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Formulation and Characterization of Nanosponge Loaded Gel of Apremilast for Topical Delivery

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ABSTRACT:Psoriasis is a common autoimmune long-lasting skin disease which varies in severity form minimum size of red patches seen to all body parts and 2% populaces of world effected with psoriasis principally due to immune dysregulation. Psoriatic arthritis also a chronic skin disorder of autoimmune system in which patches of abnormal skin is seen. Main objective of this research toevaluate the estimated potential of topical systems for drug apremilast as a powerful healing approach for psoriasis and psoriatic arthritis via topical route. Nanosponges manufactured by using several polymers/copolymers and crosslinkers throughemulsion solvent diffusion method. Among all batches of ethyl cellulose polymeric nanosponge F-2 batch of nanosponge shows spherical shape and spongy nature with size of nanosponge were 156.5 nm. F-2 batch of apremilast nanosponge show highest loading efficiency of 86.14%, drug content of 95.62% and drug release of 84.19% at 12 hr as compare to other five batches. Optimized F-2 ethyl cellulose nanosponge loaded gel of apremilast show good spreadability and viscosity about 11041 cps. Drug content of optimized nanosponge loaded gel were found to be 94.08%. Nanosponge loaded gel shows controlled drug release at an extended period of time (81.37% up to 12 h) and shows good permeation through skin. Additionally, Skinirritation studies of developed optimized gel shows no irritant effect and accelerated stability studies shows no significant change in product till 3 months. Formulated ethyl cellulose nanosponge loaded topical gel of apremilast shows greater drug release and it highly effective to treat skin infections than to conventional gel form. Henceforward, all results of it showed the capable applicability as newer delivery system for treatment of psoriasis & psoriatic arthritis.

KEYWORDS: Apremilast, Nanosponges, Emulsion solvent diffusion, Carbopol and Topical gel.

I. INTRODUCTION

Nanotechnology is characterized as a control of matter on an atomic, molecular and supra-atomic scale including plan, generation, characterization and application of various nanoscale materials in several potential areas giving novel innovative basically within different medicine. It is a science, engineering, and mechanical at nanometre scale, which is approximately 1 to 100 nm. Nanotechnology is quickly rising science of manufacturing and applying a Nano-scale particle that found in size of nanometres means it is an art of evaluation and organize matter systemically at Nano in scale. In expansion it's profoundly utilized in specialized series like brain targeting, tumor targeting, and gene targeting. There is various polymer have been considered and studied use for developing newer drug delivery system. [1,2]

Nanosponges are class of materials made up of little sponge like structure with small cavity of few nanometres, with an average diameter less than 1μm.[3]Nanosponges are more like a 3-D structure and sponge may be a long length of polyester which is blended in solution with crosslinkers that act like minor hooking snares to secure distinctive parts of polymer together.[4] This little sponge can circulate around body until they reach particular target location and adhere on surface and started to release medicine in a controlled manner. Since drug can be discharged at particular target location rather than circulating throughout body it will be more successful for a specific given dose. NS have a high control of entrapping wide ranges of excipients and can tie less soluble drug inside its network and enhance their bioavailability. [5]

Psoriasis is a common autoimmune long-lasting skin disease which varies in severity form minimum size of red patches to all body parts covering. Psoriatic arthritis also a chronic skin disorder of autoimmune system in which patches of abnormal skin is seen. Apremilast is novel drug approved by FDA which inhibit phosphodiesterase-

International Journal of Pharmaceutical Research and Applications
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4 enzymes and increases c-AMP level. Effect of inhibition of phosphodiesterase-4 which gives spontaneous inhibition of tumor necrosis factor-alpha (inflammatory cytokines) formation from human rheumatoid synovial cell. Nanosponge of apremilast is improved bioavailability, decrease dosing frequency and increased the stability of drug. Topical apremilast nanosponge loaded gel permeates through skin and helpful to deliver higher therapeutic amount of drug in skin via epidermis. It increases the residence time of drug which improve concentration of drug into skin for a prolonged period of time and that effectively beneficial in treatment of psoriasis and psoriatic arthritis.[8,9]

II. METHODOLOGY

Materials

Apremilast drug was taken from Stermone Chemicals Pvt. Ltd, Paldi, Gujarat. Other polymers were taken from reliable manufacturer i.e., Ethyl cellulose (Research- lab fine chem industries, Mumbai), PVA (Suvidhanath laboratories) and Methanol (Burgoyne Urbidges & Co India, Mumbai).

