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Formulation and evaluation of diphenhydramine gel using different gelling agents

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ABSTRACT

Diphenhydramine (DPH) was used to treat a number of conditions including allergic symptoms and itchiness, common cold, insomnia, motion sickness, and extrapyramidal symptoms, are associated with some adverse effects such as dry mouth and throat, increased heart rate, pupil dilation, urinary retention and etc. This study aims to evaluate hydrogel drug delivery of DPH by tree gelling agents. Carboxy methyl cellulose (CMC), Hydroxy propyl methyl cellulose (HPMC) and methyl cellulose (MC) in the presence of 1 and 2% of DPH. All gel samples were evaluated for physical appearance, drug release and stability for the period of two months. Drug release studies were done by Franz diffusion cell. This in vitro study demonstrates the advantages of gelling polymers in transdermal drug delivery applications. The ability of molecules to diffuse into (drug loading) and out of (drug release) a hydrogel enables to use this system for drug delivery. DPH gel formulations prepared with different gelling agents HPMC, CMC and MC showed acceptable physical properties and drug release study. Among all gel formulations, MC gels revealed superior physical properties and drug release. The result obtained suggests the feasibility of designing transdermal delivery systems for DPH successful and effective besides overcoming the drawbacks of oral administration.

Key words: Diphenhydramine; hydrogel; drug delivery; drug release; In vitro; Diffusion cell

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INTRODUCTION

The term hydrogel describes three-dimensional network structures obtained from a class of synthetic and/or natural polymers which can absorb and retain significant amount of water [1]. The hydrogel structure is created by the hydrophilic groups or domains present in a polymeric network upon the hydration in an aqueous environment. Polymeric hydrogels have found extensive applications, are available in various physical forms, such as powders, discs, or microspheres, these hydrogels are generally glassy in the dehydrated state, but swell to become elastic gel upon water penetration [2]. Hydrogel form of many synthetic and natural polymers have been produced with their end use mainly in tissue engineering, pharmaceutical, and biomedical fields [3]. Due to their high water absorption capacity and biocompatibility, they have been used in wound dressing, drug delivery, agriculture, sanitary pads as well as trans-dermal systems, dental materials, implants, injectable polymeric systems, ophthalmic applications, hybrid-type organs (encapsulated living cells) [4]. One of the best advantages of hydro gels is controlled and sustained drug release at the target site, improving the therapeutic efficacy and reducing side effects. Drug loading is relatively high and may be achieved without chemical reactions; this is an important factor for preserving drug activity Controlled in drug delivery systems, which are intended to deliver drugs at predetermined rates for predefined periods of time which have been used to overcome the shortcomings of conventional drug formulations [5].

Drug delivery is the method of administering a bioactive compound to achieve a therapeutic effect, in humans or animals. Drug delivery systems are formulations that modify the drug release profile and the ability to cross

biological barriers, the bio distribution and pharmacokinetics, improving its efficacy and safety, as well as the patient compliance [6].

Hydro gels can be made from virtually any water-soluble polymer, encompassing a wide range of chemical compositions and bulk physical properties [1]. Hydro gels now play a critical role in many tissue engineering scaffolds, biosensor and BioMEMS devices, and drug carriers. Among these applications, hydro gel-based drug delivery devices have become a major area of research interest with several commercial products already developed [7]. Hydrogels are also generally highly biocompatible, as reflected in their successful use in the peritoneum [8] and other sites *in vivo*. A variety of synthetic and natural polymers have been studied as drug carriers [9] and DDSs have capitalized on their wide-ranging hydrophobic and hydrophilic components, and their polymer–polymer, polymer–drug, polymer–solvent or polymer–physiological medium interactions. Diphenhydramine is used to treat a number of conditions including: allergic symptoms and itchiness, the common cold, insomnia, motion sickness, and extrapyramidal symptoms [10]. Sometimes it leads to the side-effects of dry mouth and throat, increased heart rate, pupil dilation, urinary retention, constipation, and, at high doses, hallucinations or delirium. Further side-effects include motor impairment (ataxia), flushed skin, blurred vision at nearpoint owing to lack of accommodation (cycloplegia), abnormal sensitivity to bright light (photophobia), difficulty concentrating, short-term memory loss, visual disturbances, irregular breathing, dizziness, irritability, itchy skin, confusion, decreased body temperature (in general, in the hands and/or feet), erectile dysfunction, and excitability [10]. The purpose of this study was to omitting some side effects of oral Diphenhydramine, by performing hydro gel drug delivery of DPH.

