Development of Essential Oil based Nanoemulsions loaded with Dimethyl Fumarate for Intranasal Drug Delivery

F.K. Tareen[1], M. Sorrenti[1], L. Catenacci[1], S. Perteghella[1], E.S.Cama[1], M.C. Bonferoni[1]

[1]Università di Pavia, Dipartimento di Scienze del Farmaco

fahadkhan.tareen01@universitadipavia.it

Dimethyl fumarate (DMF) is a first line medication for the treatment of multiple sclerosis (MS), a neurodegenerative disease characterized by inflammation with demyelination and gliosis. Despite a good therapeutic effect of DMF, it is associated with ambiguous safety profile and several adverse events. These adverse events are attributed to the high doses of DMF, and consist of GIT problems, flushing, skin irritability and in severe cases can cause progressive multifocal leukoencephalopathy (PML).[1-3] Now-a-days, intranasal drug delivery is in the limelight among pharmaceutical innovations owing to its advantages over conventional drug delivery routes. Intranasal drug administration has the potential to deliver the drug directly to brain by passing the blood brain barrier and generating a therapeutic effect promptly. A relevant hindrance in this route is the mucociliary clearance that may cause flushing of the formulation reducing absorption.

Intranasal drug delivery of DMF can help in utilization of minimum doses and can directly initiate a therapeutic response in the brain. It would avoid first pass effect as well as GIT related adverse events. Furthermore, essential oils in combination with drugs can help in achieving a synergistic effect and can help in reducing the adverse events. Carvacrol (CV), a monoterpene phenolic compound, have neuroprotective effects and in combination with DMF can help in ameliorating the need for higher doses leading to mitigation of adverse events.

Nanoemulsions of CV loaded with DMF intended for intranasal route can help in addressing the problems associated with the drug, patient compliance, and disease management. Essential oils have gained recognition in these past few years as potential therapeutic entities, but it is necessary to evaluate them for solubility studies and molecular interactions with the drugs.

First, solubility of DMF in CV was determined and found to be 150 mg/ml at 25±1 °C. Physical mixtures of DMF-CV in molar ratios of 1:1, 1:2, and 2:1 were prepared and analyzed by means of FT-IR and thermal analysis (TGA). In the next phase, oil in water (o/w) nanoemulsions by self-nanoemulsification method, incorporating CV oil and encapsulating DMF in the oil were prepared. Chitosan was utilized as surfactant with oleic acid to physically stabilize the nanoemulsions and to impart mucoadhesive properties required for efficacious intranasal drug delivery.[4] Oil and chitosan-oleic acid was fixed at 1:1, with chitosan utilized at 0.1% w/v of the overall volume for chitosan and oleic acid mixture in accordance with previously reported method.[5]

Blank and drug loaded nanoemulsions were investigated for particle size, PDI, zeta potential, and entrapment efficiency. The particle size was below 200 nm for blank and for drug loaded nanoemulsions below 250 nm with a PDI of less than 0.5. Encapsulation efficiency was found to be 90%. For the stability studies, nanoemulsions were stored at room temperature (25ºC) and at refrigerated temperature (4°C) for 8 weeks. It was inferred from the obtained results that at room temperature, particle size increased to range of 300 to 400 nm and PDI was found to be more than 1. On the other hand, nanoemulsions at refrigerated temperature were able to sustain their mean particle size of below 250 nm and PDI below 0.5. Thus, it is concluded that nanoemulsions based on CV as oil loaded with DMF are more stable at refrigerated temperature.

Furthermore, design of experiment is planned to investigate different parameters such as surfactant ratio, speed of addition of organic phase to aqueous phase, and probe sonication time to better optimize the formulation before leading to cell permeability studies on cell lines.

References

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