Manufacturing method of Apremilast nanosponges

Apremilast nanosponge were manufactured by emulsion solvent diffusion method by using appropriate polymer or copolymer. Various two phase were developed one was inner phase and second was outer phase. Inner phase consists of definite amount of drug and polymer which was dissolved in suitable quantity of organic solvent. External phase prepared by contains of definite amount of PVA dissolved in 100 ml of distilled water. Now, inner phase was added drop by drop into external phase by stirring on magnetic stirrer at different rpm speed for approximately 2 hrs. Obtain nanosponges were collected by filtration and dried in oven at 40℃ for nearby 24 hrs. This nanosponges kept in vacuum desiccators to remove the residual solvent. [5]

Solubility study of Apremilast

Apremilast solubility study was checked by taking excess quantity of drug which dissolved in 5-10 ml particular solvents and analysed by using UV-Visible spectrophotometer.

Evaluation of Apremilast loaded nanosponges

Particle size analysis

Particle size can be performed by using Zeta sizer, Malvern Instrument. From result of this study, mean diameter and polydispersity index can be determined.

% Yield

For calculating production yield of nanosponge following formula is used.

$$\% \text{ yield} = \frac{\text{Practical weight of NS}}{\text{Theoratical weight of NS[drug + polymer]}} \times 100$$

% Loading Efficiency

For calculating percentage loading efficiency following formula is used.

$$\% \text{ Loading efficiency} = \frac{\text{Actual Drug content}}{\text{Theoritical Drug content}} \times 100$$

Drug Content

Weight accurate amount of nanosponges and mix it with suitable solvent for 1 hr with continuous stirring. Filter this solution using filter paper and analysed at given wavelength using UV. Estimate drug content of NS by using suitable formula.

Particle Morphology

For surface morphology of nanosponges, scanning electron microscope is used to analyse the sample.

In Vitro Drug Release Study

Drug invitro release from nanosponge was study by using Dialysis Bag diffusion method. Drug release study from nanosponge were checked in Phosphate buffer of pH 7.4 and methanol in ration of 70:30. Approximately 20 mg of apremilast nanosponge were mixed in 10 ml above mixture and added in dialysis bag known as donor compartment which was sealed at both ends. This dialysis bag was deep in receptor compartment containing 100 ml of above buffer mixture and it was stirred at 100 RPM and maintain temperature 37°C ± 0.5°C. Receptor compartment was enclosed with paper to prevent evaporation of medium. At different time intervals samples were taken from receptor compartment and same quantity of medium was added to maintain diffusion medium. Samples are taken up to 12hrs. Apremilast present in medium samples were checked in a UV-Visible spectrophotometer.Above same procedure was taken out for pure apremilast and measured invitro release of drug by using UV-Visible spectrophotometer.

Stability study

Drug and dosage form quality may affect

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under impact of varying temperature, humidity and light with time which can be find out by stability testing. It can be

carriedoutatroomtemperatureforthe selected formulationfor60days.Samplesare withdrawn after 0^{th}, 15^{th}, 30^{th} and 60^{th} days and are analyzed for physical appearance and drugcontent. [5,12,13,14,15,]

Formulation of apremilast loaded nanosponges topical gel

Accurately weighed of gelling agent was taken and liquefied in water for 2 hours soaking with 500 RPM agitation to complete swelling. In this carbopol gel base developed nanosponges were uniformly dispersed and add penetration enhancer into it which may prevent drying of gel. In this gel methyl paraben and propyl paraben were added as a preservative. Triethanolamine was added drop by drop with slow stirring using stirrer for adjusting pH. For comparison study drug loaded plain gel was also developed in same way by using pure drug instead of using nanosponges.[6]

Evaluation of apremilast loaded nanosponges topical gel

Physical evaluation

Organoleptic property and Occlusiveness is checked in this physical characterization.

pH Measurement

1 gram of topical gel was dissolved in 10 ml of distilled water. pH meter was prior standardized with standard buffers and pH had checked by this digital pH meter.

Viscosity Measurement

Viscosity of gel is measured by using brookfield viscometer at room temperature. Sample is tested using a vessel and spindle 5 at different speed in viscometer. Perform this test three times and observed the results and take a mean of viscosity.

