EFFECT OF CHEMICAL ENHANCERS ON IN VITRO RELEASE OF SALBUTAMOL SULPHATE FROM TRANSDERMAL PATCHES

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ABSTRACT
The effect of combination of PG with DMSO, BC, IPM, Tween 80 and SLS on drug release rate was studied in vitro. The mechanism of drug release was also studied by using power law. Significant difference (One way ANOVA; $p<0.05$) in release rate among the 16 formulations was seen in the study. The release profiles of various formulations also showed that the added enhancers in individual batches affect the release rate of the drug. The concentration of DMSO and Tween 80 showed directly proportional where as concentration of BC and SLS showed inversely proportional relationship with drug release rate. The increase followed by decrease in drug release rate was seen with increase in IPM concentration. In most of the formulations, drug release occurred by diffusion partially through a swollen matrix and water-filled pores.

INTRODUCTION
A transdermal drug delivery is a formulation or device that maintains the blood concentration of the drug within the therapeutic window ensuring that drug levels neither fall below the minimum effective concentration nor exceed the minimum toxic dose [1]. Transdermal delivery of drugs promises many advantages over oral or intravenous administration, such as a better control of blood levels, a reduced incidence of systemic toxicity, an absence of hepatic first-pass metabolism, etc [2]. However, drugs should possess several physico-chemical prerequisites such as shorter half-life, small molecular size, low dose etc to be a suitable candidate for transdermal drug delivery system (TDDS) due to formidable barrier action of keratinized cells present in stratum corneum (SC) of skin. In order to permeate and absorb sufficient amount of drug to show the therapeutic effect, permeation should be enhanced. Many approaches such as use of chemical, physical, chemical-chemical, chemical-physical and physical-physical enhancers have been applied for permeation enhancement of drugs [3]. Chemical enhancers partition into and interact with the SC constituents to induce a temporary, reversible increase in skin permeability where as physical enhancers induce the skin permeability by using physical forces such as magnetic field, electric current, vibration etc. Combination of chemical-chemical, chemical- physical and physical-physical enhancers had been shown the synergistic effect in the permeation enhancement. However, it had been suggested that it would be better to choose the combination that works in a natural way (combination having different mechanisms of permeation enhancement) in order to obtain greater enhancement and to prevent the permanent and irreversible disruption in the skin [3]. Besides the natural combination, S. Mitragotri suggested controlling the amount of

combination of chemical enhancers in TDDS because of side effect due to deep accumulation of the enhancers under the skin.

Salbutmol/albuterol sulphate (SS) is an β-adrenergic agonist, which acts by stimulating β-adrenergic receptors. Its low dose, 1st pass metabolism and shorter half-life make it suitable for TDDS. However, its low permeability is the main barrier for using it in TDDS.

The chemical agents that had been incorporated in the present study had been shown permeation enhancement in the transdermal delivery of various drugs. The effect of surfactants {benzalkonium chloride (BC), sodium lauryl sulphate (SLS) and Tween 80} on the permeation of lorazepam had been studied by A. Nokhodchi et. al. [2]. Arellano et. al. studied the synergistic effect of Isopropyl myristate (IPM) and propylene glycol (PG) on the permeation of diclofenac sodium. [4]. Similarly, Soni et. al. examined the influence of dimethyl sulphoxide (DMSO) on the permeation of timolol maleate [5]. Funke et. al. had mentioned that PG has its own enhancing effect [6].

The objective of the present study was to examine the influence of different concentration of chemical enhancers with PG (0.6 ml) on the drug release rate and determine the mechanisms of the drug release from the corresponding transdermal patches.

MATERIALS AND METHODS

Chemicals and reagents:

Salbutamol sulphate, SS and Eudragit RL 100 (Rohm, Germany) were provided as a gift by Deurali Janta Pharmaceuticals Pvt. Ltd. (DJPL), Kathmandu, Nepal and Degussa, Bombay, India respectively. Similarly, LR grade of PG and DMSO (S.D. Fine-Chem Ltd., India), Propane -2-ol, Sodium hydroxide, SLS and Tween 80 (Qualigens Fine Chem,) and BC and IPM (CDH, India) were used. Aforementioned chemicals were used as supplied.