MATERIALS AND METHODS

2.1. Materials

Carboxy methyl cellulose (CMC), Hydroxy propyl methyl cellulose (HPMC), methyl cellulose (MC), Diphenhydramine (DPH) were purchased from Sigma-Aldrich company, Germany.

2.2. Equipment

UV -Visible spectrophotometer (UV-1700A Shimadzu corporation, Japan), Digital balance (Shimadzu Corporation, Japan), pH meter (Metrohm827 Swiss), Magnetic stirrer Heidolph (Germany), Rheometer (BrookfieldE DVIII USA) were used in the present study.

2.3. Preparation of polymer solutions

Hydrogel formulations were prepared by dispersing 2, 4 and 6% w/w HPMC, CMC, MC in water by continuous stirring for a period of 2 h. Stock solutions of DPH were prepared by dissolving an exactly weighted quantity (1 and 2 g) of Diphenhydramine in 100 mL distilled water. These solutions were stirred for 2 h on a magnetic stirrer and added gradually to HPMC, CMC and MC dispersed under continuous stirring. The mixture was stirred gently with a stirrer until homogeneous gel was formed. All the samples stored in closed containers to prevent evaporation of water and allowed to equilibrate for at least 24 h at room temperature.

2.4. Rheological measurements

Because of low viscosity of 2% and high viscosity of 6%,viscosity of 4% hydrogel samples at different ratio were measured by using a Brookfield rheometer, model DV-III by taking 8 mL of the sample into a removable sample chamber equipped with a temperature probe within an accuracy of 0.1ºC. The removable sample chamber was then inserted into the water jacket assembly; an insulation cap was placed on the chamber to minimize the heat loss during measurements. Suitable spindles were used and rotated at various rpm with the % torque in the range of 10 to 90 (i.e., within the recommended optimum range). Before taking readings, the rheometer scale was auto zeroed. Data were collected at 37ºC.

2.5. pH measurement

Every samples PH was measured by (Metrohm 827 Swiss made), which was calibrated before each use with buffered solutions at pH4, 7 and 10.

2.6. Drug content studies

About 1g of the gels was dissolved in 25 ml of phosphate buffer pH 6.8 saline, appropriate dilutions were made with the same buffer solution, filtered and measured by spectrophotometric analysis at 257 nm.

2.7. Drug release

Release of Diphenhydramine from various gel formulations was studied using a Franz diffusion cell. A standard cellophane membrane (soaked in pH 6.8 for two hours before use) was fixed to one end of the cylinder with the aid of an adhesive to result in permeation cell. One gram of gel was exposed on the cellophane membrane surface

(donor compartment) and free phosphate buffer pH 6.8 (15 ml) was receptor compartment, agitated using a magnetic stirrer and as well as temperature of 37 ± 1ºC was maintained. Sample (1 ml) of the receptor compartment was taken at various interval of time (15, 30, 60, 90, 120, 150 min) and assayed for DPH at 257 nm. The volume withdrawn at each time was replaced with drug free phosphate buffer. Amount of DPH released at various intervals time was calculated and plotted against time.

2.8. Stability study

For the evaluation of stability study, maintaining the formulations at an ambient condition (4 and 40°C and room temperature) over a period of two months. The physical appearance, pH value, drug content, drug release studies were determined periodically after the 1st and 2nd month after topical gels preparation.