Spreadability test

Topical gel under study was placed on ground slide. Topical gel was sandwiched between two slide and second glass slide having similar dimension as that of fixed ground slide. Second glass slide is tied with hook. 100 gm weight was placed on top of two slides for 5 min to eject air and to offer a uniform film of gel among two slides. Measured quantity of weight was placed in pan attached to pulley with the help of hook. Time in seconds is note by two slides to slip off from gel and placed in between slides under direction of certain weight. Smaller time taken for separation of two slides, greater spreadability. It can be checked by using formula**. S = M x L / T**

Homogeneity

Gel consistency is measured by pressing the gel between thumb and index finger. Some quantity of gel is spread on skin of hand to measured grittiness of particles.

Drug content

Minor quantity of gel has dissolved in suitable solvent in volumetric flask with appropriate stirring speed. Finally, when it diluted, filter this solution. If further dilution is needed it was prepared by diluting this gel with 10 ml of suitable solvent and again 1 ml was withdrawn from above solution and diluted again with 10 ml suitable solvent. Drug absorbance of diluted solution had measured at in UV spectroscopy and calculates drug content by using suitable formula.

In vitro drug release study

Franz diffusion cell and simulation cellophane membrane has used for diffusion study of optimized nanosponge loaded gel. Receptor chamber is filled with freshly prepared phosphate buffer and it is stirred by magnetic stirrer. Samples are collected at suitable time interval and which are analyzed for drug content by UV visible spectrophotometer.

Kinetics of Drug Release

To study release kinetics of in-vitro drug release, data was applied to kinetic models such as zero order, first order, Higuchi, Hixon Crowell and Korsmeyer-Pappas. In short, results obtained from in-vitro release studies were plotted in kinetic models.

Ex-vivo permeation study

Ex-vivo permeation study is carried out using modified diffusion cell (with effective diffusion area 3.14 cm2 and 2.3 cm diameter). A small section of rat skin is cutted and mounted on one end of diffusion cell in such a way that dorsal side is upward. Optimized NS loaded gel is applied onto surface of skin evenly. Receptor chamber is filled with freshly prepared phosphate buffer and this chamber is stirred by magnetic stirrer. The samples are collected at suitable time interval. Samples are analyzed for drug content by UV visible spectrophotometer at suitable wavelength maxima.

International Journal of Pharmaceutical Research and Applications
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Primary skin irritancy study

These studies are carried out with the permission of an animal ethical committee (CPCSEA) and all guidelines are followed for handling and care of animal. Skin irritation studies carried out on healthy rats which are distributed in three groups of each contains six rats. Hair of the dorsal slice of all group rats had shaved and wiped using surgical spirit. Accurate amount of topical gel is applied over the site of Group-II, Group-III, whereas Group-I are left as standard as shown in Table. Test sites are checked for Erythema and edema for 24 and 48 hrs.

Accelerated stability study

Stability studies have been carried to point out any physical visual or chemical stability of optimized batch at 25°C ± 2°C/ 60% RH ± 5% RH and 40°C ± 2°C/ 75% RH ± 5% RH as per ICH guidelines for three months. Samples are taken out at various days of 0th, 30th, 60th and 90th day and checked their physical property and drug content. [16,17].

III. RESULTS &DISCUSSIONS

Identification of Apremilast drug

Organoleptic Properties of Apremilast

Physicalappearance was determined visually and Apremilast was found to be white, crystalline, odorless powder.

Melting Point of Apremilast

Melting point of Apremilast was checked by melting point apparatus. Drug apremilast filled in one end close capillary. This capillary and thermometer were tied in melting point apparatus. Temperature range was checked at which apremilast was finally melted. Melting point of drug found to be 150 °C ± 2℃.

Solubility study of Apremilast

solubility study was conducted by tacking excess amount of the drug in small number of respective solvents and it found that drug is insoluble in water but freely soluble in methanol, ethanol, chloroform and acetone.

Analytical method

Determination of Wavelength max of Apremilast

Wavelength of apremilast was found to be 230.33 nm on UV spectrophotometer.

