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Formulation and Evaluation of topical delivery system of antihistaminic drug

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INTRODUCTION

Our previous data demonstrated that prolonged intake of desloratadine (DESS, Clarinex), a commonly used blocker of H1 histamine receptors, in rats induced development of an obesity-like phenotype and signs of metabolic syndrome together with fat maldigestion. These alterations include an excessive weight gain, increased density of abdominal subcutaneous fat, high blood triglycerides with their re-routing towards portal blood, high fasting blood glucose levels with potential development of insulin resistance, high liver/body weight ratio and liver steatosis (fatty liver). These changes were associated with dysfunction of mesenteric lymphatic vessels (MLVs), specifically high lymphatic tone and resistance to flow together with greatly diminished abilities to respond properly to postprandial increase of lymph flow.

HYPOTHESIS

Considering these novel findings and available clinical reports on association of antihistamines oral intake and obesity, to further test our hypothesis on association of oral antihistamines-induced MLVs dysfunction with obesity/metabolic syndrome, we are proposing an alternate topical route of antihistamines delivery in order to prevent development of obesity and metabolic syndrome.

METHODS

Determination of Drug Solubility: Drug solubility in phosphate buffer pH 7.4 and various permeation enhancers (PEG400, Propylene Glycol (PG), Transcutol (TC) was determined at 25 ^{o}C.

In vitro permeation studies: Drug diffusion rate was determined using polyethersulfone membrane (Strat-M^{TM}, Merck Millipore, Darmstadt, Germany) and pig ear dermatomed skin. The in vitro permeation studies were carried out in a Franz Diffusion Cell (Hanson Research, Chatsworth, LA, USA) with a diffusion area of 1.767 cm^2 and receptor cell volume of 12 mL. The membrane was carefully placed at the interface between the donor and receptor compartments. Saturated DES solution (1 ml) was transferred into donor compartment. Receptor cell was filled with 12 ml phosphate buffer pH 7.4 maintained at 32 ^{o}C and stirred at 350 rpm to ensure mixing of diffused drug with the medium during the experiments. Aliquots of 0.3 mL were collected at time 0.5, 1, 2, 3, 4, 5, 6, and 24 h. Sink conditions were maintained with the replacement of the same volume of receptor medium held at 32±0.5 ^{o}C. The samples were analyzed by developed and validated HPLC method.

In-vitro permeation in the presence of hydroxypropyl-β-cyclodextrin (HPβC)

Permeation studies were also performed in the presence of HPβC (5 and 10%) to increase the concentration gradient and achieve the sink condition.

Hydrogel preparation: Different polymers were evaluated for hydrogel (Carbopol® 934, Carbpol ® 980, Carbopol ® ETD 2020, HPMC K15, HPMC K100M). Effect of formulations variables on the quality attributes of gel were studied by design of experiment (Table 1). HPMC K100M, 2-3%, TC conc (15-20%), and drug conc (2.5-5%) were selected as independent variables.

METHODS (contd.)

The prepared hydrogel formulations were tested for rheological properties, pH, drug content, and in-vitro permeation. The data were analyzed using JMP software.

Table1: Factorial design of 2^3 of DES hydrogel formulations

		Polymer conc.	Drug conc.	Transcutol conc.	Polymer conc.	Drug conc.	Transcutol conc.
F1	- - +	-1	-1	1	2%	2.5%	20%
F2	+ - +	1	-1	1	3%	2.5%	20%
F3	000	0	0	0	2.5%	3.75%	17.5%
F4	+ + +	1	1	1	3%	5%	20%
F5	+ - -	1	-1	-1	3%	2.5%	15%
F6	+ + -	1	1	-1	3%	5%	15%
F7	- + -	-1	1	-1	2%	5%	15%
F8	- + +	-1	1	1	2%	5%	20%
F9	- - -	-1	-1	-1	2%	2.5%	15%

RESULTS

- Drug solubility was highest in Transcutol (Figure 1.) among the studied enhancer. It was selected as a cosolvent as well permeation enhancer.
- Diffused drug was higher in pig ear skin than synthetic membrane (Figure 2). Furthermore, drug diffusion was increased in the presence of HPβC indicating that rate limiting step in drug diffusion was drug solubility (Figure 3).
- Drug precipitated in Carbopol polymer as it required addition of NaOH. No drug precipitation was observed in HPMC based gel (Figure 4).

