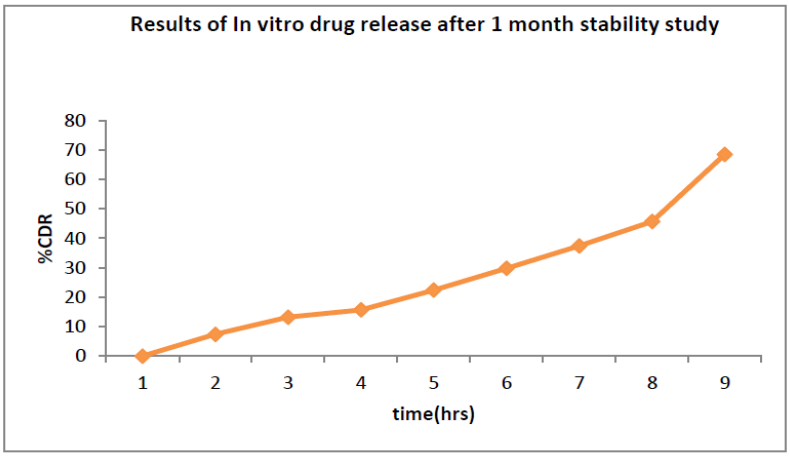


Fig. 11: Results of in vitro drug release after 1 month stability study.

CONCLUSIONS

The sulfasalazine-loaded nanoemulgel formulation (F4) demonstrated promising potential for topical application in the treatment of rheumatoid arthritis. The formulation displayed favorable characteristics, including high drug entrapment efficiency, small particle size, and good electrostatic stability, all contributing to its effectiveness as a drug delivery system. The in vitro release studies revealed a controlled and sustained release of the drug, with formulation F4 showing the highest release rate, which adhered to zero-order kinetics. The release mechanism followed Fickian diffusion, indicating a gradual and predictable drug release. Furthermore, the stability studies confirmed the formulation's resilience, with no significant changes observed in its dissolution patterns. These findings suggest that the sulfasalazine-loaded nanoemulgel could offer an efficient, localized treatment for rheumatoid arthritis, reducing systemic side effects and enhancing patient adherence to therapy.

REFERENCES

1. Radu AF, Bungau SG. Management of rheumatoid arthritis: an overview. Cells, 2021; 23, 10(11): 2857.
2. Gaffo A, Saag KG, Curtis JR. Treatment of rheumatoid arthritis. American journal of health-system pharmacy, 2006; 15, 63(24): 2451-65.
3. Anita C, Munira M, Mural Q, Shaily L. Topical nanocarriers for management of Rheumatoid Arthritis: A review. Biomedicine & Pharmacotherapy, 2021; 1, 141: 111880.
4. Finckh A, Gilbert B, Hodkinson B, Bae SC, Thomas R, Deane KD, Alpizar-Rodriguez D, Lauper K. Global epidemiology of rheumatoid arthritis. Nature Reviews Rheumatology, 2022; 18(10): 591-602.
5. Jang S, Kwon EJ, Lee JJ. Rheumatoid arthritis: pathogenic roles of diverse immune cells. International journal of molecular sciences, 2022; 14, 23(2): 905.
6. Romão VC, Fonseca JE. Etiology and risk factors for rheumatoid arthritis: a state-of-the-art review. Frontiers in medicine, 2021; 26, 8: 689698.
7. Firestein GS. Immunologic mechanisms in the pathogenesis of rheumatoid arthritis. JCR: Journal of Clinical Rheumatology, 2005; 1, 11(3): S39-44.
8. Kung TN, Bykerk VP. Detecting the earliest signs of rheumatoid arthritis: symptoms and examination. Rheumatic Disease Clinics, 2014; 1, 40(4): 669-83.
9. Sierakowski S, Cutolo M. Morning symptoms in rheumatoid arthritis: a defining characteristic and marker of active disease. Scandinavian Journal of Rheumatology, 2011; 1, 40(125): 1-5.
10. Gravallese EM, Harada Y, Wang JT, Gorn AH, Thornhill TS, Goldring S. Identification of cell types responsible for bone resorption in rheumatoid arthritis and juvenile rheumatoid arthritis. The American journal of pathology, 1998; 152(4): 943.
