Journal of Pharmaceutical Advanced Research

(An International Multidisciplinary Peer Review Open Access monthly Journal)

Available online at: www.jparonline.com

RESEARCH ARTICLE JPAR 2024

Development and Characterization of Solid Lipid Nanoparticles for Topical Drug Delivery System

Dhananjay, Pankaj Kumar*

Department of Pharmaceutics, School of Pharmacy, Chouksey Engineering College, Lalkhadan, Masturi Road, Bilaspur – 495004, *Chhattisgarh*, India.

Received: 04.04.2023 Revised: 15.04.2024 Accepted: 21.04.2024 Published: 30.04.2024

ABSTRACT: Background: Aceclofenac are reported for use in the allopathy systems of medicines for the treating rheumatoid arthritis. It has non-steroidal anti-inflammatory drug (NSAID) properties. **Aim:** The objective of this study was to develop solid lipid nanoparticles and create a gel for improved topical delivery of aceclofenac. **Method:** The solid lipid nanoparticles were synthesized using the ultrasonic emulsification technique containing polyvinyl alcohol (PVA), tween 20, ethanol, lecithin soya, glycerine, glyceryl monostearate etc. and optimized based on stirring speed. **Results:** The optimized formulation was assessed for various parameters including particle size (216 nm), zeta potential (30.5 mV), drug loading efficiency (93 %), *in-vitro* drug release study, surface morphology, differential scanning calorimetry, and X-ray diffraction etc. The performance of the aceclofenac-loaded solid lipid nanoparticles gel exhibited prolonged efficacy in treating rheumatoid arthritis. **Conclusion:** These findings suggest that the aceclofenac– solid lipid nanoparticles formulation designed for skin targeting holds promise as a carrier for the topical delivery of aceclofenac.

Corresponding author:
Mr. Pankaj Kumar
Assistant Professor
School of Pharmacy, Chouksey Engineering College,
Lalkhadan, Masturi Road, Bilaspur – 495004, Chhattisgarh, India.
Tel: +91-9300292707
E. Mail ID: pankaj22ggu@gmail.com

Keywords: Aceclofenac, Solid lipid nanoparticles, Gels, Characterization, Topical application, Rheumatoid arthritis.

INTRODUCTION:

Aceclofenac is a non-steroidal anti-inflammatory drug (NSAID) taken orally to reduce pain and inflammation in osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. Oral aceclofenac long-term use may cause side effects such as stomach ache, abdominal pain, gastric irritation, ulcer and bloating [1,2]. In order to achieve superior effectiveness and high compliance with the treatment, these specialists ought to be administered once day by day and their helpful activity ought to last for 24 h indeed with a day-by-day single-dose organization. A controlled-release formulation could be a better option that will provide prolonged action, with minimum side effects and improved patient compliance [3,4]. The mode of action of aceclofenac is largely based on the inhibition [4] of prostaglandin synthesis. Aceclofenac is a potent inhibitor of the

enzyme cyclo-oxygenase, which is involved in the production of prostaglandins [5,6].

Solid lipid nanoparticles are novel controlled release carriers that have been proposed for different routes of administration such as parenteral, orally and topically. They are made up of biocompatible and biodegradable material, with the ability to incorporate lipophilic and hydrophilic drugs [7,8]. In the last decade, these carriers have gained wide interest in topical administration due to their occlusive properties or film formation on the skin surface [9]. They also reduce the trans epidermal water loss and may enhance the penetration of drugs through the stratum corneum (SC) by increased hydration [10]. Solid lipid nanoparticles not only function as an alternative carrier but are also well suited for dermal application on inflamed skin, because of the non-irritant and nontoxic lipid content [11,12]. Moreover, solid lipid nanoparticles could be formulated into creams and gels without altering their properties, for better skin retention and improved topical delivery [13,14].

The present investigation was aimed to develop and characterize aceclofenac-loaded solid lipid nanoparticles, and incorporate them into a solid lipid nanoparticles gel. Solid lipid nanoparticles were prepared using the ultrasonic emulsification technique, with glyceryl monostearate as the solid lipid. The results of aceclofenac-loaded solid lipid nanoparticles formulation may be a promising carrier for topical delivery of aceclofenac.

