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FORMULATION AND CHARACTERIZATION OF NANOSPONGE LOADED GEL OF MOMETASONE FUROATE FOR TOPICAL DELIVERY

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ABSTRACT

This research study was aimed to developed nanosponges loaded topical gel of mometasone furoate with purpose of to reduce particle size, increase permeation of drug, decrease systemic side effects, reduce dose frequency and enhance diffusion performance than conventional form. Organoleptic properties, Melting point, FTIR and DSC was carried out for identification of drug & to check interaction between drug & polymers. Preformulation study of drug showed that drug was pure and further take for formulation development. Nanosponges were prepared by Emulsion solvent diffusion method. From the evaluation of all batches of nanosponges which shows good % yield, drug content and loading efficiency. Among all the results F-3 batch shows a highest % yield, drug content and loading efficiency compare to other five batches. So, it was taken further for preparation of nanosponge loaded gel. Optimized F-3 nanosponge loaded topical gel of momentane furoate was prepared by using carbopol and it show 94.02% drug content and 83.84% drug release at 12 hrs. Formulated gel shows an excellent spreadability, viscosity, and ex-vivo drug release 81.09 % at 12 hrs. No skin irritation was seen in rat skin and no other changes in product was seen during stability study. So, Mometasone furoate nanosponge loaded gel may be decent choice for control release of drug for prolonged period of time at targeted site with avoiding systemic side effects.

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

INTRODUCTION

Nanotechnology has been investigated for different biomedical applications for over a decade. In general, use of nano-sized particles offers numerous advantages over other delivery systems. They are used to enhance solubility of hydrophobic drugs, provide sustained and controlled release of encapsulated drugs, improve stability of therapeutic agents by chemical or physical means, it delivers higher concentrations of drugs to target areas due to an enhanced permeation and retention effect. Drug-loaded in any nanotechnology often accumulate in hair follicles and thereby facilitate penetration of drug molecules through superficial layers of SC, followed by drug release into the deeper layers of skin. Nanosponges are small size of nanoporous particles with an average size of less than to 1µm. These nanoporous particles are rotate everywhere in body until bind to target site, stick-on surface of site and start to release active drug in prolonged and predictable manner.[1,2]

Mometasone Furoate is distinctive power of topical corticosteroid that reduces production, release, and action of endogenic mediators of irritation, containing prostaglandins, kinins, histamine and liposomal enzymes which changes body immune response. Mometasone furoate is a 17-ester of 16α-methyl analogue of beclomethasone shows better potency with higher anti-inflammatory effect to a longer duration of action. Mometasone furoate is a BCS class-II drug which has a low solubility so convert this drug into nanosponge will enhance solubility. This investigate work develops topical gel of mometasone furoate which are safer and it transfer active agent locally in an actual concentration for its action.[3] Dermatitis (eczema) is more common in people who have a family history of the condition. Red, dry and itchy rashes usually seen where skin are flexes. Different treatments like steroid creams, immunosuppressive drugs and Vit. D creams can be beneficial to control symptoms of dermatitis and psoriasis. But all among of that topical corticosteroid's formulation is most preferable for treatment of dermatitis and psoriasis. Nanosponge of mometasone furoate is improved efficacy & stability of drug. Mometasone furoate nanospongic gel permeates a drug into stratum corneum and rise therapeutic concentration of drug into skin without going in systemic circulation so it avoids further systemic effect.[4,5]

METHODOLOGY

Materials

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

Method of preparation of Mometasone nanosponges

Mometasone furoate 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 Dichloromethane. 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. Nanosponges kept in vacuum desiccators to remove residual solvent.[6]

Solubility study of mometasone furoate

Mometasone furoate 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.

Characterization of mometasone furoate loaded nanosponges

Particle size analysis

Particle size of nanosponge is an important parameter in optimization. Particle size can be performed by using Zeta sizer, Malvern Instrument. From result of this study, mean diameter and PDI can be determined.

Percentage yield

For calculating production yield of nanosponge following formula is used.

$$\%\ yield = \frac{Practical\ wt\ of\ NS}{Theoratical\ wt\ of\ NS} \times 100$$

Loading efficiency

For calculating percentage loading efficiency following formula is used.

$$LE = \frac{Actual\ Drug\ content}{Theoritical\ Drug\ content} \times 100$$

Drug content

Weight accurate amount of nanosponges and mix it with suitable solvent for 1 hr with continuous stirring. Filter this solution using Whatman paper and further analysed at given wavelength next to blank using UV spectrophotometer. Estimate content of nanosponge by using suitable formula.