11. Aletaha D, Smolen JS. Diagnosis and management of rheumatoid arthritis: a review. Jama, 2018; 2, 320(13): 1360-72.
12. Thakur S, Riyaz B, Patil A, Kaur A, Kapoor B, Mishra V. Novel drug delivery systems for NSAIDs in management of rheumatoid arthritis: An overview. Biomedicine & Pharmacotherapy, 2018; 1, 106: 1011-23.
13. Morrison E, Capell HA. Corticosteroids in the management of early and established rheumatoid disease. Rheumatology, 2006; 1, 45(9): 1058-61.
14. Goodman SM. Rheumatoid arthritis: perioperative management of biologics and DMARDs. InSeminars in arthritis and rheumatism, 2015; 1, 44, 6: 627-632). WB Saunders.
15. Plosker GL, Croom KF. Sulfasalazine: a review of its use in the management of rheumatoid arthritis. Drugs, 2005; 65: 1825-49.
16. Rains CP, Noble S, Faulds D. Sulfasalazine: a review of its pharmacological properties and therapeutic efficacy in the treatment of rheumatoid arthritis. Drugs, 1995; 50: 137-56.
17. Dale J, Alcorn N, Capell H, Madhok R. Combination therapy for rheumatoid arthritis: methotrexate and sulfasalazine together or with other DMARDs. Nature clinical practice rheumatology, 2007; 3(8): 450-8.
18. Moura CS, Schieir O, Valois MF, Thorne C, Bartlett

SJ, Pope JE, Hitchon CA, Boire G, Haraoui B, Hazlewood GS, Keystone EC. Treatment strategies in early rheumatoid arthritis methotrexate management: results from a prospective cohort. Arthritis Care & Research, 2020; 72(8): 1104- 11.
19. Li EK, Tam LS, Tomlinson B. Leflunomide in the treatment of rheumatoid arthritis. Clinical therapeutics, 2004; 1, 26(4): 447-59.
20. Yamaoka K. Janus kinase inhibitors for rheumatoid arthritis. Current opinion in chemical biology, 2016; 1, 32: 29-33.
21. Kahlenberg JM, Fox DA. Advances in the medical treatment of rheumatoid arthritis. Hand clinics, 2011; 1, 27(1): 11-20.
22. Visser K, van der Heijde D. Optimal dosage and route of administration of methotrexate in rheumatoid arthritis: a systematic review of the literature. Annals of the rheumatic diseases, 2009; 1, 68(7): 1094-9.
23. Cheng OT, Souzdalnitski D, Vrooman B, Cheng J. Evidence-based knee injections for the management of arthritis. Pain medicine, 2012; 1, 13(6): 740-53.
24. Anita C, Munira M, Mural Q, Shaily L. Topical nanocarriers for management of Rheumatoid Arthritis: A review. Biomedicine & Pharmacotherapy, 2021; 1, 141: 111880.
25. Nagai N, Yoshioka C, Ito Y. Topical therapies for rheumatoid arthritis by gel ointments containing indomethacin nanoparticles in adjuvant-induced arthritis rat. Journal of oleo science, 2015; 64(3): 337-46.
26. Jurca T, Józsa L, Suciu R, Pallag A, Marian E, Bácskay I, Mureșan M, Stan RL, Cevei M, Cioară F, Vicaș L. Formulation of topical dosage forms containing synthetic and natural anti-inflammatory agents for the treatment of rheumatoid arthritis. Molecules, 2020; 23, 26(1): 24.
27. Karnam S, Donthi MR, Jindal AB, Paul AT. Recent innovations in topical delivery for management of rheumatoid arthritis: A focus on combination drug delivery. Drug Discovery Today, 2024; 26: 104071.
28. Wang Y, Zeng L, Song W, Liu J. Influencing factors and drug application of iontophoresis in transdermal drug delivery: an overview of recent progress. Drug delivery and translational research, 2021; 23: 1-2.
29. Pleuvry BJ. Factors affecting drug absorption and distribution. Anaesthesia & Intensive Care Medicine, 2005; 1, 6(4): 135-8.
30. Ghasemiyeh P, Mohammadi-Samani S. Potential of nanoparticles as permeation enhancers and targeted delivery options for skin: Advantages and disadvantages. Drug design, development and therapy, 2020; 12: 3271-89.
31. Dikmen G, Genç L, Güney G. Advantage and disadvantage in drug delivery systems. Journal of Materials Science and Engineering, 2011; 1, 5(4): 468.