MATERIAL AND METHOD:

Aceclofenac pure drugs were procured as a gift sample from Dhamtech drugs Pvt.Ltd., Mumbai, India. Polyvinyl alcohol (PVA) collected from ACS chemical Ahmadabad and Loha Pvt.Ltd., Mumbai. Tween 20, ethanol, lecithin soya, glycerine, glyceryl monostearate, water and other material chemicals used for the were of analytical grade.

Preparation of solid lipid nanoparticles by ultrasonic emulsification technique:

Solid lipid nanoparticles were prepared by ultrasonic emulsification technique, with slight modifications. Briefly, aceclofenac was dissolved in a minimum quantity of alcohol at 50 °C. After evaporation of ethanol, the melt was dispersed in preheated water (50 °C) containing a mixture of emulsifier (soya lecithin and tween 20, at a ratio of 1:1) under mechanical stirring (Remi, India) at 4000 rpm for 10 min. The resulting emulsion was subjected to ultrasonication using a probe sonicator (Soni weld, India) for 6 min at 40 watts. Further, the dispersion was immediately dispersed in cold distilled water (4 °C), followed by continued mechanical stirring for 10 min. The suspension is then filtered through a 0.45 mm filter to remove impurities from the material [15,16].

Characterization of Solid Lipid Nanoparticles:

***Particle size*:**

Particle size analysis the particle size should be less than 1000 nm in nanoparticles. It can be analysed by using malvern particle size analyser (Malvern Mastersizer Hydro 2000MU). Particles in the size range of colloids display constant random thermal motion which is known as brownian motion. The zeta sizer has a correlation with 64 channels. Each of these channels measures changes in light fluctuation over a defined time span [17].

***Zeta potential*:**

Zeta potential is highly useful for assessment of the physical stability of colloidal dispersions. Zeta potential of the solid lipid nanoparticles was measured by malvern zetasizer (Malvern Zetasizer ZS ZEN 3600) [18].

***X-ray diffraction (XRD)*:**

X-ray powder diffraction is a rapid analytical technique primarily used for phase identification of a crystalline material and can provide information on unit cell dimensions. The analysed material is finely ground, homogenized and the average bulk composition is determined by X-ray diffraction (Rigaku MiniFlex XRD 600-C) [19].

***DSC analysis*:**

Thermal analysis was performed using the differential scanning calorimeter (PerkinElmer DSC 6000) equipped with the computerized data. The sample of pure drug and physical mixture were heated at a scanning rate of 10 °C /min between 30°C and 350 °C and 40 ml/min of nitrogen flow; the differential scanning calorimeter analysis gives an idea about the interaction of various materials at different temperatures [20].

***Scanning electron microscopy (SEM)*:**

The SLN was placed on a double-side adhesive tape stuck to an aluminium stub and dried under vacuum. The samples were made conductive by sputtering a thin coat of platinum under vacuum using JEOL JFC-1600 auto fine coater and then the images were recorded.

***Drug loading efficiency*:**

Drug loading efficiency is determined by both the carrier and drug properties, which include molecular weight, the

solubility of the drug in the carrier, volumetric size of the carrier, and also chemical interactions between the drug and the carrier [21].

***In-vitro release study for solid lipid nanoparticles*:**

In-vitro release studies were carried out by modified franz diffusion cells; 10 mg equivalent weight of solid lipid nanoparticles was placed on a cellophane membrane which was placed between donor and receptor compartment of diffusion cell assembly. The donor compartment is wetted by 0.5 ml of phosphate buffer. The donor compartment is filled by 50ml phosphate buffer pH 7.4. The receptor compartment was continuously stirred using the magnetic stirrer. The temperature was maintained at 35 °C. The study was carried out for 24 h, and the sample was withdrawn every 30 min time interval and the same volume was replaced with a free phosphate buffer. The content of aceclofenac from the withdrawn sample was measured after suitable dilution at 273 nm [22].

Preparation of aceclofenac-loaded solid lipid nanoparticles gel:

For preparation of aceclofenac-loaded solid lipid nanoparticles gel, Carbopol 934 (1gm) was dispersed in solid lipid nanoparticles dispersion (1.5 g of aceclofenac) followed by addition of glycerine (10 ml) after 12 h, triethanolamine (0.4 ml) was added and gently stirred with a glass rod. Similarly, plain aceclofenac loaded gel was also prepared [23].