Particle morphology

For surface morphology of nanosponges, scanning electron microscope is used to analyse 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 mometasone furoate nanosponge were mixed in 10ml 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 900 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. Mometasone present in the medium samples were checked in a UV-Visible spectrophotometer. Above same procedure was taken out for pure mometasone furoate and measured *invitro* release of drug by using UV-Visible spectrophotometer.

Stability study

Drug and dosage form quality may affect under impact of varying temperature, humidity and light with time which can be find out by stability testing. It can be carried out at room temperature for the selected formulation for 60 days. Samples are withdrawn after 0^{th}, 15^{th}, 30^{th} and 60^{th} days and are analyzed for physical appearance and drug content.[5]

Development of mometasone furoate 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.[7]

Characterization of mometasone furoate 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. This 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 the spreadability. It can be calculated by using formula.
$S = M \times L / T$

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. The receptor chamber is filled with freshly prepared phosphate buffer and it is stirred by magnetic stirrer. The samples are collected at suitable time interval and which are analyzed for drug content by UV visible spectrophotometer at suitable wavelength maxima.

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 four kinetic models of data treatment.

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 nanosponge 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 spectrophotometer at suitable wavelength maxima.

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. Test sites are checked for Erythema and edema for 24 hrs 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 3 months. Samples are taken out at various days 0th, 30th, 60th and 90th and checked their physical property and drug content.[13,14]

RESULTS AND DISCUSSIONS

Identification of drug
Organoleptic properties of drug
Mometasone furoate was seen in white colour with odourless characteristic having a white crystalline powder in appearance.

Determination of melting point
Melting point of mometasone furoate was checked by melting point apparatus. Drug mometasone furoate filled in one end close capillary. This capillary and thermometer were tied in melting point apparatus. Temperature range was checked at which mometasone was finally melted. Melting point of drug found to be 225 °C ± 1℃.

Solubility study of drug
Drug is insoluble in water but freely soluble in methanol, chloroform and acetone.

Analytical method
Determination of wavelength max of drug
Wavelength of Mometasone furoate was found to be 247.39 nm on UV.

Calibration curve of drug
Standard stock solution was prepared by dissolving drug equivalent to 10 mg of drug dissolved in methanol and volumetric was made up to 100 ml with same solvent in a volumetric flask. From stock solution, 1, 2, 3, 4, 5, 6, and 7 ml were pipette out and volume was made up to

100 ml with. methanol to produce concentration of 1, 2, 3, 4, 5, 6 and 7 µg/ml respectively. Solution was scanned in UV regions to 248 nm then absorption was measured at maximum Λmax. Calibration curve was plotted by using absorbance and concentrations.[6]

Identification of drug by FTIR spectroscopy and DSC

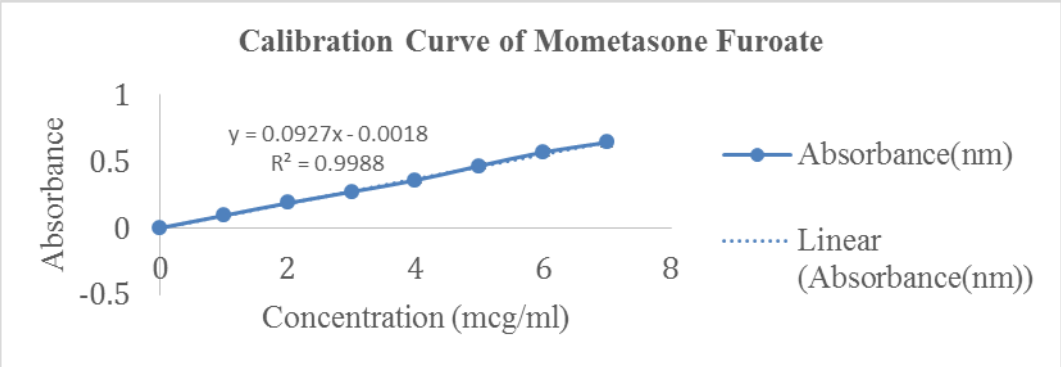


Figure 1: Calibration curve of Mometasone Furoate.

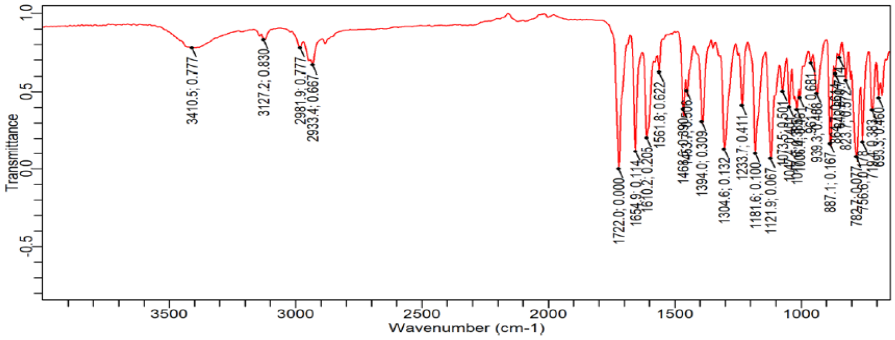


Figure 2: FTIR graph of Mometasone furoate drug.

