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Nanoparticles Containing Gel Formulation for the Treatment of Psoriasis

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ABSTRACT

Background: Psoriasis is a widespread chronic disease affecting 1-3% of total population and in most cases, treated by topical application of corticosteroids. Though, the topical route is very demanding because of the physicochemical nature of diseased stratum corneum and so no, single treatment works for every patient. The oral route is evidence for harsh side effects because of systemic immunosuppression which can be avoided by topical route. **Objectives:** The objective of the present study is to design, develop, and evaluate nanoparticulate gel containing Cyclosporine A for the treatment of psoriasis. **Methods:** Cyclosporine loaded nanoparticles were formulated by the modified nanoprecipitation technique and characterized for particle size, encapsulation efficiency, morphological analysis, drug-polymer compatibility study, powder x-ray diffraction analysis. Optimized formulation of Cyclosporine nanoparticles further converted into the gel using Carbopol 934. **Results:** Cyclosporine loaded nanoparticles showed a spherical shape with smooth surface. *In vitro* antiproliferative activity proved that cell viability was not affected with blank nanoparticles, as there was no effect of concentration and types of surfactant on cell viability causing no cell death. The gel formulation hydrates the skin which helps in the higher permeation of Cyclosporine loaded nanoparticulate gel. **Conclusion:** *In vitro* anti-psoriatic study suggested that the developed Cyclosporine nanoparticulate gel formulation exhibits improved dermal delivery of Cyclosporine and also nanoparticles had a superior effect on cell growth as compared to the free Cyclosporine. Dermal pharmacokinetic study established that the amount of Cyclosporine reaching the viable layer is slightly high for nanoparticulate gel as compared to free Cyclosporine. Thus, Cyclosporine loaded nanoparticulate gel formulation might be the potential delivery system for the treatment of psoriasis.

Key words: Cyclosporine A, Dermal pharmacokinetic study, *In vitro* anti-psoriatic study, Nanoprecipitation technique, Topical gel.

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INTRODUCTION

Psoriasis is a prevailing, chronic inflammatory most common skin disorder affecting just about 0.5%-1% of children as well as 2%-3% of the world's population.[1] It is a bi-modally distributed skin disorder with one main age of onset at 20-30 years in addition to a later on lesser peak of onset at 50-60 years of age.[2,3] This is a T-cell mediated autoimmune disorder that leads to keratinocyte hyper proliferation.[4] Psoriasis confers significant physical and psychological distress and impairment usually resulting in a detrimental impact on patient quality of life.[5,6] The exact cause of the origin of the disease is unknown, but it is considered as a multifactorial disorder associated with an overexpression of proinflammatory chemokines and cytokines produced by Th1 cells.[7,8]

Cyclosporine A (CsA) is a potent immunosuppressive agent and used for the treatment of moderate to severe psoriasis.[9] CsA is a polypeptide calcineurin inhibitor that acts by inhibiting calcineurin, as a result of inhibition it decreases the production of Interleukin-2, which is helpful in the activation of T-cell.[10] The key side effects of CsA after systemic administration for the treatment of psoriasis are hypertension, cancer, and nephrotoxicity with reduced renal transplant function[11,12] which may be reduced by topical administration of CsA. Furthermore, the most frequent type is mild psoriasis, which mainly requires the topical treatment. In spite of several advantages offered by topical route, only a few molecules are administered topically because of the formidable barrier nature of the stratum corneum. A major problem for topical use of CsA is insufficient percutaneous penetration, hydrophobicity, limited passive diffusion, and high molecular weight (1203 Da).[13,14] Moreover, physiological factors must be considered, for example, psoriatic lesions may thicken the stratum corneum and epidermis. However, new strategies to improve topical administration of CsA developed such as amphiphilic gels,[15] microemulsions,[16] amorphous nanoparticles,[17] polymeric nanoparticles,[18] and lipid nanoparticles.[9,19,20]