Evaluation of solid lipid nanoparticles Gel:

***Homogeneity*:**

All formulation gels were tested for homogeneity by visual inspection after the gel had been set in the container. They were tested for their appearance and presence of any aggregates [24].

***Grittiness*:**

All the formulations were evaluated microscopically for presence of particles if any no appreciable particulate matter was seen under light microscope. Hence obviously the gel preparation fulfils the requirement of freedom from particular matter and from grittiness as desired for any topical preparation [24].

***pH*:**

It was measured by a digital pH meter and it is necessary for minimising skin irritation [24].

***Viscosity*:**

The viscosity of developed gel formulation was performed using brookfield digital viscometer (Model RV-1) equipment with spindle no. 7 in 5, 10, 20, 50, and 100 rpm under room temperature. The formulated gel was poured into the small adapter of the brookfield synchro lectric viscometer [24].

***Spread ability test*:**

The rheological behaviour of the topical formulation was investigated since it related to the spread ability of the formulation and contact time on the skin surface. The degree of dispersion and particle-particle association was estimated from the rheological profile of the nano lipid carrier enriched gel. It may also influence the therapeutic efficacy a gel with good spread ability can be easily applied on of a topical formulation. Two sets of circular glass plates (diameter 2 cm) were taken. solid lipid nanoparticles gel (1 g) was placed over one of the plates and the other plate was on the top of the solid lipid nanoparticles gel. The Standard weight applied on the upper plates was 100 g weighted for 1 min. The spread ability of the gel was determined by measuring the area of circle spreading formed [25].

***Percentage of drug content*:**

Upon dissolving 500 mg of aceclofenac gel in 50 ml of phosphate buffer pH 7.4 and allowing it to sit for 2 h, and shake well in a shaker to mix it properly. The solution was passed through the filter paper and the drug content was measured spectrophotometrically at 273 nm against corresponding gel concentration as blank [26,27].

***Stability studies*:**

Stability studies were conducted to find out stable products under storage following ICH guidelines. The prepared formulations (F1, F2, F3, F4 and F5) were tested for stability at room storage conditions (25±2 ºC, 70±5 % RH). Formulations were stored for a period of one months and observed for change in drug content at intervals of 5, 10, 15, 20, 25, and 30 day. The graphs were plotted between percent residual drugs against time (one month) [27].

RESULTS AND DISCUSSION:

Particle size distribution:

The mean particle size of the formulations was found to be 216 nm shown in Fig 2, indicating, that the particles are in an acceptable nm**.**

Zeta potential:

The zeta potential of the SLN dispersion is shown in Fig 3. Zeta potential of selected SLN F3 was +30.3. The presence of drug causes a diminution of surface charge of all the investigated samples because probably a share of drug is situated on the lipid nanoparticles surface.

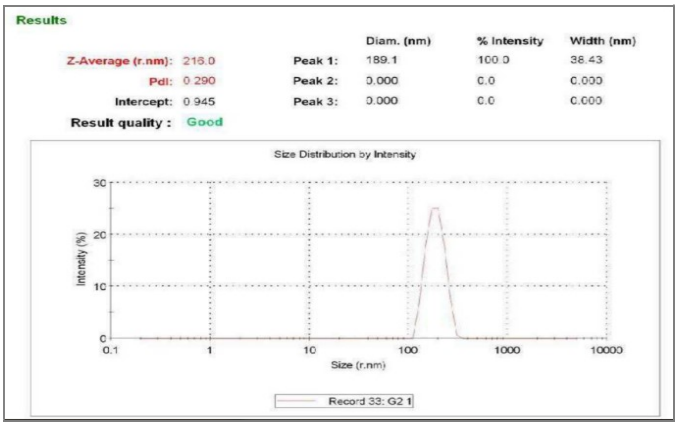

Fig 2. Particles size distribution of optimized nanoparticle formulation.