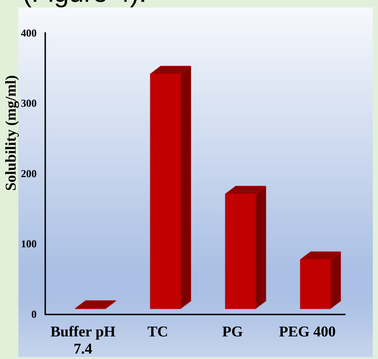

Figure 1. Solubility of DES in various permeation enhancers

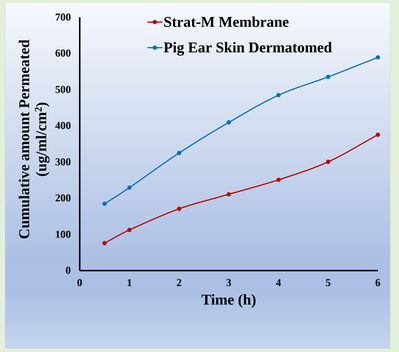

Figure 2. DES permeation through synthetic membrane and pig ear skin

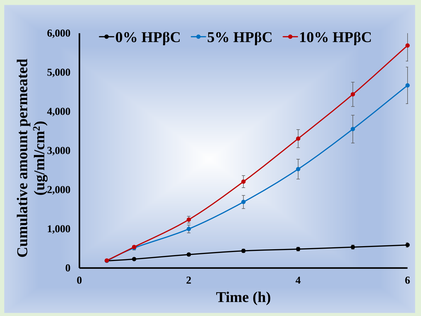

Figure 3. DES diffusion in the presence of HPβC

HPMC Carbopol®

Figure 4. Hydogel based on HPMC and Carbopol® polymers

Results (contd.)

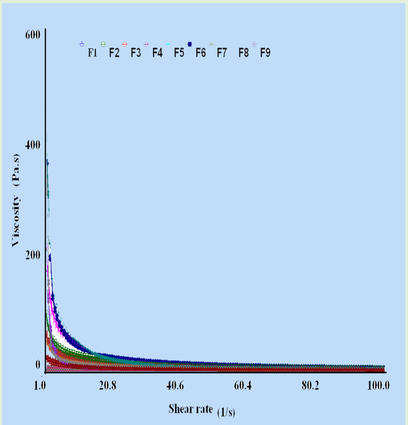

Figure 5. Viscosity profile of gel formulations.

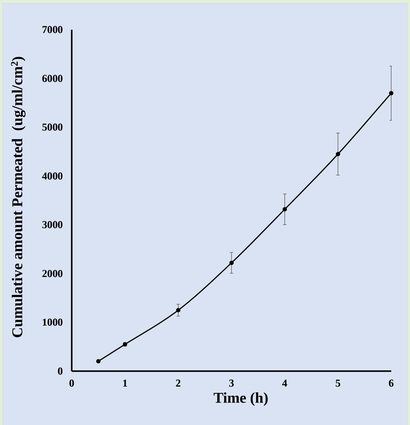

Figure 6. Drug permeation from the gel formulation.

FUTURE EXPERIMENTS

- Drug diffusion through human cadaver skin.
- Internal structure of the hydrogel formulations by small angle X-ray Diffraction
- Comparative pharmacodynamics and pharmacokinetics evaluation of oral and topical formulation of DES.

CONCLUSION

- Drug diffusion is dependent on the solubility of the drug in the solvent.
- The investigated formulation parameters significantly affect quality attributes of the formulations e.g. viscosity and drug permeation.
- The thermo-rheological evaluation indicated that storage of the formulations above 35 ^{o}C may cause irreversible changes in storage modulus.

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