Polymeric nanoparticles have been extensively utilized as carrier systems to increase the percutaneous absorption of therapeutic agents for transdermal delivery. A number of natural and synthetic polymers have been used as carriers for transdermal delivery.[18] Eudragit L100 a stimuli-responsive polymer has been used as a carrier in the present study because the pH-dependent dissolution behavior of Eudragit L100 is thought to be very useful in the topical routes because the pH of the skin is 5.5 while that of the systemic circulation is 7.4.[21] And anionic acrylic acid-derived polymer Carbopol 934 was selected as a gelling agent due to its excellent gelling properties and rheological behavior. Carbopol 934 has the advantage of greater viscosity at a lower concentration, better thermal stability, and good adhering property.[22]

In the present work, an attempt was made to develop CsA loaded polymeric nanoparticles for topical application. Developed CsA loaded nanoparticles were incorporated into Carbopol 934 based gel which can be used as the final formulation for topical application to increase the permeation and to facilitate the adherence and retention properties of the nanoparticles on the surface of the skin. This delivery system is expected to have better patient compliance, and we have reported the enhancement in the topical delivery of CsA as well.

MATERIALS AND METHODS

The selected drug CsA was obtained as a gift sample from Accufine Pharma Pvt. Ltd. (Gujarat, India), Eudragit L100 and Carbopol 934 was purchased from Research Lab Chemical Centre, (Mumbai, India), polyvinyl alcohol, methanol, and acetone belong to Molychem, (Mumbai, India). All other materials or chemicals used were of analytical grade.

Preparation of Cyclosporine A loaded nanoparticles

CsA loaded nanoparticles were prepared through a modified nanoprecipitation method using the different polymer concentrations as shown in Table 1.[23] Eudragit L100 and CsA were dissolved in methanol. The mixture formed was added drop-wise into the aqueous solution of polyvinyl alcohol (PVA) as a surfactant and was magnetically stirred at 500 rpm for 180 min for complete removal of organic solvent. The hardened CsA nanoparticles were recovered by centrifugation at 15000 rpm, washed repeatedly with deionized water, collected, and dried at 40°C for 1 h.

Physicochemical characterization of nanoparticles

Particle size and zeta potential study

A dynamic light scattering particle size analyzer (Zetasizer Nano S90 Malvern, UK) was used for the measurement of a mean size, zeta potential, and PDI of the prepared nanoparticles.[24]

Encapsulation efficiency and drug loading

The encapsulation efficiency (% EE) and drug loading of prepared CsA loaded nanoparticles were determined by dissolving a known quantity of nanoparticles in 10 mL of methanol under sonication for 1 hr. The samples were then filtered through a membrane filter and analyzed at 215 nm using high-performance liquid chromatography (HPLC) (Shimadzu $LC_{10}AD$). The % EE and the loading of CsA into nanoparticles were determined according to the following equations:

$$\% \text{ EE} = \left[\frac{\text{Actual drug content in nanoparticles}}{\text{Total drug used in formulation}}\right] \text{X } 100$$

Table 1: Formulation design for preparation of nanoparticles.

Formulation code	[a]CsA (mg)	[b]Eudragit L (mg)	[c]PVA (%)
A1	100	100	0.5
A2	100	200	0.5
A3	100	300	0.5
A4	100	400	0.5
A5	100	500	0.5
A6	100	100	1.0
A7	100	200	1.0
A8	100	300	1.0
A9	100	400	1.0
A10	100	500	1.0
A11	100	100	1.5
A12	100	200	1.5
A13	100	300	1.5
A14	100	400	1.5
A15	100	500	1.5

[a] Cyclosporine; [b] Eudragit L100; [c] Polyvinyl alcohol

$$\% \text{ Drug Loading} = \left[\frac{(\text{Total amount of drug} - \text{Unincorporated drug amount})}{\text{Amount of nanoparticles recovered}}\right] \text{X } 100$$

Morphological analysis

The surface morphological observations of CsA loaded nanoparticles were examined via a high-resolution scanning electron microscopy (Model JSM 5610 LV SEM, Japan).

Fourier-transform infrared spectroscopy and differential scanning calorimeter analysis

The Fourier-transform infrared spectroscopy (FTIR) spectra of pure CsA and CsA loaded nanoparticles were obtained by a computerized FTIR spectroscopy (Shimadzu 8400s FTIR spectrometer, Japan) operating in the scanning wave number range of 4000 and 700 cm^{-1}.

