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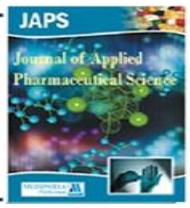

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The effect of formulation factors on the release of oxybutynin hydrochloride from transdermal polymeric patches

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ABSTRACT

The aim of the present study was to formulate oxybutynin in a relatively stable and more acceptable and bioavailable dosage form. Gels and patches were formulated according to the standard methods. The prepared formulations were tested for their hygroscopicity, content uniformity, weight variation and tensile strength. Also the release profile and the stability of patches were determined. The results showed that the amount of humidity absorbed by and F_{19} was 9.21±0.199 and 9.51±0.306 respectively. The results of tensile strength measurement showed 1.97 and 2.55 g. cm^{-2} for formulation F_5 and F_{19}, respectively. Statistical analysis showed that F_5 was significantly more flexible than F_{19}. Regarding their content uniformity, there was the maximum value for both formulations and no significant difference was shown. The results presented in the present study suggest that transdermal patches containing oxybutynin HCl may produce acceptable systemic concentration for therapeutic effect.

Keywords: Oxybutynin, patch, transdermal, gel.

INTRODUCTION

Transdermal drug delivery is an appealing alternative to many other types of administration. It offers good patient compliance and the possibility of controlled release over time, which avoiding possible degradation resulting from gastrointestinal tract or first pass liver degradation. The skin also provides a painless interface for systemic drug delivery (Khafagy *et al*., 2007). Transdermal patches are new approaches for enhancement of the efficacy of many therapeutic agents. They provide a relatively constant release which may lead to decreased side effects. There are two main classes of patches according to their mechanism of drug release (Barry, 2002; Uhrich *et al*., 1999) In membrane patches, a polymeric layer modifies the drug release, while in matrix or monolithic patches, a hydrophilic or hydrophobic polymeric matrix controls the release profile (Margetts and Sawyer, 2007). Oxybutynin is an antimuscarinic drug used to treat urinary tract disorders (Appell and Brantley, 2002). Discontinuing of the drug always occurs due to the adverse effects especially dry mouth (Staskin, 2003). Regarding its low oral bioavailability (about 6%), it was decided to formulate the drug in a relatively stable and more acceptable and bioavailable dosage form.

MATERIALS AND METHODS

Hydroxy propyl methyl cellulose (HPMC) and hydroxy ethyl cellulose (HEC), dibutylphthalate (DBP), Glycerin (GLY) and propylene glycol (PG) were purchased from Merck

Table 1. Amount of ingredients used in selected patch formulations containing 0.9% oxybutynin HCl.

	Polymer	Plasticizer			Release accelerator	Solvent		
Code		PG	Gly	DBP	Triacetin	Ethanol 70^0	Ethanol 95^0	Methanol/methylene chloride
F_3	HPMC 25%	12	13	-	-	50	-	-
F_5		16	9	-	-	50	-	-
F_7		7.5	8.5	-	9	50	-	-
F_{19}		16	-	-	9	50	-	-
F_{26}		12	4	-	9	-	50	-
E_3	HEC 25%	12	13	-	-	50	-	-
E_7		7.5	8.5	-	9	50	-	-
E_{10}		12	13	-	-	-	-	50
E_{12}		16	-	-	9	-	-	50
E_{14}		7.5	8.5	-	9	-	-	50

PG: propylene glycol, Gly: glycerin, DBP: dibutylphthalate

(Germany). Oxybutynin hydrochloride was obtained from PCAS Finland Oy (Finland). The solvents were of the analytical grade. The amount of drug in each formulation was 36 mg (Dmochowski *et al*., 2006), ethanol 60^o and 80^o, and methanol/methylene chloride (8:2 ratio) were used as solvents. Dibutylphthalate, glycerin and propylene glycol were utilized as plasticizers.

Preparation of gels

2g finely powdered HPMC was accurately weighed and dispersed in 30 ml preheated (90^0C) deionized water using an electric mixer. The volume of dispersion was raised to 100 ml while continuing mixing. 5% HEC gels were prepared by dispersing the powder in deionized water. The dispersions were heated to 70^0C and mixed gently until full dispersion. Then to achieve full deaeration and hydration, the samples were refrigerated for 24 hours (Nafee *et al*., 2003).

Formulation of patches

Polymers were separately mixed with different amounts of plasticizer and enhancers (table 1). The drug solution (0.9% w/w of total weight) was added and the mixture was stored at 30-32^0C for 24 hrs (Aquil *et al.*, 2003). Weights of the patches before solvent evaporation were considered to be 4g. Then the patches were placed on the Omnifilm® as a protective impermeable layer and a film of aluminum foil was placed on the patches as a disposable layer (Aquil *et al.*, 2003). A full factorial design was utilized to determine the effective range of concentration of solvents and the plasticizers. Too dry patches were excluded from the study. The patches were observed visually for completeness and surface texture. They were compared according to their film forming ability, clarity and transparency, homogeneity, ease of separation, and plasticity. The formulations with acceptable range of characteristics were analyzed for their ability of drug release, tensile strength, and hygroscopicity.