32. Kolarsick PA, Kolarsick MA, Goodwin C. Anatomy and physiology of the skin. Journal of the Dermatology Nurses' Association, 2011; 1, 3(4): 203-13.
33. Bani KS, Bhardwaj K. Topical drug delivery therapeutics, drug absorption and penetration enhancement techniques. Journal of Drug Delivery and Therapeutics, 2021; 15, 11(4): 105-10.
34. Singh Malik D, Mital N, Kaur G. Topical drug delivery systems: a patent review. Expert opinion on therapeutic patents, 2016; 1, 26(2): 213-28.
35. Singh Malik D, Mital N, Kaur G. Topical drug delivery systems: a patent review. Expert opinion on therapeutic patents, 2016; 1, 26(2): 213-28.
36. Singhvi G, Patil S, Girdhar V, Dubey SK. Nanocarriers for topical drug delivery: approaches and advancements. Nanoscience & Nanotechnology-Asia, 2019; 1, 9(3): 329-36.
37. Solans C, Izquierdo P, Nolla J, Azemar N, Garcia-Celma MJ. Nano-emulsions. Current opinion in colloid & interface science, 2005; 1, 10(3-4): 102-10.
38. Israelachvili J. The science and applications of emulsions—an overview. Colloids and Surfaces A: Physicochemical and Engineering Aspects, 1994; 3, 91: 1-8.
39. Patil PB, Datir SK, Saudagar RB. A review on topical gels as drug delivery system. Journal of Drug Delivery and Therapeutics, 2019; 15, 9(3-s): 989-94.
40. Panwar A, Upadhyay N, Bairagi M, Gujar S, Darwhekar G, Jain D. Emulgel: A review. Asian J Pharm Life Sci, 2011; 2231: 4423.
41. Chellapa P, Mohamed AT, Keleb EI, Elmahgoubi A, Eid AM, Issa YS, Elmarzugi NA. Nanoemulsion and nanoemulgel as a topical formulation. IOSR J Pharm, 201; 5(10): 43-7.
42. Aithal GC, Narayan R, Nayak UY. Nanoemulgel: A promising phase in drug delivery. Current pharmaceutical design, 2020; 1, 26(2): 279-91.
43. Sengupta P, Chatterjee B. Potential and future scope of nanoemulgel formulation for topical delivery of lipophilic drugs. International journal of pharmaceutics, 2017; 30, 526(1-2): 353-65.
44. Abdallah MH, Lila AS, Unissa R, Elsewedy HS, Elghamry HA, Soliman MS. Preparation, characterization and evaluation of anti-inflammatory and anti-nociceptive effects of brucine-loaded nanoemulgel. Colloids and Surfaces B: Biointerfaces, 2021; 1, 205: 111868.
45. Chellapa P, Mohamed AT, Keleb EI, Elmahgoubi A, Eid AM, Issa YS, Elmarzugi NA. Nanoemulsion and nanoemulgel as a topical formulation. IOSR J Pharm, 2015; 5(10): 43-7.
46. Gurpreet K, Singh SK. Review of nanoemulsion formulation and characterization techniques. Indian Journal of Pharmaceutical Sciences, 2018; 1: 80(5).
47. Çınar K. A review on nanoemulsions: preparation methods and stability. Sole I, Maestro A, González C, Solans C, Gutiérrez JM. Optimization of nano-emulsion preparation by low-energy methods in an ionic surfactant system. Langmuir, 2006; 26, 22(20): 8326-32.
48. Sokolov YV. Nanoemulsion formation by low-

energy methods: A review. News of Pharmacy, 2014; 12(3 (79)): 16-9.
49. Jasmina H, Džana O, Alisa E, Edina V, Ognjenka R. Preparation of nanoemulsions by high-energy and lowenergy emulsification methods. InCMBEBIH 2017: Proceedings of the International Conference on Medical and Biological Engineering, 2017; 2017: 317-322. Springer Singapore.
50. Håkansson A, Rayner M. General principles of nanoemulsion formation by high-energy mechanical methods. InNanoemulsions, 2018; 1: 103-139. Academic Press.
51. Sipos E, Szász N, Vancea S, Ciurba A. Evaluation and selection of gel base for the formulation of dexpanthenol products. Tropical Journal of Pharmaceutical Research, 2014; 13(12): 1987-92.
52. Malay NJ, Chandresh PP, Bhupendra GP. Nanoemulgel innovative approach for topical gel based formulation. Nanoemulgel Innov approach Top gel based Formul, 2018; 15.
