Design of invasomal nanovesicles for improved transdermal permeation and bioavailability of asenapine maleate for treatment of schizophrenia

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Background: Asenapine Maleate (ASPM) is a second generation antipsychotic used for the management of schizophrenia with very limited oral bioavailability due to its extensive first pass metabolism. Transdermal administration of ASPM might offer an excellent alternative to its oral administration in order to enhance the bioavailability and provide a sustained action with subsequent improved compliance especially with the help of nanosystems. Invasomes are considered among the nano-vesicular systems that perfectly enhance the transdermal flux of different drugs.

Methods: ASPM-loaded invasomes were successfully prepared by thin film hydration technique; meanwhile the penetration enhancing effect of terpenes (cineole and limonene) was compared to hydromiscible cosolvent (Transcutol®). The prepared nanovesicles were characterized in terms of mean particle size (PS), polydispersity index (PDI), zeta potential (ZP), entrapment efficiency (EE%), Ex- vivo skin permeation. Selected formulations were stored at 4 ± 1◦C and re-evaluated for the change in particle size and zeta potential after two and six months as an index for their stability status. The optimized formulation was further studied using Transmission electron microscopy and FTIR techniques. In vivo pharmacokinetic study was carried out in rats with the optimized invasomal formulation and the pharmacokinetic parameters such as Cmax, Tmax, AUC_{0-t}, $AUC_{0-\infty}$, MRT of ASPM upon intravenous, oral and transdermal administration were estimated.

Results: Soft nanovesicles containing Transcutol® displayed smaller particle sizes than invasomes containing limonene and cineole while invasomes showed higher efficiency to encapsulate asenapine. Ex- vivo skin permeation revealed that invasomes with limonene are more efficient than those with cineole for the transdermal delivery of asenapine. Invasomes employed 1% limonene (F2) showed the highest values of both entrapment efficiency and asenapine permeation across rat skin. Transmission electron microscopy showed uniform spherical vesicles with intense outline and lighter core and FTIR study emphasized that ASPM was completely incorporated within the vesicles. The in- vivo pharmacokinetic study revealed that transdermal invasomes achieved 2 folds higher Cmax compared to oral suspension and delayed the Tmax from 1.5h to around 4h. The bioavailability of asenapine loaded invasomes after transdermal application was above 50% exceeding the bioavailability of sublingual tablets currently available in the market and exhibited sustained release kinetics over 72h which permits reduction of dosing frequency to increase patient adherence to medication.

Conclusions: The current work described the successful use of invasomes as a very promising vesicular carrier system for the transdermal delivery of drugs; especially hydrophobic ones. Synergistic effect of ethanol and terpenes is the underlying cause of enhanced permeation of invasomes. The optimized invasomal formulation displayed relatively small particle size (82.03 nm ± 0.62) and considerable ex-vivo permeation of asenapine along with optimum stability on storage for six months. A sustained transdermal delivery of ASPM up to 72 hours was achieved that could reduce dosing frequency, enhance bioavailability and improve patient compliance.