

In Vitro and In Vivo Evaluation of Hydroxyzine Hydrochloride Microcapsules for skin delivery

Christianne Mounir Zaki Rizkalla¹, Randa Latif Aziz¹, Iman Ibrahim Soliman¹

1) Faculty of pharmacy, Cairo university, Egypt

Statement of purpose: Hydroxyzine HCL is used in oral formulations for the treatment of urticaria and atopic dermatitis. Dizziness, blurred vision and anticholinergic responses, represent the most common side effects. It has been shown that controlling the release of the drug from a delivery system to the skin could reduce the side effects while reducing percutaneous absorption. Therefore, the aim of the present study was to produce microcapsules containing Hydroxyzine HCL, enabling its controlled release into the skin.

Methods: Hydroxyzine HCL microcapsules were prepared using thermal phase separation (coacervation) method using ethyl cellulose/ cyclohexane system in the presence of coacervation inducers (Polyisobutylene, Polyethylene). The prepared microcapsules were studied for their drug content (U.V spectrophotometric assay), particle size, morphology, flowability, in-vitro drug release in phosphate buffer pH 5.5. Optimization of the formulation parameters was carried out by: 1) varying the type and the percentage concentration of the coacervation inducer with microcapsules prepared with three different core: wall ratios, 2) by using ethyl cellulose with two different viscosities, 3) and by the addition of pore inducers such as pregelatinized starch and sucrose in order to enhance the drug release (1).

The antihistaminic effect of the chosen microcapsules preparation was tested on the shaved back of sensitized rabbit (suppression of wheal and flare)(2). Histopathological studies were driven for the detection of the healing of inflamed tissues.

Results: Microcapsules with optimum encapsulation efficiency, flow properties and particle size were obtained using 1%w/v polyisobutylene as a coacervation inducer, and the following core to wall ratio 1:0.5, 1: 0.2, and 1:0.1. The addition of 0.5 % w/v polyisobutylene failed to produce microcapsules with adequate flow properties which were ascertained by the determination of their angle of repose, Carr's index and Hausner ratio. The use of 2 % or 5% w/v polyethylene as coacervation enhancer resulted in aggregated microcapsules. Microcapsules prepared using 1:1 core to wall ratio dried in the form of lumps although they were prepared using both types and concentrations of coacervation inducers. The release profiles of the three successful microcapsules preparation revealed that maximum percent of drug released was 85 % (figure 1), and it was

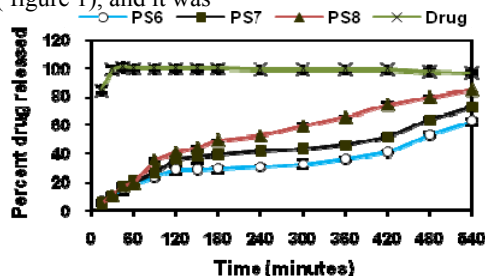


Figure 1. The In vitro Release Profile of HYD - HCL from Microcapsules Prepared by Thermal phase Separation.

obtained after 9 hours, for microcapsules having 1: 0.1 core : wall ratio (PS6). In order to enhance the rate of drug release to be adequate for topical delivery, low viscosity ethyl cellulose (10 cp) was used to prepare formula containing 1: 0.1 core to wall ratio. The microcapsules prepared showed the same release pattern compared to those prepared using the higher ethyl cellulose viscosity (45 cp). However lower encapsulation efficiency was obtained with those prepared by 10 cp ethyl cellulose. Optimum encapsulation efficiency associated with almost complete drug release within 3 hours, were obtained with microcapsules prepared using pregelatinized starch as a pore inducer with 1:0.1 core : wall ratio.

After The application of the chosen microcapsules on the back of sensitized rabbit, the formula was able to block the wheal and flare response of histamine. The onset and the extent of wheal suppression determined during the experiment revealed effective therapeutic response. The histopathological study of the skin tissues showed optimum healing of the dermal and epidermal layers of the skin treated with the medicated microcapsules compared to those treated with plain formula (figure 2).

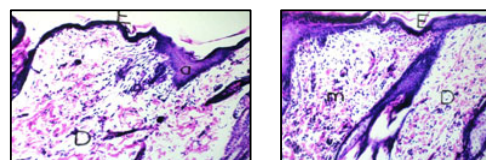


Figure 2. Treated Skin Untreated skin

Conclusions: On the basis of previous findings the following could be concluded: the addition of Polyisobutylene 1% w/v was essential for the preparation of microcapsules by thermal phase separation – coacervation method. Polyisobutylene (0.5 or 1% w/v) resulted in aggregated microcapsules in the presence of high amount of polymer (1:1 core: wall ratio). Polyethylene either in 2 % or 5 % w/v concentration failed to prepare microcapsules and agglomerates were formed. Decreasing ethyl cellulose viscosity to 10 cp didn't show any enhancement in the release pattern of the drug when compared to the same formula prepared by ethyl cellulose of viscosity (45 cp). Pregelatinized starch when used as pore inducer succeeded to prepare microcapsules with complete drug release after nearly three hours. The epicutaneous skin test represented a reliable easily performed evaluation for the antihistaminic activity of topically applied dosage forms. Topically applied microparticles containing 10 mg of Hydroxyzine HCL, were therapeutically effective allowing the passage of the drug to the epidermis.

References:

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Conflict of Interest:

No conflict of interest or any financial benefit is required from all co-authors. Any experiments involving the use of animals were conducted in accordance with the principles of Laboratory Animal care and were approved by the Ethical Committee of the Faculty of Pharmacy ,Cairo University, Egypt.