Calibration curve of Apremilast

Standard stock solution was prepared by dissolving drug equivalent to 10 mg dissolved in methanol and volume was made up to 10 ml with same solvent in a volumetric flask. From stock solution, 1, 2, 3, 4, 5 and 6 ml were pipette out and volume was made up to 10 ml withmethanol to produce concentration of 10, 20, 30, 40, 50 and 60 µg/ml respectively. Solution was scanned in UV regions to 230.33nm then absorption was measured at maximum Λmax. Calibration curve was plotted by using absorbance and concentrations. [7]

Identification of drug by FTIR spectroscopy and DSC

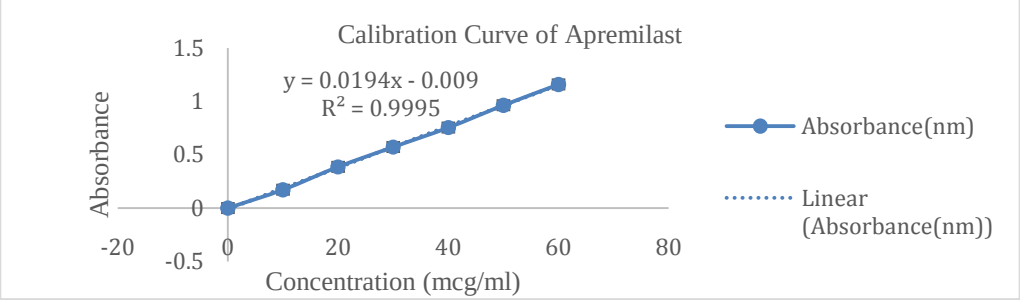

Figure 1: calibration curve of Apremilast

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 47-55 www.ijprajournal.com ISSN: 2249-7781

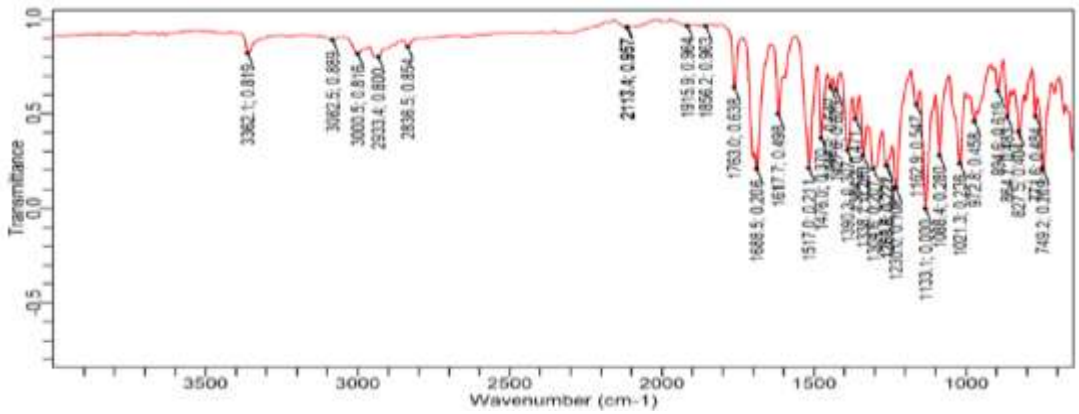

Figure 2: FTIR of Apremilast drug

Table 1: Identification IR Peak of Apremilast

Type of vibration	Standard wave Number (cm^{-1})	Observed wave Number (cm^{-1})
-OH Stretching	3500 - 3200	3362
-C–F Stretching	1400 - 1000	1230
-C=O Stretching	1760 - 1690	1688
-C–Cl	800 - 600	749

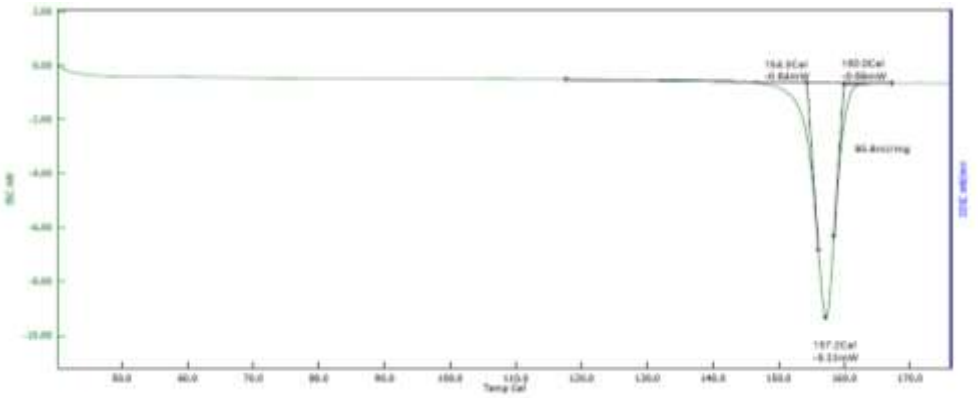

Figure 3: DSC graph of Apremilast drug

DSC curve of apremilast in figure displays a wide-ranging peak from 154.3°C to 160°C and sharp peak at 157.2°C might be due to melting point of apremilast. DSC graph complies with standard data which further authorize identity and purity of drug.