Table 1: Identification IR Peak of Mometasone Furoate.

Type of vibration	Standard wave Number (cm^{-1})	Observed wave Number (cm^{-1})
-OH Stretching	3500 - 3200	3410
-C–F Stretching	1400 - 1000	1394
-C=O Stretching	1760 - 1690	1654
-C–Cl	800 - 600	756

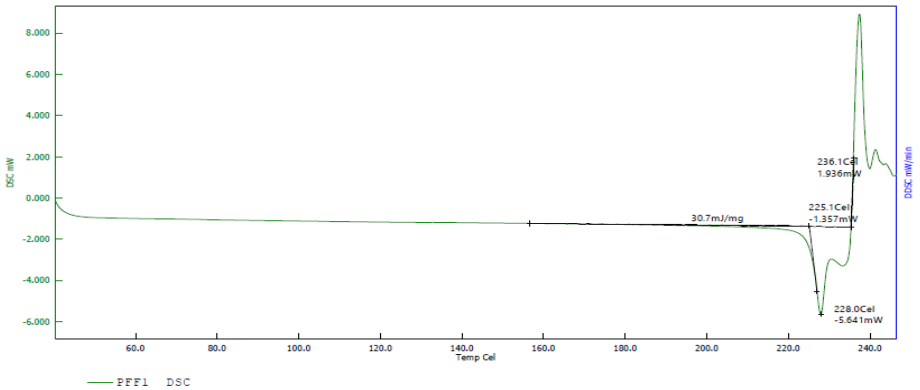


Figure 3: DSC curve of Mometasone furoate.

DSC curve of mometasone furoate in figure displays a wide-ranging peak from 223°C to 236.1°C and sharp peak at 225.1 °C might be due to melting point of mometasone furoate. Found DSC graph complies with standard data which further authorize identity and purity of drug.

Table 2: Formulation of Mometasone Furoate Nanosponges.

Ingredients	F1	F2	F3	F4	F5	F6
MF: Ethyl cellulose	1:1	1:2	**1:3**	-	-	-
MF: 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
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 Mometasone Furoate Nanosponges.

Parameters Mean± S.D. (n=3)	F1	F2	F3	F4	F5	F6
Yield (%)	78.43±1.2	79.42±1.25	**81.19±1.6**	72.28±1.5	74.06±1.1	75.82±1.2
Loading efficiency (%)	85.14±1.1	89.56±1.5	**91.14±1.2**	83.28±1.6	86.22±1.7	87.45±1.6
Drug content (%)	91.25±0.1	93.24±0.1	**96.84±0.2**	90.12±0.1	90.45±0.2	92.20±0.9
Particle size (nm)	139±2	131±3	**128±2**	912±5	931±4	965±0.02
CDR (%)	84.06±1.2	87.73±1.1	**90.14±1.3**	82.3±1.1	86.5±1.5	88.2±1.6

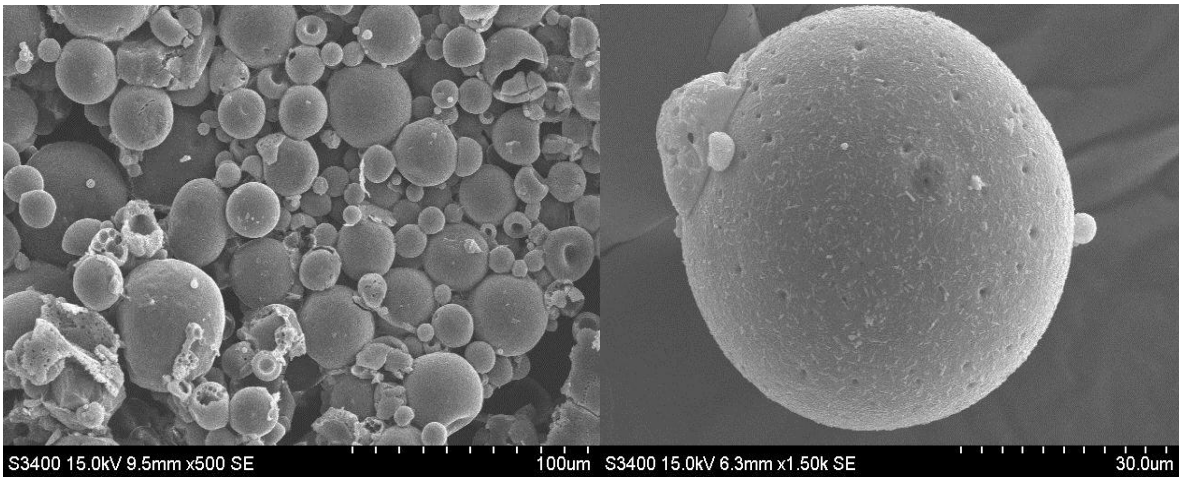


Figure 4: SEM study of Optimized batch F-3.