2.9. Statistical analysis

The results obtained from the experiments of release studies were analyzed statistically using multi variant tests. When a statistically significance difference was found, Tukey HSD (honestly significant difference) test was then conducted (using SPSS version 13). A statistically significant difference was considered when $p<0.05$ [11].

RESULTS

All gel formulations were made but only hydrogels by 4% concentration of CMC, HPMC and MC found smooth, pliable, homogenous and acceptable in appearance when applied on the skin with the finger.

Figures 1-4 show the structure of gelling agents and DPH. Rheology studies of MC Gels were showed pseudoplastic properties (shear thinning properties), which meaning gels are thick (viscous) under static conditions and will flow (become less viscous) over time when shaken or stressed. They then take a fixed time to return to a more viscous state. These gels properties cause to appropriate exit from tubes and skin distribution. (Figs. 5-7). *In vitro* dissolution profile of 1 and 2% diphenhydramine hydrogels containing 4% CMC, HPMC, MC are shown in figure 8 and data are presented in Table1. The initial concentration of DPH in all of formulations was kept as constant at 1 and 2%. The drug content was in the range of 92.88 to 98.15. The pH of all formulations was between 6.01 to 6.52 which lies in the normal pH range of the skin and did not produce any skin irritation.

DISCUSSION

Drug can be incorporated into hydrogel matrices by two ways [12]: (i) Post-loading, (ii) In-situ loading. In the post-loading method a hydrogel matrix is formed and then the drug is absorbed to this matrix. For an inert hydrogel system diffusion is the major force for drug uptake. Drug release will be determined by diffusion and/or gel swelling. For hydrogel containing drug-binding ligands the release will be determined by a drug-polymer interaction and drug diffusion. In the in-situ loading a polymer precursor solution is mixed with drugs or drug-polymer conjugates. Hydrogel network formulation and drug encapsulation are accomplished simultaneously. The drug release will be determined by diffusion, hydrogel swelling, reversible drug-polymer interactions or degradation of labile covalent bonds. As illustrated earlier part [2, 3] hydrogels were prepared via in-situ loading method. Due to the high water content of hydrogels, their molecular release mechanisms are very different from other DDSs comprised of less hydrophilic or hydrophobic polymers. Previous modelistic studies predict that the release of an active agent froma hydrogel, as a function of time, is based on the rate-limiting step for controlled release and therefore categorized as diffusion-controlled, swelling-controlled, or chemically-controlled. Diffusion-controlled release through the hydrogel mesh is the primary mechanism of release of many drugs from hydrogels, which regulates therapeutic release [13, 14]. Typical mesh sizes reported for biomedical hydrogels range from5 to 100 nm (in their swollen state) [15], which are much larger than the size of most small molecule drugs. As a result, the diffusion of such drugs is not significantly retarded in the swollen state, whereas macromolecules like protein and peptides, due to their hydrodynamic radii, will have a sustained release unless the structure and mesh size of the swollen hydrogels are designed appropriately to obtain the desired rates of macromolecular diffusion. In case of the swelling-controlled mechanism when diffusion of a drug is significantly faster than hydrogel distention, swelling is considered to be controlling the release behavior [16].

Finally, chemically-controlled release is determined by chemical reactions occurring within the gel matrix. These reactions include polymeric chain cleavage via hydrolytic or enzymatic degradation. Chemically-controlled release can be further categorized according to the type of chemical reaction occurring during drug release. Generally, the liberation of encapsulated or tethered drugs can occur through the degradation of pendent chains or during surface erosion or by bulk degradation of the polymers [12]. It is clear from the Table 1 that drug release decreased ($p<0.05$) with increase in the concentration of the gelling agents. Unlike the harsh environment of the GI tract, low-molecular weight drugs can be administered by local transdermal Drug Delivery System (DDS), which benefit from sustained

drug release and easy therapy. Viscosity of prepared gel was found to be significantly affected by concentration and molecular weight. The density of chain structure which has been observed in gels' microstructure increases at the higher polymer concentration and this limits the active substance's movement area [17-21]. Generally as polymer concentration increases, viscosity increases as well. Viscosity is the most widely utilized reference for the characterization of polymer structure, although it is not sufficiently comprehensive for the full determination of hydrogel strength [22].