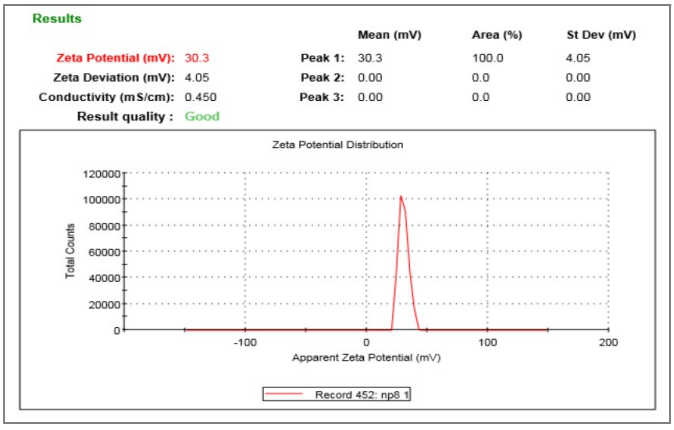

Fig 3. Zeta potential data of optimized nanoparticle formulation.

X-ray diffraction (XRD):

The X-ray diffraction patterns of pure aceclofenac, bulk glyceryl monostearate, blank SLN and drug-loaded SLN are shown in Fig 4 revealing significant difference between diffraction of pure Aceclofenac and drug-loaded SLN.

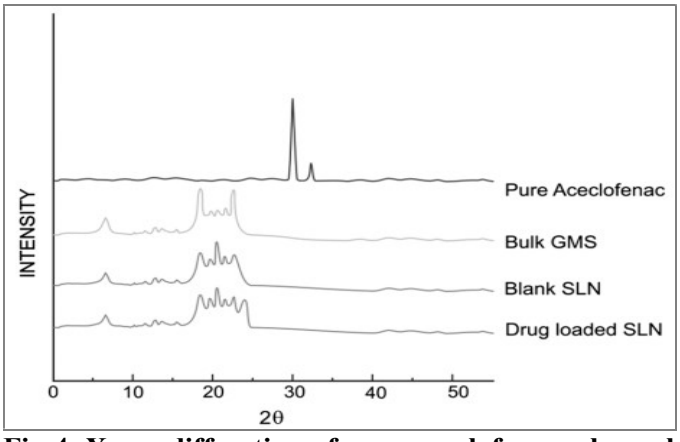

Fig 4. X-ray diffraction of pure aceclofenac, glyceryl monostearate, blank SLN, and drug-loaded SLN.

It could be inferred via X-ray diffraction that the aceclofenac existed in the amorphous form, because of the absence of a sharp peak of aceclofenac in the diffraction pattern of drug-loaded SLN. The X-ray diffraction of SLN was broader and much weaker than that of bulk glyceryl monostearate.

Differential scanning calorimetry:

DCS is a plot of heat flux (rate) versus temperature at a specified temperature. Polymorphic transformation of the lipid drug delivery system may occur during the preparation of the dosage form. Therefore, the differential scanning calorimetry thermograms of pure aceclofenac, glyceryl monostearate, blank SLN, and drug-loaded SLN were investigated. Differential scanning calorimetry graph confirmed that aceclofenac presented a sharp peak at 178 °C, corresponding to the melting point behaviour of the crystalline form of the drug, and glyceryl monostearate presented a sharp peak at 54.46 °C shown in Fig 5.

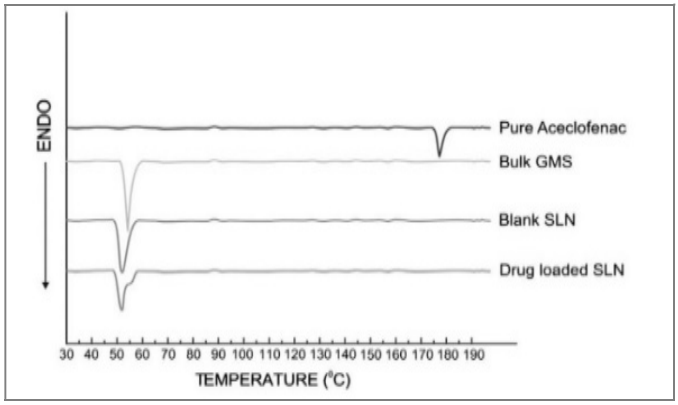

Fig 5. Differential scanning calorimetry curve of pure aceclofenac, glyceryl monostearate, blank SLN, and drug-loaded SLN.