53. Lal DK, Kumar B, Saeedan AS, Ansari MN. An overview of nanoemulgels for bioavailability enhancement in inflammatory conditions via topical delivery. Pharmaceutics, 2023; 7, 15(4): 1187.
54. Gaber, D. A., Alsubaiyel, A. M., Alabdulrahim, A. K., Alharbi, H. Z., Aldubaikhy, R. M., Alharbi, R. S., Albishr, W. K., & Mohamed, H. A. Nano-Emulsion Based Gel for Topical Delivery of an Anti-Inflammatory Drug: In vitro and in vivo Evaluation. *Drug design, development and therapy*, 2023; *17*: 1435–1451. https://doi.org/10.2147/DDDT.S407475.
55. Amgaonkar YM, Kochar NI, Chandewar AV, Umekar MJ, Wadher KJ. Boswellic Acid Loaded Nanoemulgel for Rheumatoid Arthritis: Formulation Design and Optimization by QbD, in vitro, ex vivo, and in vivo Evaluation. Ind. J. Pharm. Edu. Res, 2024; 58(2): 546-54.
56. Bashir M, Ahmad J, Asif M, Khan SU, Irfan M, Y Ibrahim A, Asghar S, Khan IU, Iqbal MS, Haseeb A, Khalid SH. Nanoemulgel, an innovative carrier for diflunisal topical delivery with profound anti-inflammatory effect: In vitro and in vivo evaluation. International Journal of Nanomedicine, 2021; 22: 1457-72.
57. Nishal S, Jhawat V, Phaugat P, Dutt R. In vitro characterization of tofacitinib loaded novel nanoemulgel for topical delivery for the management of rheumatic arthritis. Drug Development and Industrial Pharmacy, 2022; 3, 48(8): 374-83.
58. ur Rehman M. *Solid Lipid Nanoparticles for Sulfasalazine: Fabrication, Characterization, InVitro and In-Vivo Assessment for Oral Bioavailability* (Doctoral dissertation, University Of Malakand, Chakdara), 2021; 5.
59. Hussain A, Samad A, Singh SK, Ahsan MN, Haque MW, Faruk A, Ahmed FJ. Nanoemulsion gel- based topical delivery of an antifungal drug: in vitro activity and in vivo evaluation. Drug delivery, 2016; 12, 23(2): 642-57.
60. Khurana, Bharat & Arora, Daisy & Narang, RK. *Topical delivery of nanoemulsion for antipsoriatic drugs.* Journal of Drug Delivery and Therapeutics, 2018; 8: 1-11. 10.22270/jddt.v8i5- s.1914.
61. Baba Shekh AO, Abdul Wahab R, Yahya NA. Formulation of roselle extract water-in-oil nanoemulsion for controlled pulmonary delivery. Journal of Dispersion Science and Technology, 2023; 8, 44(10): 1830-41.
62. Shoaib A. Shaikh, Sharav A. Desai1, Ravi S. Khandare and Bhagwat H. Garje. Formulation, Evaluation, Development, Characterization, and In Vitro Evaluation of Sulfasalazine hydrogel for the treatment of Oral Lichen Planus. Biological forum-an international journal, 2023; 20, 15(5): 481-491.
63. Bhattacharya SA, Prajapati BG. Formulation and optimization of celecoxib nanoemulgel. Asian J Pharm Clin Res, 2017; 10(8): 353-65.
64. Mishra R, Jain N, Kaul S, Nagaich U. Central composite design–based optimization, fabrication, and pharmacodynamic assessment of sulfasalazine-loaded lipoidal nanoparticle-based hydrogel for the management of rheumatoid arthritis. Drug Delivery and Translational Research, 2023; 13(4): 994-1011.
65. Puppala RK, A VL. Optimization and solubilization study of nanoemulsion budesonide and constructing pseudoternary phase diagram. Asian J Pharm Clin Res, 2019; 7, 12(1): 551-3.
66. Ardi, Bita & Shirmard, Leila & Rahimpour, Elaheh & Fathi Azarbayjani, Anahita & Jouyban, Abolghasem. The effect of cosolvents and surfactants on the solubility of sulfasalazine. Physics and Chemistry of Liquids, 2022; 60: 1-9. 10.1080/00319104.2022.2076234.