The formulations viscosity ranged from 0.37±0.09 to 14.326±0.51 cps, the results of 150 min percentage drug release showed that formulation with high molecular weight have slowest drug release of 7.8 (HPMC+1%drug) and highest release was observed 88.35 in the case of MC in the presence of 2%DPH at the end point time. Viscosity is negatively related to release of active substance from formulation and its penetration through the diffusion barriers. This decrease in the release could be attributed to increased micro viscosity of the hydrogel by increasing polymer concentration. Thus, both high concentration of polymer and high viscosity complete each other in decreasing the release of active substance release from the formulation [23, 26]. The percentage release of specific adsorbed drug was calculated from the equation:

Release % = $(w_t / w_{sp}) \times 100$

Where w_t is the weight of released drug at time t and w_{sp} is the total weight of specific adsorbed drug in the gel system. Drug release study of prepared gel showed all the factors like polymer concentration, and molecular weight showed negative effect, which can be utilized to get desired release pattern from the formulation. Increase in polymer concentration and molecular weight leads to increase in viscosity which may be the main cause of decrease in drug release.

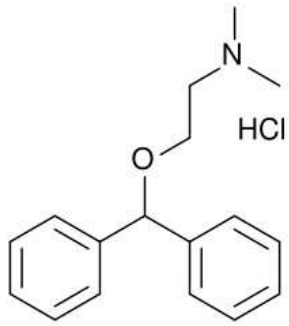

Fig.1. Structure of DPH

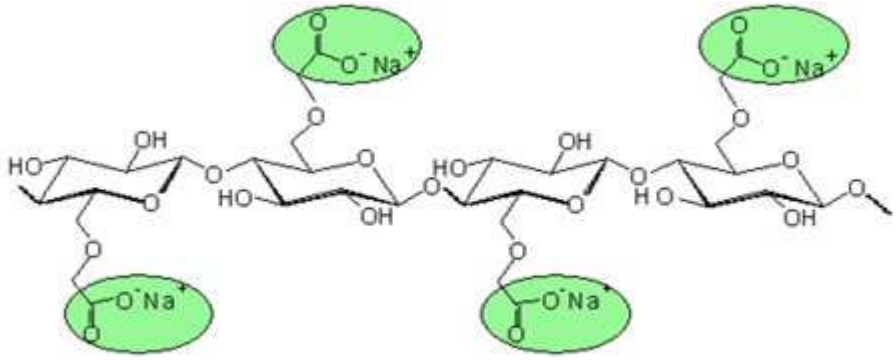

Fig.2. Structure of CMC

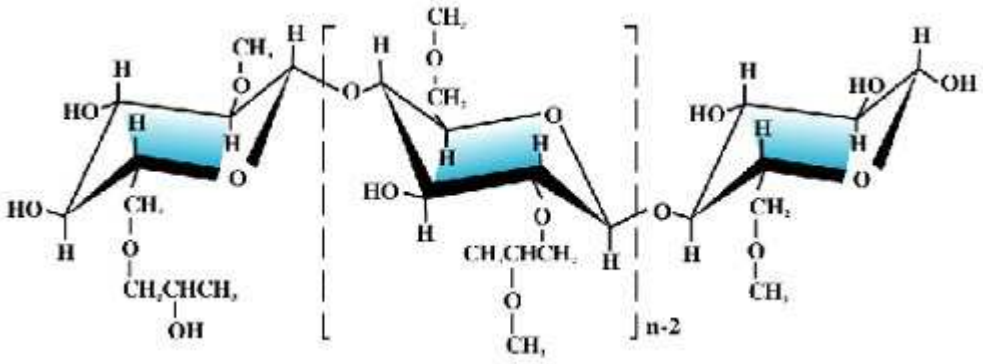

Fig.3. Structure of HPMC

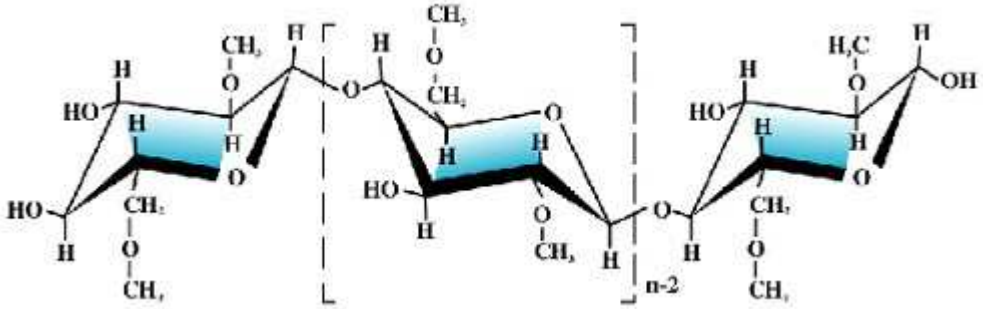

Fig.4. Structure of MC

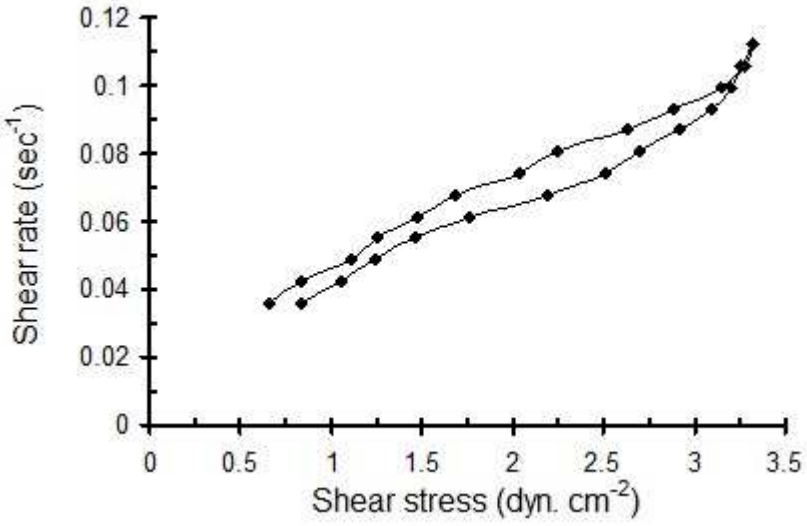

Fig.5. Rheogram of HPMC gel

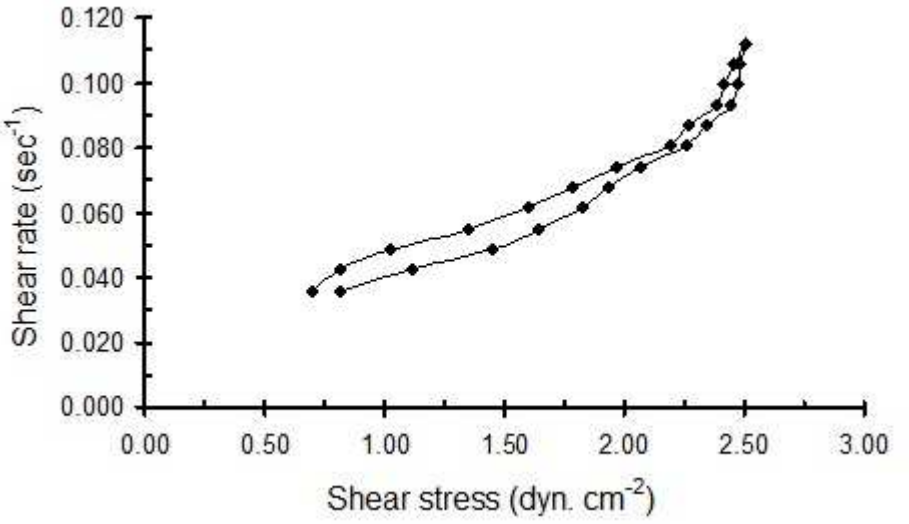

Fig.6. Rheogram of CMC gel

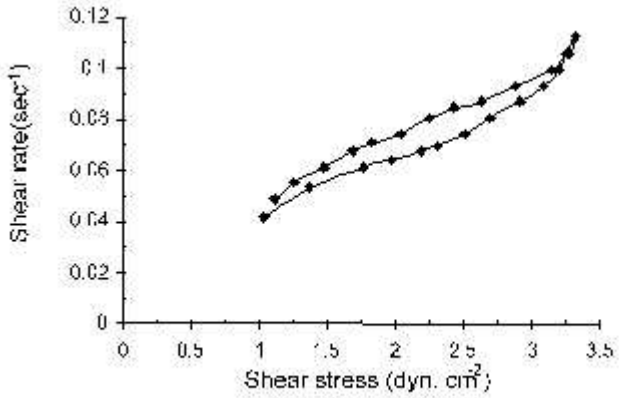

Fig.7. Rheogram of MC gel