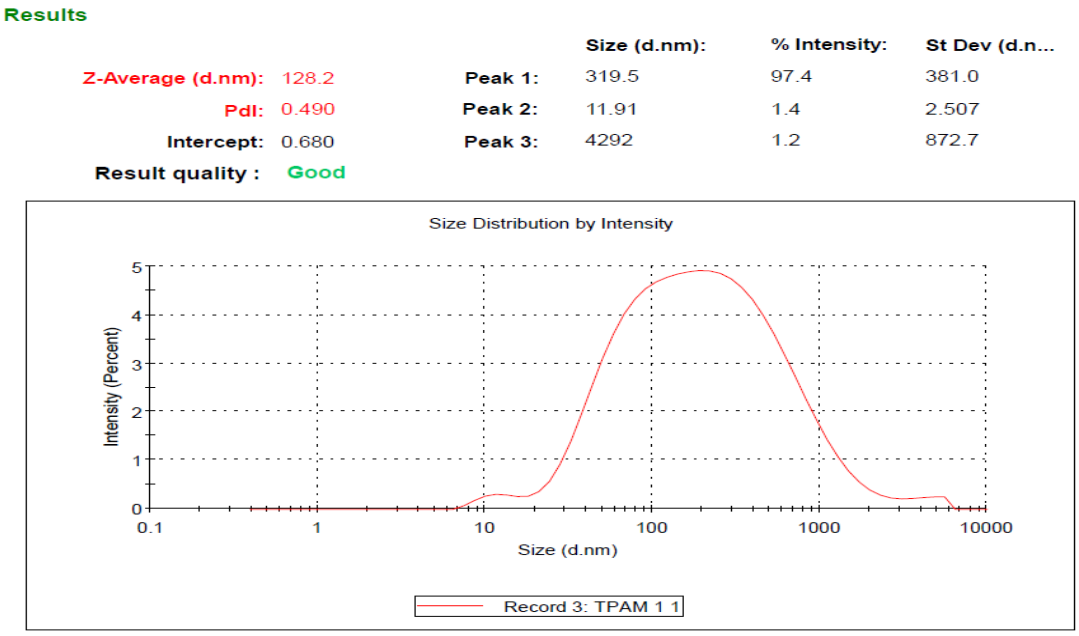
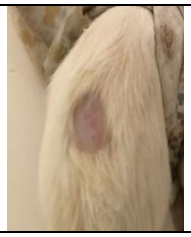


Figure 5: Particle size study of Optimized batch F-3.

Table 4: Formulation of Mometasone Furoate Nanosponges Loaded Gel.

Ingredients	**F1**	**F2**	**F3**
Mometasone furoate NS (mg)	20	**20**	20
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 Mometasone Furoate Nanosponges Loaded Gel.

Parameters Mean± S.D. (n=3)	**F1**	**F2**	**F3**
Clarity	Clear	**Clear**	Clear
Odour	Odour-free	**Odour-free**	Odour-free
pH	6.94±0.03	**6.70±0.04**	6.90±0.03
Spreadability (gm*cm/sec)	10.42±0.38	**11.20±0.08**	10.80±0.08
Viscosity (cps)	9960±12	**10020±15**	99850±10
Drug content (%)	90.56±1.20	**94.02±1.06**	91.32±1.12
In vitro Diffusion (%)	92.64±1.23	**83.84±1.06**	92.64±1.23
Ex-vivo permeation (%)	91.12±1.16	**81.09±1.16**	90.07±1.16
Skin Irritation Study	No Irritation	**No Irritation**	No Irritation
			

CONCLUSION

Main intent of present research work to developed novel polymeric nanosponge loaded gel of mometasone furoate for topical application. Nanosponges were developed by using polymers like Ethyl cellulose via emulsion solvent diffusion method. Nanosponge form at 1:3 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. Carbopol gel base was taken for preparation of final nanosponge loaded gel. Mometasone nanosponge loaded gel shows better spreadability and viscosity as well as drug release from extent period of time greater than 12 hrs. There was no irritancy found on skin after spread gel on to skin. So, last it conclude that polymeric nanosponges of mometasone furoate topical gel are very effective in dermatitis (eczema) and psoriasis.

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