67. Priya, Sneh & Koland, Marina & Kumari, Suchetha.Nanoemulsion components screening of quetiapine fumarate: Effect of surfactant and co surfactant. Asian J Pharm Clin Res, 2015; 8: 136- 140.
68. SAHELI D, Sharadha M, MP V, SUBHASHREE S, JOGABRATA TRIPATHY DV. Formulation and evaluation of topical nanoemulgel of methotrexate for rheumatoid arthritis. Int J App Pharm, 2021; 13(5): 351-7.
69. Verma V, Easwari TS. A novel approach of leflunomide Nanoemulgel for topical drug delivery system. Int. J. Pharm. Investig, 2022; 1, 12(2): 199-204.
70. Chandra A, Arya RK, Pal GR, Tewari B. Formulation and evaluation of ginger extract loaded nanoemulgel for the treatment of rheumatoid arthritis. Journal of Drug Delivery and Therapeutics, 2019; 20, 9(4): 559-70.
71. Shaikh NM, Swamy SV, NARSING NS, Kulkarni KB. Formulation and evaluation of nanoemulsion for topical application. Journal of Drug Delivery and Therapeutics, 2019; 15, 9(4-s): 370-5.
72. Bakshi P, Jiang Y, Nakata T, Akaki J, Matsuoka N, Banga AK. Formulation development and

characterization of nanoemulsion-based formulation for topical delivery of heparinoid. Journal of Pharmaceutical Sciences, 2018; 1, 107(11): 2883-90.
73. Siddiqui A, Jain P, Alex TS, Ali MA, Hassan N, Haneef J, Naseef PP, Kuruniyan MS, Mirza MA, Iqbal Z. Investigation of a minocycline-loaded nanoemulgel for the treatment of acne rosacea. Pharmaceutics, 2022; 28, 14(11): 2322.
74. Baibhav, Joshi & Singh, Gurpreet & Rana, A.C. & Seema, Saini. Development and Characterization of Clarithromycin Emulgel for topical delivery. International Journal of Drug Development and Research, 2012; 4: 310-323.
75. Rains CP, Noble S, Faulds D. Sulfasalazine: a review of its pharmacological properties and therapeutic efficacy in the treatment of rheumatoid arthritis. Drugs, 1995; 50: 137-56.
76. Costa MA, Villa AL, Barros RD, Ricci-Júnior E, Santos EP. Development, characterization and evaluation of the dissolution profile of sulfasalazine suspensions. Brazilian Journal of Pharmaceutical Sciences, 2015; 51: 449-59.
77. McDonnell JP. Sulfasalazine. InAnalytical profiles of drug substances, 1976; 1, 5: 515-532). Academic Press.
78. Plosker GL, Croom KF. Sulfasalazine: a review of its use in the management of rheumatoid arthritis. Drugs, 2005; 65: 1825-49.
79. Taffet SL, Das KM. Sulfasalazine: adverse effects and desensitization. Digestive diseases and sciences, 1983; 28: 833-42.
80. Wadworth AN, Fitton A. Olsalazine: A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in inflammatory bowel disease. Drugs, 1991; 41: 647-64.
81. Niranjan D. Bachewad, Mr. Nandan C. Jadhav, Dr. R. O. Sonawane: A Review On Source, Physicochemical Properties, Grades, Preparation, Evaluation, Applications And Patents Of Carbopol In Various Formulations. Indo Am. J. P. Sci, 2022; 09(6).
82. Fartasch M, Breuer D. Triethanolamin (TEA): A relevant allergen in metalworking fluids (MWF). Contact Dermatitis, 2006; 55: 39-40.
83. Al-Rajhi AM, Ghany TA. Nanoemulsions of some edible oils and their antimicrobial, antioxidant, and anti-hemolytic activities. BioResources, 2023; 1, 18(1): 1465.
84. Chong WT, Tan CP, Cheah YK, B. Lajis AF, Habi Mat Dian NL, Kanagaratnam S, Lai OM. Optimization of process parameters in preparation of tocotrienol-rich red palm oil-based nanoemulsion stabilized by Tween80-Span 80 using response surface methodology. PLoS One, 2018; 24, 13(8): e0202771.
85. Costa MA, Villa AL, Barros RD, Ricci-Júnior E, Santos EP. Development, characterization and evaluation of the dissolution profile of sulfasalazine suspensions. Brazilian Journal of Pharmaceutical Sciences, 2015; 51: 449-59.