Preparation and Evaluation of Nanocarrier Based Drug Delivery for the Management of Psoriasis

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Summary

Psoriasis is a chronic, multifactorial autoimmune-inflammatory skin disorder. It affects more than 7 million Americans & 2-4% peoples worldwide. It was characterized by appearance of thick skin red patches with silvery scales, Keratinogenesis over the entire body. [1,2] Both hereditary and immunological imbalance was responsible for prevalence of this disease. It hinders not only physically, socially but also economical well-being state of peoples. Although, there is no complete cure therapy for psoriasis till date. That's why, therapy strategies were made in such a way that it would provide symptomatic relief as well as better compliance towards the patients. Topical therapies were mainly considered to get symptomatic relief from mild or severe psoriatic conditions. There are various nanocarriers which are available such as nanoparticles, ethosomes, liposomes, niosomes, (SLN) solid lipid nanoparticles, micelles, (NLC) nanostructured-lipid-carriers, nanocapsules, and nanofibers. Among these, nanofibers & (NLC) nanostructured-lipid-carriers were widely being used for effective treatment. Due to their antipsoriatic properties, tazarotene and calcipotriol, respectively, were chosen as therapeutic candidates. The biological properties of pharmaceuticals placed in lipid vesicles were anticipated to be improved by the encapsulation and targeting capabilities. These were used in the current investigation as model medications. These active moieties have drawbacks such as poor solubility, limited absorption, low bioavailability, drug metabolism, adverse effects, and patient noncompliance, which can be remedied by employing lipid-based nanocarriers.The gel was selected as the preferred delivery strategy for the administration of both medications into a co-delivery carrier in order to accomplish the aforementioned objective. As alone therapy is not completely eradicating the psoriatic lessions providing non-effective therapy towards psoriasis, while combination therapies exhibit efficient as well as better multi-drug combination regimens are quite helpful. Additional issues with current topical delivery technologies for combination dosage forms include increased dosing recurrence, severe side effects, poor permeability, and more. The current situation centres on creating new medicine delivery systems based on nanocarriers. Therefore, our present work involves the development & characterization of both nanocarriers i.e nanofibers as well as nano-lipid carriers. Further, the prepared formulation is intended to optimize and characterize various in-vitro and *in-vivo* parameters. Besides these, antipsoriatic efficacy was also determined to explore the antipsoriatic activity of TZT & CPT in combination versus TZT alone. In psoriatic skin, calcipotriol has a special immune

modulating and anti-inflammatory action on cytokines which adds to provide better synergistic antipsoriatic activity with tazarotene against psoriasis.

PART-I

In the part-I, Tazarotene and calcipotriol-loaded nanofibers mat was successfully prepared first time using different concentrations of PVA/PVP blend polymers. The electrospinning technique was used to prepare these nanofibers. Further, prepared nanofibers are incorporated into carbopol-based hydrogel films to provide better adhesion over the skin. The prepared nanofibers were characterized both *in-vitro* & *in-vivo* respectively. The obtained SEM results confirm that prepared nanofibers were found smooth, flexible, and fine in appearance. The prepared nanofibers exhibited optimum tensile strength and good biodegradability. It also tends to provide desirable moisture content to manage psoriatic lesions more efficiently. In *in-vitro* studies, the % *in-vitro* drug release of prepared nanofibers was determined and it was found that nanofibers exert a sustained release pattern for a longer period. Furthermore, the histological study confirmed the potential antipsoriatic activity of nanofibers by promoting the regeneration phenomenon of the epithelial layer facilitating better curing of psoriatic lesions. *The in-vitro* evaluation involved cell line study via MTT assay which determines the toxicity nature of prepared nanofibers towards HaCaT cells and it was found in a result that TZT-CPT-PVA/PVP-NF was less toxic toward HaCaT cells. Additionally, *in-vivo* studies were performed on the IMQ-induced wistar rat model. Biochemical and antioxidant studies were also performed. From the observations, it was clear that the treatment groups indicated better curing and healing rate than the control group. Therefore, the prepared nanofiber TZT-CPT-PVA/PVP-NF could be said to have better antipsoriatic efficacy towards the psoriatic lesions. It was due to the fact that, calcipotriol was used in conjunction with tazarotene tends to improve its efficacy and tolerability. Due to their distinct mode of action, it might be supposed that tazarotene and Calcipotriol altogether would provide additional clinical benefits over monotherapy with either agent. It was also observed that inflammation, psoriatic lesions elevation, and scaling were also reduced more quickly upon combination therapy. On completion of therapy, there was a reduction in perilesional erythema and more complete eradication of the psoriatic lesions than in the early weeks of treatment. In this study, it was found that TZT-CPT-PVA/PVP-NF has more potential to manage psoriatic lesions than alone TZT-PVA/PVP-NF formulation. It could be a novel

synergistic approach toward psoriasis treatment for future perspective and commercialization as TZT-CPT-PVA/PVP-NF (combination) has great potential to treat psoriatic lesions effectively and provide better antipsoriatic activity. Further long-term studies may be pursued in this direction.