Scanning electron microscopy (SEM):

Scanning electron microscopy analysis of the optimized formulations depicted the aceclofenac-loaded solid lipid nanoparticles as smooth and nearly spherical structures. The particles were observed to aggregate into clusters as shown in Fig 1.

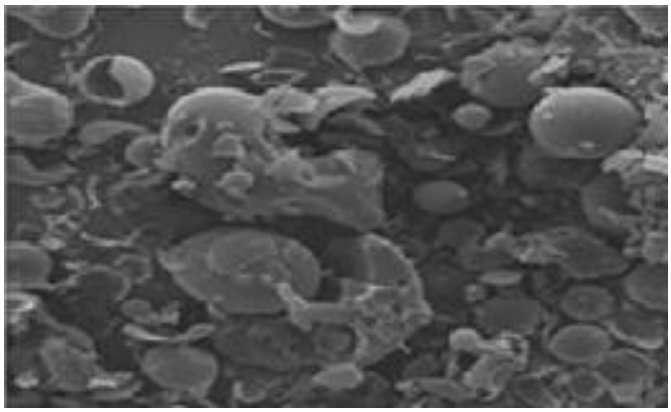

Fig 1. SEM image for optimized nanoparticle formulation.

Drug loading efficiency:

From the results it has been observed that the high lipid concentration containing formulation solid lipid nanoparticles F3 have higher drug loading as compared to other formulations. The solid lipid nanoparticles F3 dispersion has 93 % loading, while solid lipid nanoparticles F1 and solid lipid nanoparticles F2 have 71 and 75 % respectively. Same as seen in solid lipid nanoparticles F4, solid lipid nanoparticles F5 have 80 and 87 % as shown in Fig 6.

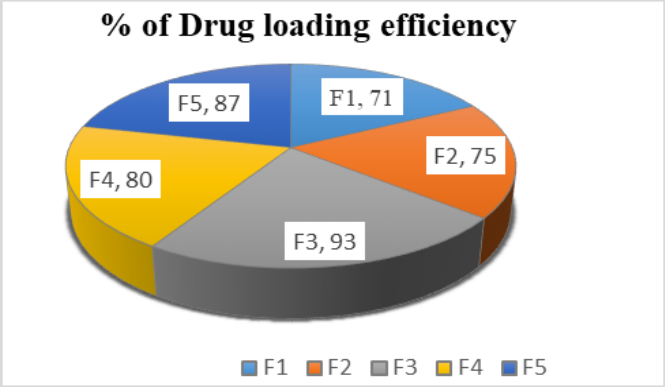

Fig 6. The Percentage of drug loading efficiency.

***In-vitro* drug release study formulations**:

F1, F2, F3, F4, F5, and F6 were subjected to *in-vitro* release studies. The release studies were performed in a phosphate buffer of pH 7.4, suspending the formulation with 100 mg equivalent of the drug results shown in Table 1 and Fig 7. The results revealed that, about 90.55 % of drug was released from F6, formulation respectively in a tween 8 or 9 h of study. So F6 formulation is taken for incorporation into gel.

Table 1. The *in-vitro* drug release study of solid lipid nanoparticles formulations in phosphate buffer pH 7.4.

Time (h)	Cumulative % drug release					
	F_1	F_2	F_3	F_4	F_5	F_6
1	4.02	6.12	7.81	7.96	7.76	7.49
2	8.95	12.37	13.95	13.74	14.74	16.23
3	19.71	23.94	26.98	28.99	30.72	32.84
4	30.51	35.84	39.98	42.41	44.56	49.64
5	40.62	45.23	50.56	53.54	56.89	60.56
6	49.02	54.06	60.56	63.26	67.23	71.36
7	58.14	62.12	69.23	72.25	75.56	78.71
8	62.44	67.31	73.43	77.13	79.67	85.03
9	65.23	70.55	75.55	79.56	82.96	90.55

Evaluation of solid lipid nanoparticles gel:

The aceclofenac loaded solid lipid nanoparticles gel was formulated and evaluated by various parameters; the results are summarized in the given in Table 2.