Differential scanning calorimeter analysis

The Differential scanning calorimeter (DSC) thermograms of CsA and CsA loaded Eudragit L100 nanoparticles were recorded by a DSC 60A (Shimadzu, Japan). Samples (10 mg) were sealed into hard-pressed plus perforated crucibles of aluminium and heated from 25°C to 300°C at a heating rate of 10°C/min.

Powder X-ray diffraction analysis

Powder X-ray diffraction analysis (PXRD) of pure CsA and an optimized batch of CsA loaded nanoparticles were analyzed by Philips PW 1729 X-ray diffractometer. Samples were irradiated with monochromatized Cu Kα-radiations (operating at 40 kV, 20 mA) and analyzed at a scanning rate of 4°C over a 2θ range of 5-40°.

Preparation of Cyclosporine A loaded nanoparticles incorporated gels

For the preparation of CsA nanoparticles containing gel, the required quantity of Carbopol 934 was taken in enough quantity of water for 24 h. After that 0.5 mL of methylparaben (0.5%w/v) added to the hydrated gel and stirred for about 4 h. The gel was neutralized by the addition of triethanolamine drop by drop until a clear transparent gel formed. Then CsA loaded nanoparticles (A9) were incorporated in to gel with mechanical mixing.[25]

Characterization of Cyclosporine A loaded nanoparticulate gel

The pH and viscosity of CsA loaded nanoparticulate gel were measured at a ambient temperature by digital pH meter (Thermo scientific) and Brooke field digital viscometer (DV-II + Pro) respectively. For the measurement of drug content, 100 mg of the CsA nanoparticulate gel was transferred to a 50 ml volumetric flask and was diluted with ethanol. 5 ml of this solution was further diluted to 25 ml with ethanol and resulting samples were analyzed by HPLC at a wavelength of 215 nm for CsA content.

The spreadability was evaluated by the already reported method.[26] Briefly, 500 mg of CsA nanoparticulate gel was placed within a circle of 1 cm diameter pre-marked on the acrylic plate at the center and another plate was concentrically positioned above it. The diameter of the circle in which the CsA nanoparticulate gel was spread was considered as the initial diameter. A weight of 500 g was then placed on the upper plate for 5 min and an increase in diameter as a function of applied weight was measured as spreadability of gel.

In vitro release study

The *in vitro* release studies of CsA from free drug dispersion, the nanoparticles, and nanoparticulate gel were carried out by dialysis Cassettes (10000 MWCO, Thermo Scientific). A dialysis Cassette

previously soaked overnight in the diffusion medium and a defined amount of CsA loaded nanoparticles and CsA loaded nanoparticulate gel was accurately inserted using a syringe into dialysis Cassettes. The dialysis Cassettes was suspended in a beaker containing 100 mL of phosphate buffer pH 7.4 at 37± 0.5°C. This assembly was kept on a magnetic stirrer at 50 rpm. Aliquots of 3 mL of samples were withdrawn at predetermined time intervals up to 12 hrs and were refilled with a fresh quantity of dissolution medium to maintain sink conditions. The concentration of CsA in the samples was analyzed by HPLC at a wavelength of 215 nm for CsA content.

In vitro antiproliferative activity

The potency of CsA nanoparticulate gel was performed using human hyperproliferative keratinocyte cell line (HaCaT). The inhibition of keratinocyte proliferation against homeostatic control of keratinocyte growth and differentiation was measured by *in vitro* 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay.[27] Briefly, the HaCaT cells were cultured in Dulbecco's modified Eagle's medium supplemented with 10 % fetal bovine serum at 37°C. The cells were treated with free CsA, blank nanoparticles, and nanoparticles loaded with CsA and incubated for 24 h. After incubation, Coenzyme Q10 was added to wells. Before the MTT test, each well was washed with phosphate-buffer saline (PBS), and 0.5% MTT 40 was added and then was incubated for 3 hr. Finally, Dimethyl sulfoxide was added to dissolve purple formazan and absorption was determined by the absorption in an enzyme-linked immunosorbent assay plate reader at 490 nm and a reference wavelength at 630 nm. The results were expressed concerning % growth inhibition.