Table 2: Formulation of Apremilast Nanosponges

Ingredients	F1	F2	F3	F4	F5	F6
APR: Ethyl cellulose	1:1	**1:2**	1:3	-	-	-
APR: PMMA	-	-	-	1:1	1:2	1:3
Dichloromethane (ml)	20	**20**	20	20	20	20
Poly vinyl alcohol (mg)	200	**200**	200	200	200	200

International Journal of Pharmaceutical Research and Applications
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Stirring Speed (RPM)	1500	**1500**	1500	1500	1500	1500
Stirring Time (Mins)	90	**90**	90	90	90	90
Distilled Water (ml)	100	**100**	100	100	100	100

Table 3: Evaluation of Apremilast Nanosponges

Parameters Mean± S.D. (n=3)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Yield (%)	77.23±1.2	**79.24±1.02**	78.10±1.6	72.08±1.5	73.08±1.1	74.22±1.2
Loading efficiency (%)	84.04±1.1	**86.14±1.6**	85.24±1.2	80.08±1.6	81.92±1.7	82.05±1.5
Drug content (%)	93.05±0.1	**95.62±0.1**	94.08±0.2	90.30±0.1	91.45±0.2	92.05±0.9
Particle size (nm)	162±2	**156±2**	168±2	910±5	930±4	955±2
CDR (%)	83.06±1.1	**84.19±1.2**	82.74±1.0	81.3±1.1	82.1±1.5	82.6±1.6

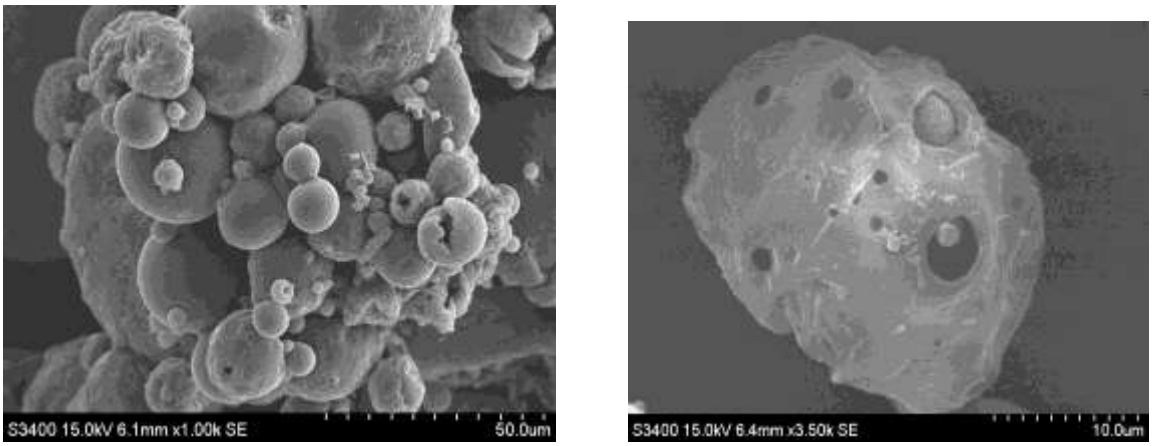


Figure 4: SEM study of Optimized batch F-2

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 47-55 www.ijprajournal.com ISSN: 2249-7781