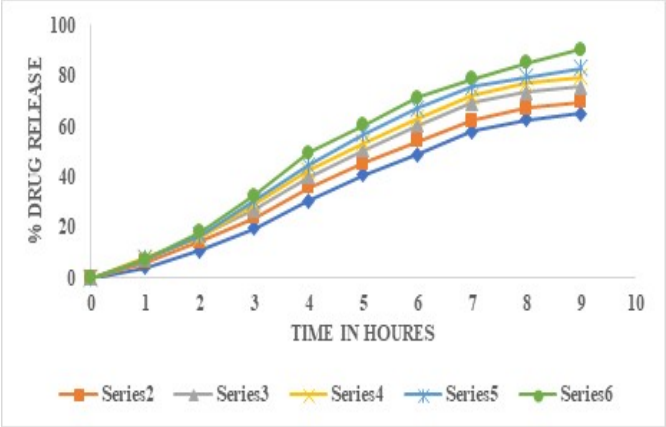

Fig 7. The *in-vitro* drug release study of solid lipid nanoparticles.

Series 1-F1, Series 2-F2, Series 3-F3, Series 4-F5, Series 6-F6

Table 2. Evaluation of solid lipid nanoparticles gel.

Sl. No.	Evaluation Parameters	Results
1	Visual inspection	Transparent, viscous with smoot and good homogeneity
2	pH	5.27
3	Spread ability	11.18 cm^2
4	Viscosity	5530.2±1.16 cp

Data is presented as Mean Standard deviation, n=3.

Percentage of drug content:

The presence in all the formulations was analysed using UV spectroscopy; all solid lipid nanoparticles formulation F-4 shows high drug content 95 % as shown in Fig 8.

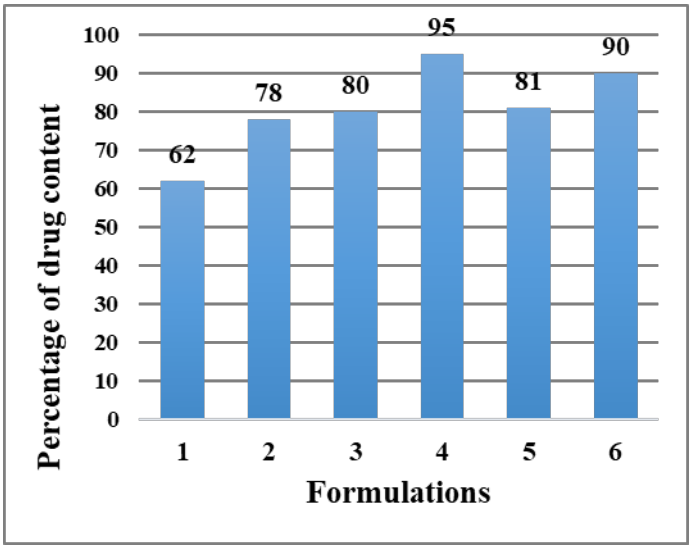

Fig 8. Percentage of drug content of solid lipid nanoparticles.

Stability of gel:

The solid lipid nanoparticles loaded gel of the formulations after one month was observed. The

stability studies of formulation F1, F2, F3, F4, F5 and F6 had been performed. The stability studies observed in physical appearance and compatibility formulations. We stored each formulation at room temperature for 3 months given in Table 3 and Fig 9.

Table 3. Stability study of solid lipid nanoparticles gel.

Sl. No.	Viscosity (Cp)			Drug Release	
	RPM	Before 3 months	After 3 months	Before 3 months	After 3 months
F1	3	58873.3	58872.2	65.23	65.22
F2	5	38673.5	38673.1	70.55	70.53
F3	10	22020.2	22019.2	75.55	75.54
F4	20	7720.3	7720.1	79.56	79.54
F5	30	6605.3	6615.2	82.96	82.94
F6	40	5530.2	5530.1	90.55	90.54

Cp – Centipoise, RMP- Revolutions per minute.