Dermal pharmacokinetic studies by using tape stripping technique

The *in vitro* skin penetration study was performed by tape stripping technique.[28-30] The skin samples were unclipped from the Franz diffusion cell after 24 h and the exposed stratum corneum surface of the skin was washed thrice with PBS and was left for air drying. The 19 mm Scotch cellophane tape (3M, USA) was utilized for this technique. The initial stripped tape was discarded as it contains superficially adhered drugs. To remove the stratum corneum layer, 15 strips were detached in a manner that the entire area of the tape was utilized. The tape samples were digested with a mixture of ethyl acetate and tetrahydrofuran (50:50). The tape, as well as skin samples, was soaked in methanol overnight to allow the extraction of the drug from stratum corneum and deeper layers respectively and further kept in the bath sonicator for 1 hr for the complete drug extraction. Then the extracted samples were analyzed by the HPLC method. The quantity present in the receptor compartment was the index of transdermal delivery (systemic absorption), whereas in the tape and skin extract was the index of topical drug delivery.

RESULTS

Physicochemical characterization of nanoparticles

Particle size and zeta potential study

The average particle size and zeta potential values of CsA loaded nanoparticles were presented in Table 2.

Encapsulation efficiency and drug loading

The finding showed that the entrapment efficiency as well as drug loading was higher at 400 mg of polymer with a 1% concentration of surfactants. Formulation A9 had the highest entrapment efficiency and the maximum percentage of drug loading presented in Table 3.

Morphological analysis

The surface morphological study of CsA loaded nanoparticles were done with scanning electron microscopy (Model JSM 5610 LV SEM, Japan). The Scanning electron microscopy of CsA loaded nanoparticles showed relatively smooth surface nanoparticles distributed uniformly and have spherical shapes.

Fourier-transform infrared spectroscopy

The FTIR study was carried out to check the compatibility between CsA and polymer. The comparative FTIR peaks of pure CsA and CsA loaded nanoparticles represented in Figure 1.

Table 2: Mean particle size and zeta potential of nanoparticles.

Formulation code	Particle size (nm)	Zeta potential (mV)
A1	144 ± 4.22	0.69 ± 0.56
A2	132 ± 0.96	0.71 ± 0.74
A3	126 ± 2.84	0.73 ± 0.46
A4	114 ± 2.01	0.69 ± 0.72
A5	106 ± 2.08	0.70 ± 0.11
A6	87 ± 1.32	0.72 ± 0.12
A7	71 ± 1.56	0.70 ± 0.46
A8	66 ± 1.28	0.65 ± 0.27
A9	58 ± 0.22	0.59 ± 0.13
A10	63 ± 1.42	0.62 ± 0.22
A11	96 ± 1.32	0.68 ± 0.24
A12	105 ± 0.42	0.77 ± 0.21
A13	126 ± 2.32	0.91 ± 0.11
A14	142 ± 2.14	0.94 ± 0.12
A15	146 ± 3.28	0.96 ± 0.32

Data are represented as Mean ± SD (n=3)

Table 3: Entrapment efficiency and drug loading of nanoparticles.

Formulation code	Entrapment efficiency (%)	Drug loading (%)
A1	35.19 ± 1.3	48.02 ± 0.04
A2	36.24 ± 1.6	60.22 ± 1.11
A3	37.12 ± 1.4	67.78 ± 2.06
A4	35.48 ± 1.2	60.02 ± 1.02
A5	36.14 ± 2.0	66.62 ± 1.03
A6	38.26 ± 1.2	64.24 ± 1.12
A7	37.18 ± 1.4	58.89 ± 1.14
A8	39.08 ± 1.4	61.13 ± 0.26
A9	41.15 ± 1.3	69.17 ± 1.34
A10	38.28 ± 1.2	56.45 ± 1.15
A11	32.66 ± 1.3	61.18 ± 2.09
A12	30.22 ± 1.1	65.48 ± 1.84
A13	29.24 ± 1.2	57.12 ± 1.48
A14	27.18 ± 1.2	62.87 ± 1.13
A15	26.50 ± 1.0	56.42 ± 1.21

Values are reported as Mean ± SD (n=3)

Differential scanning calorimeter (DSC) analysis

DSC study of pure CsA and CsA loaded nanoparticles was performed to investigate the crystalline or amorphous nature of formulation as well as to find out the interaction between drug, polymer, and other excipients.