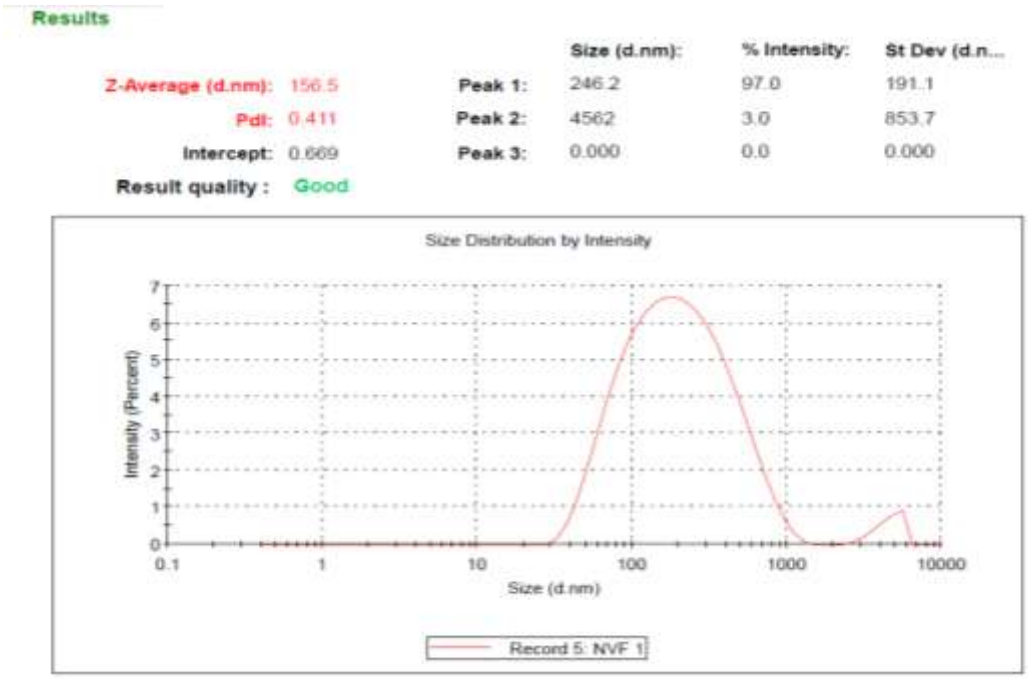


Figure 5: Particle size study of Optimized batch F-2

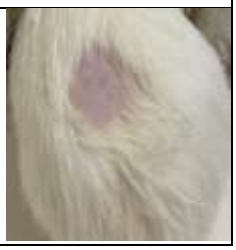
Table 4: Development of Apremilast Nanosponges Loaded Gel

Ingredients	**F1**	**F2**	**F3**
Apremilast NS (mg)	100	**100**	100
Carbopol 934 (gm)	0.5	**1**	1.5
Propylene glycol (ml)	10	**10**	10
Triethanolamine (ml)	2	**2**	2
Methyl paraben (mg)	0.1	**0.1**	0.1
Propyl paraben (mg)	0.05	**0.05**	0.05
Distilled Water (ml)	up to 20	**up to 20**	up to 20

Table 5: Evaluation of Apremilast Nanosponges Loaded Gel

Parameters Mean± S.D. (n=3)	**F1**	**F2**	**F3**
Clarity	Clear	**Clear**	Clear
Odour	Odour-free	**Odour-free**	Odour-free
pH	6.90±0.03	**6.71±0.04**	6.92±0.03
Spreadability (gm*cm/sec)	10.39±0.03	**11.68±0.06**	10.70±0.05
Viscosity (cps)	9960±10	**11041±15**	9996±12
Drug content (%)	90.44±1.20	**94.08±1.04**	91.30±1.12
In vitro Diffusion (%)	91.87±1.20	**81.37±1.05**	90.64±1.16

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 47-55 www.ijprajournal.com ISSN: 2249-7781

Ex-vivo permeation (%)	90.61±1.14	**78.68±1.18**	90.45±1.10
Skin Irritation Study	No Irritation	**No Irritation**	No Irritation
			

IV. CONCLUSION

Main purpose of this research work to developed innovative polymeric nanosponge formulation of apremilast for topical delivery. NS were developed by using polymers like Ethyl cellulose via emulsion solvent diffusion method. Nanosponge form at 1:2 ratio of drug polymer, 20 ml dichloromethane, 200 mg PVA and 1500 rpm for 90 min shows highest yield and loading efficiency and drug content. Optimized batch of nanosponges were taken for developing apremilast nanosponge loaded gel for topical delivery. Carbopol gel base was taken for preparation of final nanosponge loaded gel. Apremilast nanosponge loaded gel prepared by carbopol shows better spreadability and viscosity as well as drug release from this gel was extent period of time greater than 12 hrs. Irritation study of skin of all batches shows there were no irritancy on skin after spread gel on to skin.So, it concludes that apremilast ethyl cellulose nanosponges based novel topical gel was very effective in psoriasis and psoriatic arthritis.

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