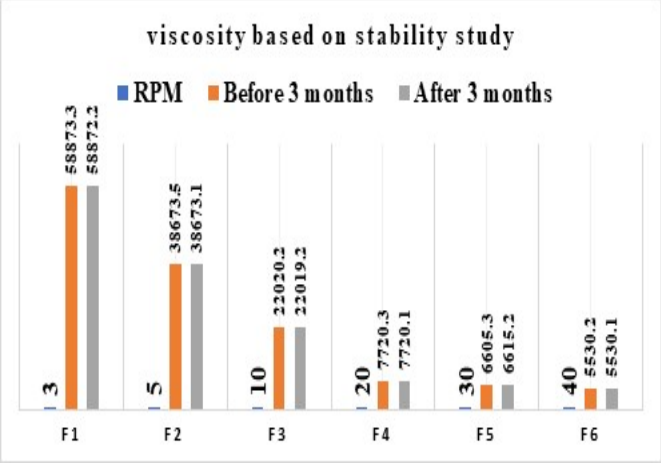

Fig 9. Viscosity based on stability study of solid lipid nanoparticles gel.

CONCLUSION:

The solid lipid nanoparticles were successfully developed for topical delivery of aceclofenac for topical delivery which represents a significant advancement in drug delivery technology. Solid lipid nanoparticle dispersions were prepared using an ultrasonic emulsification method. Physicochemical characterization including particle size, zeta potential, scanning electron microscopy, X-ray diffraction, differential scanning calorimetry and in-vitro drug release profile were carried out. The observed in-vitro drug release pattern of solid lipid nanoparticles gel showed fast and controlled release. Immediate releases as well as sustained release both are of interest for topical application. Immediate release can be useful to improve the penetration of drug & maintain the concentration work as loading dose, while sustained release supplies the drug over a prolonged period of time.

ACKNOWLEDGEMENTS:

The authors would like to thank Dhamtech drugs Pvt.Ltd., Mumbai, India for supplying the purest drug as a gift sample.

REFERENCES:

1. Chakraborty S, Khandai M, Sharma A, Khanam N, Patra CN, Dinda SC, Sen KK. Preparation, *in vitro* and *in vivo* evaluation of algino pectinate bioadhesive microspheres: an investigation of the effects of polymers using multiple comparison analysis. Acta Pharm, 2010; 60(3): 255-266.
2. Dua K, Pabreja K, Ramana MV. Aceclofenac topical dosage forms: *in vitro* and *in vivo* characterization. Acta Pharm, 2010; 60(4): 467-478.
3. Beaulieu AD, Peloso PM, Haraoui B, Bensen W, Thomson G, Wade J. Once-daily, controlled-release tramadol and sustained release diclofenac relieves chronic pain due to osteoarthritis: A randomized controlled trial. Pain Res Manage, 2008; 3(2):103-110.
4. Pareek A, Chandurkar N, Gupta A, Sirsikar A, Dalal B, Jesalpura B. Efficacy and Safety of Aceclofenac-CR and Aceclofenac in the Treatment of Knee Osteoarthritis: A 6-Week, Comparative, Randomized, Multicentric, Double-Blind Study. The J Pain, 2011; 12(5): 546-553.
5. Sharma M, Kanika, K, Neeraj, KR. Aceclofenac co-crystal nanoliposomes for rheumatoid arthritis with better dermatokinetic attributes: a preclinical study. Nanomed, 2017; 12(6): 615-638
6. Dannhardt G, Ulbrich H. *In-vitro* test system for the evaluation of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) inhibitors based on a single HPLC run with UV detection using bovine aortic coronary endothelial cells (BAECs). Inflamm Res, 2001;50(5): 262–269.
7. Urade PK, Bodhankar MM. Solid Lipid Nanoparticle: A Novel Lipid Based System of Coenzyme Q10 for Skin Enrichment. J Pharm Adv Res, 2021; 4(3): 1162-1172.
8. Jenning V, Gysler A, Schafer-Korting M, Gohla SH. Vitamin A loaded solid lipid nanoparticles for topical use: occlusive properties and drug targeting to the upper skin. Eur J Pharm Biopharm, 2000; 49(3): 211-218.