Powder X-ray diffraction analysis

The PXRD technique was employed to measure the physical state of the encapsulated drug which represented in Figure 2.

Characterization of Cyclosporine A loaded nanoparticulate gel

The pH of CsA loaded nanoparticulate gel was found to be 6.8 and the drug content was found to be 97.4%. The spreadability of CsA loaded nanoparticulate gel were 41.15 ± 1.3 cm.

In vitro release study

The data of percentage drug release formulation was shown in Figure 3. The amount of CsA from free drug dispersion demonstrated 96.99% release in 1 hr, while the release behavior of CsA from nanoparticles dispersion and the nanoparticulate gel was controlled over a time period of 12 h. It was observed that approximately 75.45% of CsA release in case of CsA nanoparticles dispersion, while 69.23% of CsA release after 12 h in the case of CsA nanoparticulate gel.

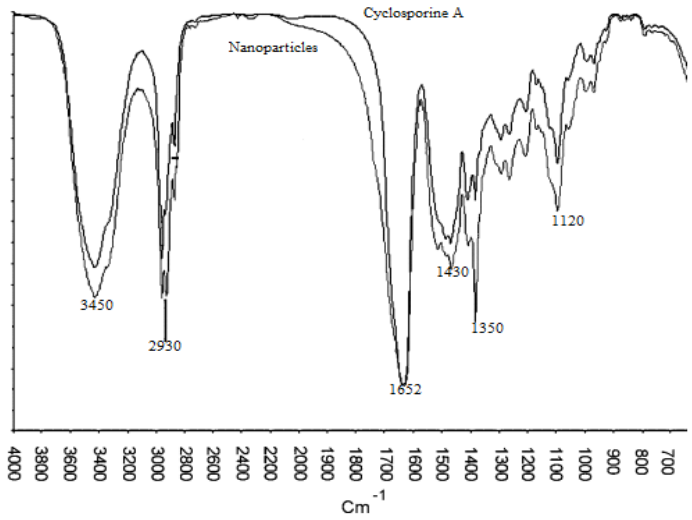


Figure 1: Comparative FTIR spectra of pure CsA and CsA loaded nanoparticles.

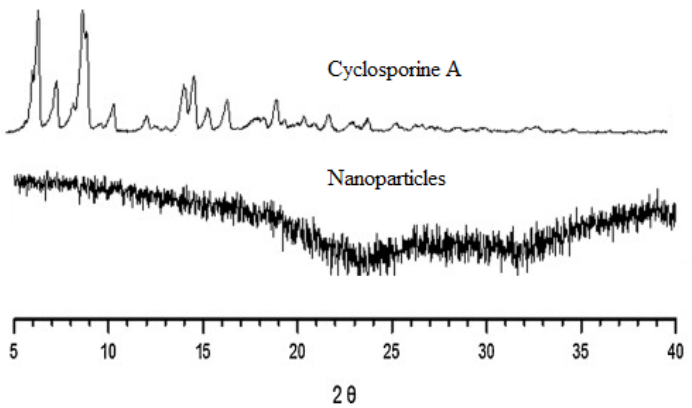


Figure 2: X-ray diffraction pattern of CsA and CsA loaded nanoparticles (A9).

In vitro antiproliferative activity

These cell lines efficiently predict the uptake of formulations by the cells. The results are shown in Figure 4(a), which explains the percent viability against the dose.

Dermal pharmacokinetic studies by using tape stripping technique

The dermal pharmacokinetic investigations presented in Figure 4 (b) clearly showed that all the formulations were uniformly distributed in stratum corneum and viable layers.