Fabrication of patches:

Solvent casting method was used to prepare the drug loaded as well as placebo patches. Pellets of Eudragit RL 100 were dissolved in an isopropanol-water mixture (6:4) by means of magnetic stirrer in conical flask closed with a stopper. The PG and SS were added to the polymer solution and were dissolved. The volume was made up with the solvent and was kept for about 10 minutes to facilitate mixing. The solution was casted on an aluminium foil of size 10cm×10cm×1cm, which was kept on a labeled glass surface of a mould (10 cm×10 cm×1cm). The solvent from the polymer was allowed to evaporate at 40±10° C for 24 hours approximately. The resultant films were peeled off from the mould, cut into the size of a metal sheet having radius 1.15 cm, wrapped between the aluminium foil and stored in a desiccator until further use. A total of 16 formulations and their corresponding placebos were prepared.

1.1 Release studies

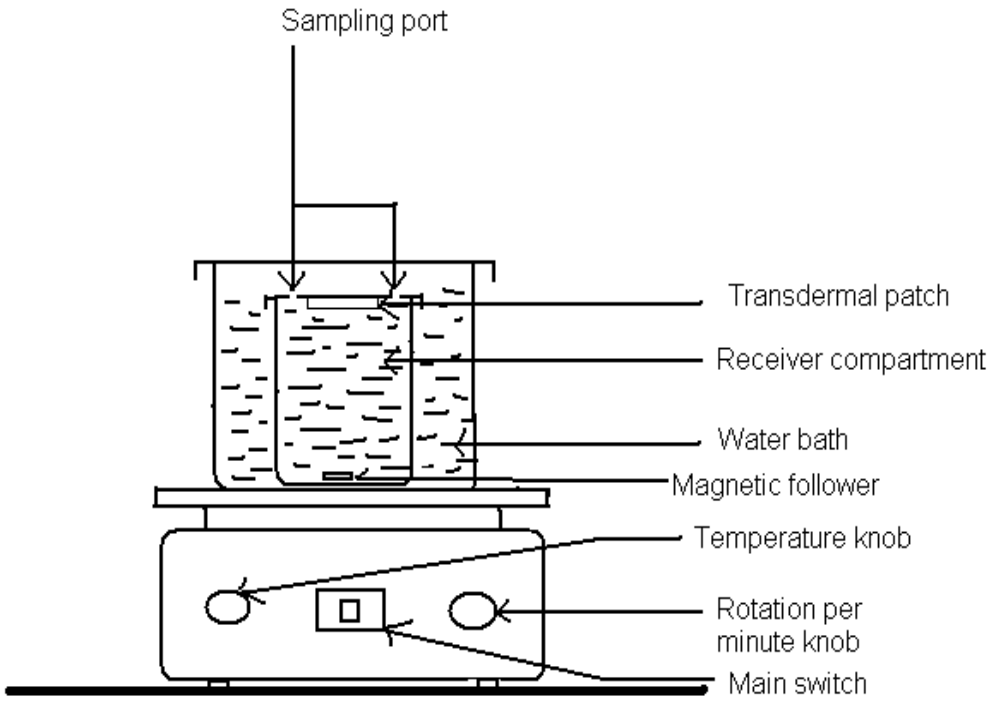

Fig. 1: Apparatus for release study.

The patch understudy was coated with glue on the seam and backing membrane (aluminum foil) of the patch was glued on inner surface of the lid facing the matrix surface towards the receiver fluid such that the two sampling ports were kept open. The set up of dissolution apparatus containing receiver fluid (distilled water, 37 ml) and water bath (Fig. 1) was heated on a magnetic stirrer with thermostat until the temperature was maintained at 37°C ± 2°C. When the set temperature was achieved, the lid having patch glued on it was replaced on the cell and to maintain the hydrodynamics of the receiver fluid, the rotation of the magnetic bead was maintained at 150 ± 50 rpm.