Hygroscopicity test

The formulations (10 samples of each) were dried at 60^0C for 4 hrs, and weighed accurately. Then they were placed in room temperature (19^0C, and 83% relative humidity) for 24 hrs, weighed again and their absorbed humidity was calculated.

Tensile strength determination

The patches (10 samples of each) were dried at 60^0C for 24 hrs. Then they were placed in an isometric transducer (Pioden Controls, UK) and the force required for their rapture was measured by an oscillograph (Harvard, UK).

Release study

In vitro release measurement was performed using a vertical Franz diffusion cell, in which the diffusion area was 3.46 cm^2 and dialysis membrane (cellulose, 12KD) was used as semi-permeable layer. Prior to the experiment, the membrane was immersed in deionized water for 24 hrs and then it was placed between the chambers. Donor chamber was containing formulated patches and the receptor compartment was filled with 0.1% HCl solution. The temperature was maintained at 32 ± 0.5^0C. While stirring at 600 rpm, 5 ml samples were drawn at definite intervals and subjected to UV-spectrophotometric analysis at 256.5 nm (BIO_TEK KONTRON INSTRUMENTS, Italy). To maintain the sink condition, it was replaced by 5 ml of the receptor phase (Dmochowski *et al*., 2006; Aquil *et al.*, 2003, Qvist *et al.*, 2002). The results were plotted as the release percent vs time (or log time). Comparing the R^2, SE and F, the release model was detected. Diffusion efficacy was also calculated for the most appropriate formulation by dividing the area under curve (AUC) of the samples by the AUC of hypothetical perfect release model (i.e. 100% release).

Content uniformity and weight variation

10 samples of each formulation were stored at 60 ^{o}C for 4 hrs, and then weighed. Weight average and standard error (SE) were calculated. Their active content was determined using a spectrophotometer (JASCO Model 7850) and the content uniformity was calculated by statistical methods (El Hamshary *et al.*, 2010).

Stability test

The samples were stored at 40 ^{o}C and 75 % humidity for 6 months and their tensile strength, release pattern and active content were compared with the initial data.

The effect of Polymer concentration

The effect of polymer concentration was studied for the most proper formula. Release rate from patches composed of 40, 45 and 50 percent polymer was determined by the mentioned method and compared together.

Statistics

All *in vitro* experiments were carried out in triplicate and presented as mean±standard error (SE). Statistical analyses of the

data were performed using ANOVA and students t- test with the level of significance set at $p < 0.05$.

RESULTS

The data from visual inspection and apparent characteristics such as film formation, clarity, ease of separation, flexibility, content uniformity and tensile resistance showed that only F_5 and F_{19} had better characteristics. Then, the selected formulations were analyzed for the properties such as hygroscopicity, tensile strength, content uniformity and release pattern. Amount of humidity absorbed by and F19 was 9.21±0.199 and 9.51±0.306 respectively. Statistical analysis of hygroscopicity data using Mann-Whitney analysis showed that there was no significant difference between the formulations (p= 0.2559). The results of tensile strength measurement showed 1.97 and 2.55 g. cm^{-2} for formulation F_5 and F_{19}, respectively. Statistical analysis showed that F_5 was significantly more flexible than F_{19} ($p<0.001$). Regarding their content uniformity, there was the maximum value for both formulations and no significant difference was shown.

Treated data of drug release from F_5 and F_{19} formulations versus time are plotted in Fig.1 It can be seen that there is a burst release from both formulations in the first hour of experiment. The phenomenon is due to constant release of drug molecules from the surface of patches, and often is seen with the majority of transdermal formulations. It also helps to achieve the effective therapeutic concentration in a short period of time. Regression analysis and statistical factors were conformed to Higuchi model rather than zero order kinetic. Higuchi coefficient for F_5 and F_{19} formulations were 0.4014 and 0.1821 respectively. Permeation coefficient for the formulations, calculated by trapezoid method, showed a relatively high value for F_5 (0.169) if compared with F_{19} (0.0756). Although F_5 had a relatively lower value of tensile strength, due to its higher release property, it was chosen as the best formulation and evaluated for the effect of polymer concentration.

Fig.2 shows the effect of polymer concentration on the release pattern of oxybutynin HCl patches. Analysis of F, R^2 and SE showed that formulations containing 40, 45 and 50 percent HPMC Higuchi model. The Higuchi coefficient value for f_5 40% was significantly more them of the others. The diffusion efficacy of the formulation was also considerably higher and there was a significant decrease in the efficacy with increasing the polymer content. The diffusion efficacies were 0.169, 0.148 and 0.121 for the formulations containing 40, 45 and 50 percent HPMC, respectively.