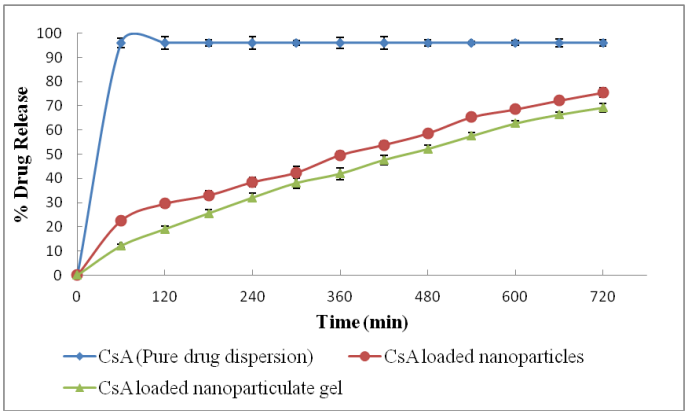
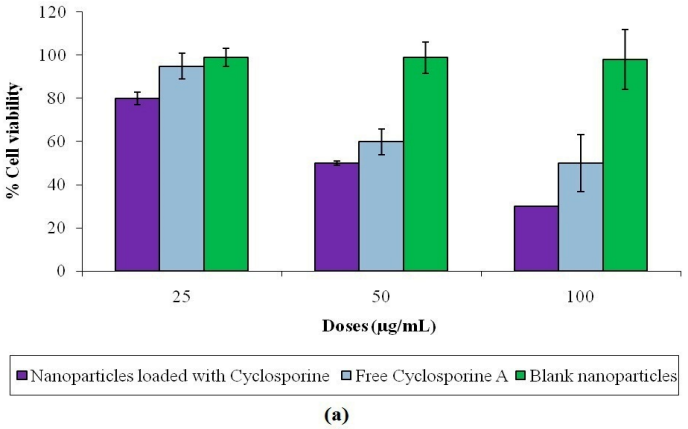


Figure 3: *In vitro* drug release profile of CsA from free drug dispersion, CsA nanoparticles and CsA nanoparticulate gel.



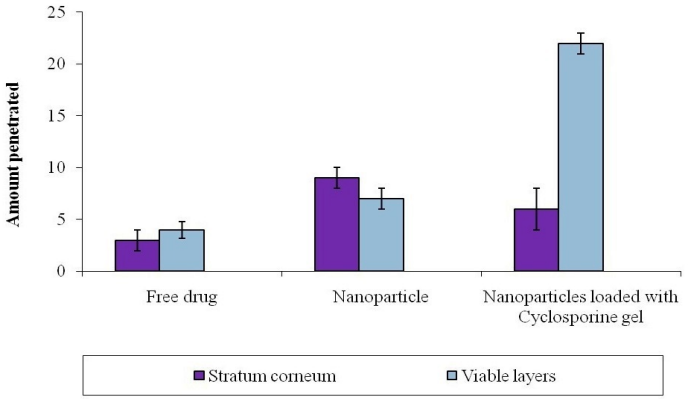


Figure 4: (a) Comparative evaluation of % cell viability of free drug, blank nanoparticles, and CsA loaded nanoparticles (b) Quantification of CsA in different skin layers in case of free drug, nanoparticle and CsA loaded nanoparticulate gel (Values are expressed as mean± SD, *n*=3).

DISCUSSION

Eudragit L 100 is a positively charged polymer that imparts cationic nature to CsA loaded nanoparticles.[23] It was observed that the higher the value of zeta potential lesser the aggregation of the particle, attributable to electric repulsion and consequently greater the stability of CsA loaded nanoparticles. It was experiential that positive charge shows on the surface of CsA loaded nanoparticles can be recognized to the existence of the quaternary ammonium groups of Eudragit L100 polymer.[23]

The basic peaks in FTIR study was retained in the pure CsA and CsA loaded nanoparticles (A9). Presence of C-H stretching in the region of 2850-3000 cm^{-1} and CH_3 bending at 1350 cm^{-1}, the emergence of the strong band found in between 1600-1720 cm^{-1} presents the existence of carbonyl group mainly because of C=O stretching, COO stretching at 1000-1300 cm^{-1} established the presence of CsA in CsA loaded nanoparticles (A9). The optimized formulation A9 showed an indistinguishable spectrum respecting the spectrum of the pure CsA indicating no chemical interaction or changes between the CsA and Eudragit L100 during the preparation of nanoparticles.