Analytical procedure:
Sample (1 ml) from the cell was withdrawn at predetermined time intervals for 12 hours in release study. Sample was filtered using G2 filter (Borosil®) in a 10-ml volumetric flask and 3 ml 0.1M NaOH was added. Volume was made up to 10 ml with distilled water. The absorbance was taken in uv-visible spectrophotometer at 245 nm [7].

Data treatment:
Power law was used to describe the mechanism of drug release from the patch [8]:

$$\frac{M_t}{M_\infty} = kt^n$$

Or, $$\log \frac{M_t}{M_\infty} = \log k + n \log t$$

Where M_t and M_α are cumulative amount of drug released at time t and infinite time respectively, k represents constant incorporating structural and geometric characteristics of the device, n is the release exponent, indicative of the mechanism of drug release.

Order of reaction was determined by graphical method. The equation for zero order of reaction is as follows:

$A_o - A_t = k_o t$

Where $A_o - A_t$ is the amount of drug released at time t, k_o represents rate constant, t is time.

Mean of $A_o - A_t$ (n = 3) was calculated and a graph of $(A_o - A_t)$ versus t was plotted for each batch. A trendline passing through the origin was drawn to see whether it followed zero order of release or not was confirmed by the value of degree of correlation (r^2).

Drug release in first order reaction was dependent on the concentration of drug and thus its equation is stated as follows:

$$\text{Log } \frac{C_o}{C} = \frac{kt}{2.303}$$

Where C_o is initial concentration of drug, C represents concentration remained at time t and k denotes rate constant.

Mean of $\text{Log}\frac{C_o}{C}$ (n = 3) was calculated and a graph of $\text{Log } \frac{C_o}{C}$ versus t was plotted for each batch. A trendline with y-intercept was drawn and the obtained degree of correlation (r^2 value) was used to confirm whether it followed first order release or not.

As the patch was of homogenous matrix type, the observed release values were also fitted in the Higuchi equation [8]:

$$Q = [D (2A - C_s) C_s t]^{1/2}$$

Where Q represents amount of drug released at time t per unit area of exposure, C_s is the solubility of the drug in polymeric matrix, D denotes diffusion coefficient of drug in the matrix and A is the amount of drug per unit volume.

Mean of Q value (n=3) was calculated and a graph of Q versus $t^{1/2}$ was plotted. A trendline passing through the origin was drawn to see whether it followed Higuchi equation or not was determined by observing the r^2 value of the graph and trendline.

The order of reaction followed by the particular formulation was determined on the basis of the highest r^2 value among the graphs obtained by fitting the data in 1st order, zero order and Higuchi equations.

One-way anova was applied to examine the similarity or difference in drug release and permeation rate among the formulations by means of software, SPSS (Ver. 10).

RESULTS AND DISCUSSION

Release study was carried out in 16 formulations of SS for 12 hours using distilled water as a receiver fluid [9]. Out of 16 formulations, B_2, B_4, B_5, B_{14} and B_{15} followed Higuchi equation where as the remaining batches followed 1st order kinetics (Table 1). It has been reported that formulation that comprised the drug above the saturation concentration in the form of a suspension gave rise to drug release profiles that followed Higuchi model [1]. It had also been mentioned that if excess solid was not present in the delivery form, thermodynamic activity decreased as the drug diffused out of the device and the drug release rate fell exponentially resulting 1st order release [10]. Therefore, the complete or incomplete dissolution (excess or inexcess solid form) of the drug in the device could be the reasons for following either Higuchi equation or 1st order release in the study.