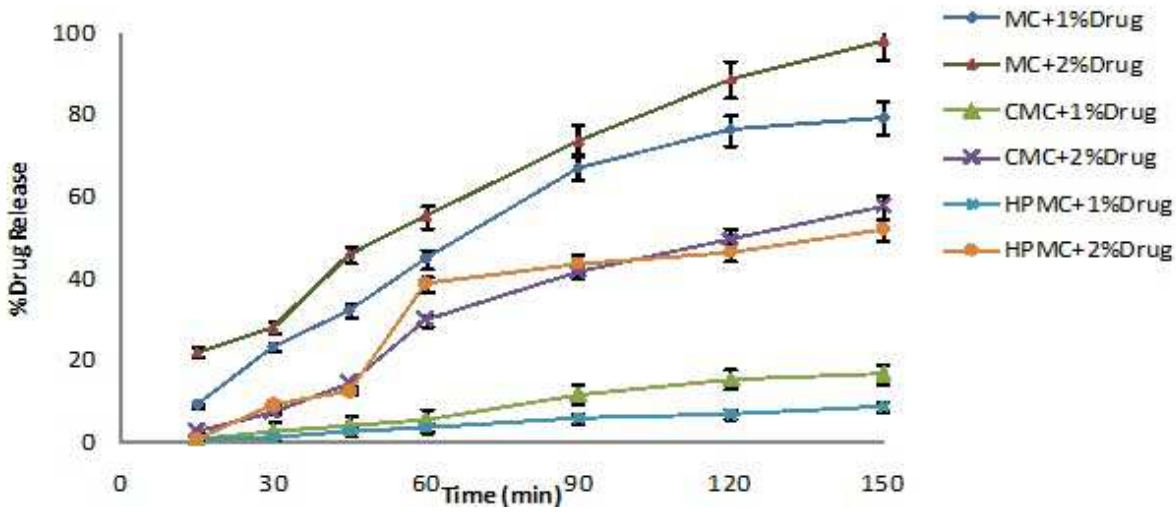

Fig.8. Release profile of hydrogels

CONCLUSION

This *in vitro* study demonstrates the advantages of gelling polymers in transdermal drug delivery applications. The ability of molecules to diffuse into (drug loading) and out of (drug release) a hydrogel enables to use this system for drug delivery. DPH gel formulations prepared with different gelling agents HPMC, CMC and MC showed acceptable physical properties and drug release study. The results obtained suggest the feasibility of designing successful and effective. Transdermal delivery systems for Diphenhydramine overcoming the drawbacks of oral administration and offering additional advantages. Therefore, this study concerning transdermal delivery of DPH seems to be a suitable entity, because of it's sustain release profile, water-soluble nature, physical stability.

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