DSC analysis showed a sharp endothermic peak at 134°C for pure CsA equivalents to it's melting point. While in CsA loaded nanoparticles melting endotherm was observed at 136°C with a sharp appearance, this slight reduction in temperature may be because of reductions of the crystallinity nature of CsA in the formulation of nanoparticles.

PXRD stated that the intensity of the peaks for the pure CsA was sharp but for CsA loaded nanoparticles (A9), the intensities of the peaks decreased as a result, the reduction of the crystallinity of the CsA.

CsA loaded nanoparticles were uniformly distributed within the gel which exhibited non-newtonian flow i.e. thixotropic (pseudoplastic) rheology as evidenced by a decrease in viscosity with an increase in shear rate.

Spreadability plays an important role in patient compliance and helps in the uniform appliance of gel to the skin. Topical gels prepared with the low concentration of Carbopol 934 belonged to the fluid gel category, having more spreadability values and formulations prepared with the higher concentration of Carbopol 934 belonged to a stiff and semi-stiff category. The results indicated that the formulation can be applied easily without being the runoff.[31] This assures that the formulation maintains a good wet contact time when applied to the site of application.

Mathematical modeling was done using DD Solver, and it was suggested that free CsA dispersion follow zero-order kinetics (R^2=0.9617), while CsA nanoparticles dispersion (R^2=0.9708) and CsA nanoparticulate gel (R^2=0.9897) demonstrated Higuchi type matrix release behavior. It is suggested that the diffusion-dependent release behavior of CsA via erosion of the solid matrix of polymers or gel may be the primary mechanism for the release of the drug. Carbopol 934 gel matrix presented an additional barrier, so further retarded the drug release from CsA nanoparticulate gel in comparison to CsA nanoparticles dispersion. Furthermore, higher viscosity of gel matrix decreases the release rate of CsA as a result of lesser penetration of water and thus, hydration of gel matrix.

In vitro antiproliferative study proved that 50% of the cells were inhibited by CsA loaded nanoparticles when a dose of 50µg/mL was given and cell viability diminished gradually as the dose was raised. On the other hand, free CsA was not able to inhibit 50% of the growth, when the highest dose of 100µg/ml was given, thereby proving the fact that nanoparticles had a better effect on cell growth as compared to the free drug which was in turn due to higher uptake by the cells.[32] It was also observed that cell viability was not affected with blank nanoparticles, which proved there was no effect of surfactant concentration and surfactant type on cell viability causing no cell death.

In dermal pharmacokinetic study for the CsA loaded nanoparticulate gel, the amount reaching the viable layers is slightly higher than the stratum corneum. Psoriatic skin is rough, hard, and flaky due to it is hard to penetrate. The presence of gel hydrates the skin which helps in the higher permeation of CsA loaded nanoparticulate gel. The nanoparticle on the other hand acted more efficiently on the stratum corneum as they face difficulty penetrating into deeper layers of the skin. In the case of the free drug the amount of drug in the stratum corneum, as well as the epidermis and a viable layer, was less, therefore explaining their minimal penetration into the skin.[29]

CONCLUSION

In the present investigation, CsA nanoparticles were successfully formulated using a modified nanoprecipitation technique, and subsequently converted into the gel using Carbopol 934 as a gelling agent. The developed CsA nanoparticulate gel formulation improved dermal delivery of CsA and exhibits enhanced *in vitro* anti-psoriatic efficacy. The *in vitro* antiproliferative activity proved that nanoparticles had a superior effect on cell growth as compared to the free CsA. Dermal pharmacokinetic study demonstrated that for CsA nanoparticulate gel the amount of CsA reaching the viable layer is slightly high as compared to the stratum corneum. These hopeful *in vitro* results can be transformed into the probably marketed product after successful *in vivo* study as well as clinical trials in humans.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ABBREVIATIONS

CsA: Cyclosporine A; **T-cell:** T lymphocyte; **Da:** Dalton; **PDI:** Poly Dispersity Index.

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