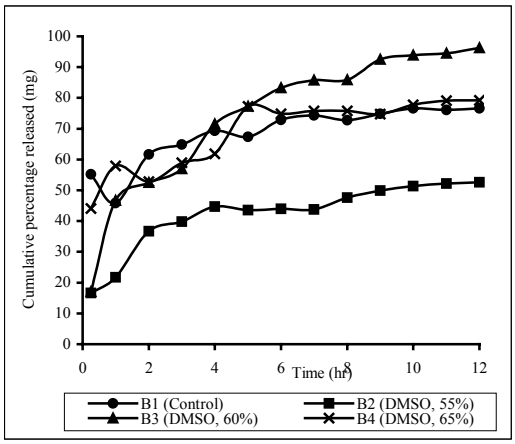

Fig. 2: Release profiles of salbutamol sulphate from DMSO and PG containing matrix of Eudragit RL 100 (n=3).

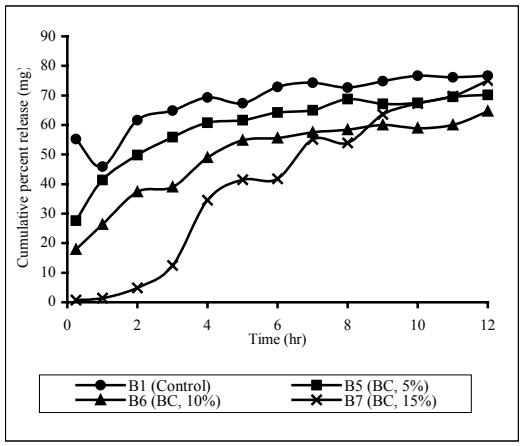

Fig. 3: Release profiles of salbutamol sulphate from BC and PG containing matrix of Eudragit RL 100 (n=3).

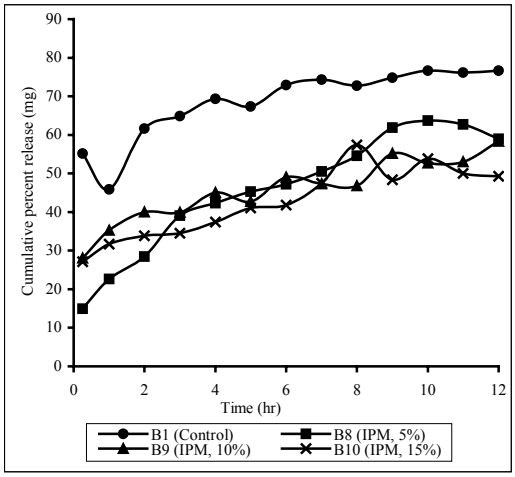

Fig. 4: Release profiles of salbutamol sulphate from IPM and PG containing matrix of Eudragit RL 100 (n=3).

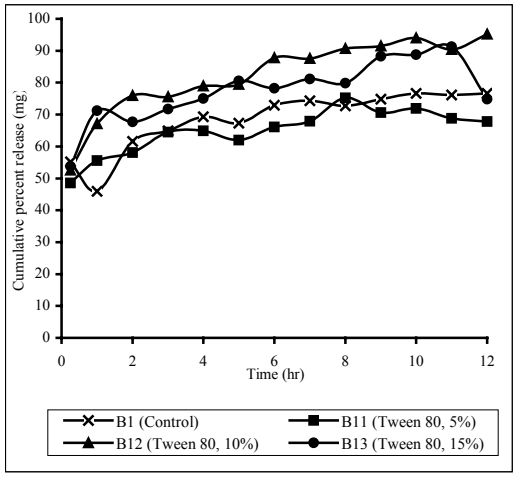

Fig. 5: Release profiles of salbutamol sulphate from Tween 80 and PG containing matrix of Eudragit RL 100 (n=3).

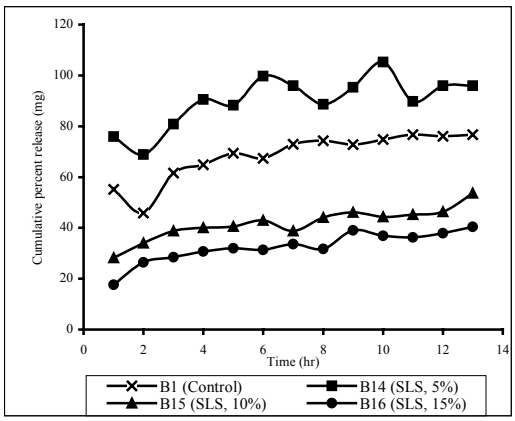

Fig. 6: Release profiles of salbutamol sulphate from SLS and PG containing matrix of Eudragit RL 100 (n=3).