Weight Variation and content uniformity evaluation showed no significant difference with P values of 0.642 and 0.162, respectively between the formulations. Active content of the patches was 26.43±0.29 mg. Statistical analysis using Mann Whitney test showed no significant difference between the values of tensile strength, hygroscopicity and active content of the patches before and after three month of storage (P value of 0.489, 0.697 and 0.121, respectively). Furthermore, the release pattern of the patches after 3 months of storage was confirmed with Higuchi

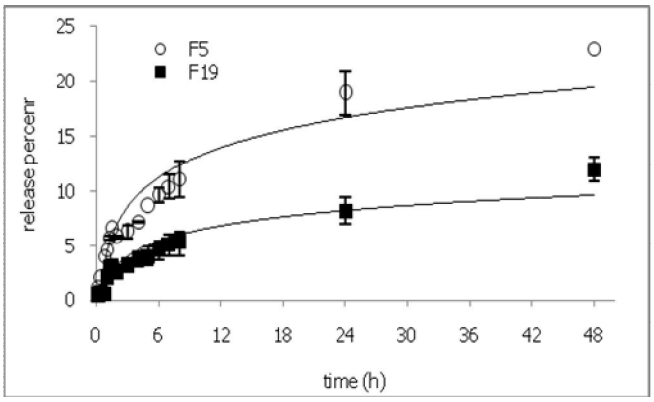

Fig1. Release profile of oxybutynin HCl from patch formulations F_5 and F_{19} (n=3-5).

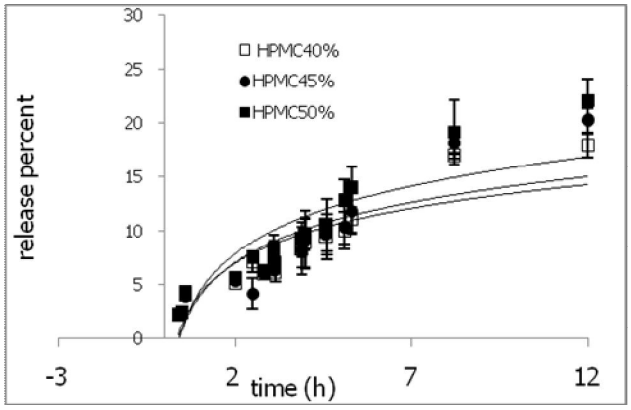

Fig2. Release profile of oxybutynin HCl from patches containing different HPMC concentrations (n=3-5).

model and there was no significant difference between their Higuchi coefficients and diffusion efficacies (P value of 0.136 and 0.295, respectively).

DISCUSSION

The importance of vehicle in the percutaneous absorption of drugs been well documented (Khafagy *et al.*, 2007; Thien Hai *et al.*, 2008; Godib and Touitou, 2007). HPLC and HEC have been known for a long time because of their effect on drug embedding and release from different delivery systems. Transdermal delivery provides a non-invasive rout of drug to the systemic circulation through skin layers. Visual inspection and physical characteristics of the patches made of HEC showed that in the most cases, there was on incompatibility between the polymer and other ingredient such as the solvent. The maximum acceptability was for the formula containing HEC, trieacetin, PG and ethanol. Also flexibility patches made of HEC, was not desirable In spite of instability of some formulation with manifestations such as phase separation and rigidity, the overall characteristics of HPMC based formulas were much desirable them HEC containing patches. There was a good cooperation between PG and triacetin to plasticize HPMC containing formulas. Glycerin did not act properly as a plasticizer and caused softening of patches. DBP caused phase separation maybe due to its hydrophobicity. High degree of hygroscpicity is generally considered as a good

characteristic for patches. Both formulations F_5 and F_{19} had good appearance and similar hygroscopicity about 10 % of their original weight, which was more than other reports. The tensile strength of the patches was comparable to the results from the other HPMC based patches. The range of acceptable tensile strength for HPMC matrices have been previously reported as 2-5 $g.cm^{-2}$ adjustment between high tensile strength and flexibility is one of the most important factors in design of matrix patches (Salaamat-Miller *et al*., 2005).

All of the formulations, that evaluated for release behavior conformed Higuchi model. There was a reverse relationship between the amount of HPMC in the patches and commutative release percent of oxybutynin. The phenomenon is probably due to the increase of the degree of enclosure of drug by polymer molecules. Data from *in vitro* release study also showed that there is about 4 mg release per day that seems to be adequate to maintain therapeutic concentration of the drug in systemic circulation.

CONCLUSION

Transdermal absorption is a multi factorial process affected by a number of factors including the type of membrane, delivery system and formulation factors. The present work was carried out to determine the effect of polymers, solvent and plasticizer of physical characteristics. The optimum formulation for in ultra permeation contained HPMC, 25 %, PG 16 %, triacetin 9 % and ethanol 70^0 50 %. The results presented in the present study suggest that transdermal patches containing oxybutynin HCl may produce acceptable systemic concentration for therapeutic effect.

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