9. Puglia C, Bonina F, Rizza L, Blasi P, Schoubben A, Perrotta R. Lipid nanoparticles as carrier for octyl-methoxycinnamate: in vitro percutaneous absorption and photostability studies. J Pharma Sci, 2012; 101(1): 301-311.
10. Mei Z, Wu Q, Hu S, Li X, Yang X. Triptolide loaded solid lipid nanoparticle hydrogel for topical application. Drug Develop Ind Pharm, 2005; 31: 161-168.
11. Swati N. Solid lipid nanoparticles (SLNs). A Comprehensive review. Int J Pharm Ind Res, 2022; 12 (4): 343-345.
12. Jenning V, Gohla S. Encapsulation of retinoids in solid lipid nanoparticles. J Microencap, 2001; 18(2): 149-158.
13. Jenning V, Gysler A, Schafer-Korting M, Gohla SH. Vitamin A loaded solid lipid nanoparticles for topical use: occlusive properties and drug targeting to the upper skin. Eur J Pharm Biopharm, 2000; 49(3): 211-218.
14. Souto EB, Wissing SA, Barbosa CM, Muller RH. Evaluation of the physical stability of SLN and NLC before and after incorporation into hydrogel formulations. Eur J Pharm Biopharm, 2004; 58(1): 83-90.
15. Jameel Ahmed M, Nitinkumar S, Panchamukhi SI, Khazi Imtiyaz Ahmed M. Formulation, Characterization and *in-vitro* Evaluation of novel Thienopyrimidines and Triazolothienopyrimidines loaded Solid Lipid Nanoparticles. Int J Res Ayurveda Pharm, 2010; 1(2): 192-200.
16. Hu FQ, Yuan H, Zhang HH, Fang M. Preparation of solid lipid nano particles with aceclofenac propionate by a novel solvent diffusion method in aqueous system and physicochemical characterization, Int J Pharm, 2002; 239(1-2): 121-128.
17. Sanad AR, Abdelmalak NS, Elbayoomy TS, Badawi AA. Formulation of a novel oxybenzone-loaded nanostructured lipid carriers (NLCs). AAPS Pharm SciTech, 2010; 11(4): 1684-1694.
18. Teeranachaideekul V, Souto E B, Junyaprasert V B, Muller H. Cetylpalmitate-Based NLC for Topical Delivery of Coenzyme Q10 Development, Physicochemical Characterization and *In Vitro* Release Studies. Eur J Pharma Biopharm, 2007; 67(1): 141-148.
19. Wen MM, Farid RM, Kassem AA. Nano-proniosomes enhancing the transdermal delivery of mefenamic acid. J Liposome Res, 2014; 24(4): 280-289.
20. Uner MK, Ayugmus Z. Solid lipid nanoparticles and nanostructured lipid carriers of loratadine for topical application, physiochemical stability and drug penetration through rat skin. Trop J Pharms Res, 2014; 13(5): 653-660.
21. Wissing SA, Muller RH. Solid lipid nanoparticles as carrier for sunscreens: *in vitro* release and *in vivo* skin penetration. J Control Release, 2002; 81(3): 225-233.
22. Vyas SP, Khar RK. Targeted & Controlled Drug Delivery Novel Carrier System. Int J Pharm, 2018; 6(1-2): 2679-2684.
23. Mei Z, Wu Q, Hu S, Li X, Yang X. Triptolide loaded solid lipid nanoparticle gel for topical application. Drug Develop Ind Pharm, 2005; 31(2):161-168.
24. Kaur LP, Garg R, Gupta GD. Development and evaluation of topical gel of minoxidil from different polymer bases in application of alopecia. Int J Pharmacy Pharm Sci, 2010, 2(3): 7-43.
25. Biswal B, Karna N, Nayak J, Joshi V. Formulation and Evaluation of Microemulsion based topical Hydrogel containing Lornoxicam. J Appl Pharm Sci, 2014; 4(12): 77-84.
26. Shiv hare UD, Jain KB, Mathur VB. Formulation development and evaluation of diclofenac sodium gel using water soluble polyacrylamide polymer. Digest J Nanomater Biostruct, 2009; 4(2): 285- 290.
27. Sera UV, Ramana MV. *In vitro* skin absorption and drug release – a comparison of four commercial hydrophilic gel preparations for topical use. Eur J Pharm Biopharm, 2008; 73(2): 356-360.

Conflict of Interest: None
Source of Funding: Nil
Paper Citation: Dhananjay, Kumar P*. Development and Characterization of Solid Lipid Nanoparticles for Topical Drug Delivery System. J Pharm Adv Res, 2024; 7(4): 2177-2183.