The drug release profiles of patches containing DMSO, BC, IPM, Tween 80 and SLS with PG (0.6ml) are shown in Figs. 2-6. The drug release rate of the formulations was found to be directly proportional to the increase in concentration of DMSO (B_2-B_4) and Tween 80 (B_{11}-B_{14}) where as it was just opposite in the case of batches containing BC (B_5 – B_7) and SLS (B_{14} –B_{16}). It has been reported that DMSO has relative polar nature and small and compact structure [5,11]. Because of the polar nature of SS, DMSO and fluid of the receiver compartment (distilled water) as well, solubility of DMSO and SS could be higher in the fluid, which could lead to the higher diffusion/release rate. Like DMSO, Tween 80 had also hydrophilic property (HLB 15). Therefore, concentration of drug at which there is no molecular interaction (activity) could present in Tween 80 and receiver fluid mixture also. Concentration of surfactants above critical micelle concentration, cmc, could make micelles of drug, which could be difficult to diffuse out from the matrix. Thus, it could retard the release rate of the drug. Therefore, the relationship between the concentration of Tween 80 and drug release rate could be due to its hydrophilic nature and its concentration below cmc. The decrease in drug release rate with increase in concentration of BC and SLS could be due to the formation of micelles in which drug molecule might get entrapped into it. Because of the larger size of the micelle, it cannot easily diffuse out of the patches due to the structure of the matrix. Greater the amount of surfactant above cmc, greater the drug entrapment inside the micelle and thus, drug release rate could be retarded more. Formulations containing IPM (B_8 – B_{10}) showed increase followed by decrease in drug release rate with increase in IPM concentration even though Arellano et. al found decrease in drug (diclofenac sodium) release rate with increase in concentration of it [4]. IPM is an unsaturated fatty acid ester with branched structure. IPM could make hindrance for the drug release if it is remained in the matrix. So drug release rate is directly proportional to the release rate of IPM. Arellano et. al. stated that the solvent drag effect due to PG exists for IPM [4]. Therefore, IPM can release from the matrix even though it is totally insoluble in water (receiver fluid) but only the limited amount of IPM can release from the matrix due to constant amount of PG. At lower IPM concentration there could be the lower solvent drag effect so that there is lower release rate of IPM. At higher concentration of IPM, higher solvent drag effect could exist for IPM so that IPM release rate can increase but the constant amount of PG cannot be sufficient to release all the IPM from the matrix. Therefore, the IPM, which remains into the matrix, will make hindrance for the release of drug and decrease the release rate of the drug.

The release exponent (n value) of different formulations ranged from 0.1046 to 1.4206 (Table 1). B_3, B_6 and B_8 followed anomalous transport ($0.5<n<1.0$) indicating both diffusion and swelling controlled release [8]. The remaining formulations showed n value less than 0.5 except B7. The drug diffusion partially through a swollen matrix and water-filled pores in the formulations could be the reason for smaller value of release exponent ($n<0.5$). B_7 ($n = 1.4206$) showed Super-Case-II transport [12].

Table 1 : Physical characteristics of different batches of patches (n=3 except the stated condition).

Formulations	Release order	n value
B1 (PG; 0.6ml)*	1st	0.1305
B2 (DMSO; 55%)	Higuchi	0.3033
B3 (DMSO; 60%)	1st	0.6178
B4 (DMSO; 65%)	Higuchi**	0.1307
B5 (BC; 5%)	Higuchi	0.3097
B6 (BC; 10%)	1st	0.5243
B7 (BC; 15%)	1st	1.4206
B8 (IPM; 5%)	1st	0.6048
B9 (IPM; 10%)	1st	0.1944
B10 (IPM; 15%)	1st **	0.1597
B11 (Tween 80;5%)	1st **	0.1213
B12 (Tween 80;10%)	1st **	0.1302
B13 (Tween 80;15%)	1st **	0.1046
B14 (SLS; 5%)	Higuchi	0.0854
B15 (SLS; 10%)	Higuchi	0.1325
B16 (SLS; 15%)	1st **	0.1839