Conclusion

Tazarotene-Calcipotriol-loaded nanofiber carbopol-based hydrogel films were prepared & evaluated successfully. The nanofiber was prepared via electrospinning technique by using two polymers i.e polyvinyl alcohol/Polyvinylpyrrolidone (K-90) (PVA/ PVP (K-90)).Then, enriched with carbopol polymer to get hydrogel based films. The prepared nanofibers were subjected for evaluations such as- *in-vitro* & *ex-vivo* as well as *in-vivo* characterization. The obtained results suggests that the prepared tazarotene-calcipotriol loaded polyvinyl alcohol/Polyvinylpyrrolidone nanofiber hydrogel film (TZT-CPT-PVA-PVP-NF) showed better antipsoriatic efficacy than tazarotene-loaded polyvinyl alcohol/Polyvinylpyrrolidone nanofiber hydrogel fim (TZT-PVA/PVP-NF) in the management of psoriatic lesions.

PART II

In part II, One of the most common consequences of psoriasis is that sufferers experience painful psoriatic lesions and despite the fact that there are many medicines as well as therapies available for the treatment of psoriasis, unfortunately, none of them offer a complete and satisfactory. For that, TZT-CPT-NLC formulations were developed through solvent melt-emulsification followed by ultrasonication method with certain modifications. Further, prepared NLCs were successfully loaded into a hydrogel (Carbopol 934) for providing better topical adhesion of formulation on the psoriatic skin. The developed formulations underwent both in-vitro as well as in-vivo. SEM and TEM results confirmed the spherical shape of prepared TZT-NLC & TZT-CPT-NLCs. The prepared hydrogel-based formulations exhibited optimum viscosity, pH, and spreadability while drug penetration into the systemic circulation was shown to be minimal in an ex-vivo investigation. Additionally, the retention experiment showed that the hydrogel formulation's ability to retain CPT was improved. No irritability was detected for the developed hydrogel formulations. The in-vitro experiments revealed that prepared NLCs followed a sustained release pattern. The histological analysis supported the possible improved antipsoriatic activity of prepared NLCs in the management of psoriatic lesions. In the MTT assay, it was found that TZT-CPT-NLCs were less toxic to HaCaT cells. Additionally, findings of cellular uptake assays showed

encapsulating efficiency as well as higher uptake of TZT-CPT-NLC into HaCaT cells. *In-vivo* studies including biochemical, cytokine profile and antioxidant studies were carried out in IMQ-induced psoriatic rats. From the observations, it was clear that the treatment groups indicated better curing and healing rate than the control group. Therefore, it could be said that TZT-CPT-NLC has better antipsoriatic efficacy towards the psoriatic lesions than TZT-NLC. It was because the efficacy and tolerability of tazarotene were improved when calcipotriol was administered in conjunction with it. It might be assumed that using TZT and CPT together would have more therapeutic advantages than using either medication alone due to their different modes of action. Conclusively, it was found that combination therapy led to faster reductions in inflammation, psoriatic lesions elevation, and scaling. Compared to the early weeks of treatment, there was the complete eradication of lesions as well as erythema around the psoriatic skin at the end of the treatment period. It was also found that TZT-CPT-NLC has a better ability to heal psoriatic lesions compared to the TZT-NLC formulation alone. In this way, it could be said that TZT-CPT-NLC-hydrogel (combination) shows tremendous potential over TZT-NLC-hydrogel (alone) in terms of providing better antipsoriatic efficacy to heal psoriatic lesions efficiently. Hence, it could be said that it would be the ideal choice for commercialization to provide synergistic dual drug-loaded-antipsoriatic efficacy towards the management of psoriasis. The reported results could be utilized for future research and further development of the commercial product. Long-term research as well as clinical trials in this area may be continued.

Conclusion

Therefore, we proposed the preparation of Nanostructured Lipid Carriers (NLCs) containing Tazarotene (TZT) & Calcipotriol (CPT) by the solvent-melt-emulsification process for topical delivery. Our research work involves preparation, optimization by Box Behnken Design (BBD) and characterization of TZT CPT nano-lipid-carrier formulation and further incorporation into Carbopol 934 gel base to provide better adhesion on the skin for alleviating psoriatic lesions. The prepared NLC gel was further subjected to various in vitro and in vivo evaluations. The prepared hydrogel-based formulations exhibited optimum viscosity, pH, and spreadability for easy topical application. No skin irritation was additionally detected for the developed hydrogel formulations. The newly developed TZT-CPT-loaded-NLC gel formulation showed improved antipsoriatic effectiveness as well as sustained release effect as compared with TZT-loaded-NLC gel, indicating that combination therapy may be a promising and viable option in topical management & treatment of psoriasis.

Future perspectives

Our results suggests that it could be a novel synergistic approach toward psoriasis treatment for future perspective and commercialization as TZT-CPT-PVA/PVP-NF & Tzt- Cpt-NLC-hydrogel (combination) has great potential to treat psoriatic lesions effectively and provide better antipsoriatic activity. Phototherapy in conjunction with these formulations could be a novel approach in order to provide efficient and better antipsoriatic activity against psoriasis. Future applications of existing results are used for further use, research purposes & for commercialization in public domain as it has better patient-compliance, improved safety and efficacy profile which were the main considerations and options for the efficient treatment. So, further long-term clinical trial studies may be pursued in this direction.