$B_2 – B_{16}$ also contain PG (0.6 ml); * denotes control ; ** = r^2 value less than 0.85; n = Release exponent; hr = hour.; PG = Propylene glycol; DMSO = Dimethyl sulphoxide; BC = Benzalkonium chlorode;
IPM = Isopropyl myristate; SLS = Sodium lauryl sulphate.

Significant difference (One way anova; $p < 0.05$) in drug release rate was seen among the formulations.

CONCLUSION

The effects of the combination of PG with different concentration of DMSO, BC, IPM, Tween 80 and SLS as enhancers in the release of SS from monolithic matrix of Eudragit RL 100 were examined. Most of the formulations followed 1st order kinetics. The release profiles (Figs. 3 to 7) showed that release rate of the drug is dependent on concentration and types of enhancers. The directly proportional relationship between release rate of the drug and concentration of DMSO and Tween 80 suggests that even greater than 65% DMSO and 15 % Tween 80 may enhance the release rate of SS but less than 5% SLS and BC of total formulation is suggested to use as enhancers to increase the release rate of SS. The maximum enhancing effect of IPM on drug release rate was found in between 5 and 10% of it in total formulation. The effect of drug release rate from the transdermal patches could be significant, specially, in permeation of drugs having neither hydrophilic nor lipophilic totally (logarithm of partition coefficient, Log P = 1 to 4).

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REFERENCES

1. Y. N. Kalia and R. H. Guy, 2001. Modeling trans-dermal drug release. Adv. Drug Del. Reviews, 48:159-172.

2. A. Nokhodchi, J. Shokri, A. Dashbolaghi, D. Hassan-Zadeh, 2003. The enhancement effect of surfactants on the penetration of lorazepam through rat skin, Int. J. Pharm. 250:359-369.

3. S. Mitragotri, 2000. Synergistic effect of enhancers for transdermal drug delivery. Pharm. Res. 17(11):1354-1359.

4. A. Arellano, S. Santoyo, C. Martin and P. Ygartua, 1998. Influence of propylene glycol and isopropyl myristate on the in vitro percutaneous penetration of diclofenac sodium from carbopol gels. Eu. J. Pharm. Sci. 7:129-135 .

5. S. Soni, S. K. Jain and N. K. Jain, 1992. Effect of penetration enhancers on Transdermal delivery of timolol maleate. Drug. Dev. Indus. Pharm. 18 (10): 1127-1135.

6. A.P. Funke, R. Schiller, H. W. Motzkus, C. Gunther, 2002. Transdermal delivery of highly lipophilic drugs: in vitro fluxes of antiestrogens, permeation enhancers, and solvents from liquid formulations. Pharm. Res. 19 (5): 661-668.

7. N. P. Dhakal, 2001. Evaluation of matrix based buccoadhesive salbutamol sulphate compact., M.Pharm. dissertation. Kathmandu University library, 1-2.

8. J. Siepmann, N. A. Peppas, 2001. Modeling of drug release from delivery systems based on hydroxy propyl methyl cellulose (HPMC), Adv. Drug Del. Reviews. 48:139-157(2001).

9. E. Touitou, 1986. Transdermal delivery of anxiolytics: in vitro skin permeation of midazolam maleate and diazepam, Int. J. Pharm. 33:37-43.

10. A. Martin, 1995. Diffusion and dissolution. Physical Pharmacy, B. I. Waverly Pvt. Ltd., 325-342.

11. H. H. Szmant. Physical properties of dimethyl sulfoxide and its function in biological sytems http://www.dmso.org/articles/information/pszmant.htmlWertwt.

12. N. A. Peppas, 1985. Analysis of fickian and non-fickian drug release from polymers. Pharm. Actahelv. 60(4): 110-111.