Journal of Kerbala University , Vol. 13 No.2 Scientific . 2015

Enhancement effect of almond oil on transdermal penetration of flurbiprofen topical gel

تأثير زيت اللوز على النفوذية الجلدية لمادة (flurbiprofen topical gel)

Muder AL Haydar, PhD
Department of pharmaceutics, College of Pharmacy, University of Kerbala, Iraq
muder.alhaydar@poatgrad.curtin.edu.au

Abstract

Flurbiprofen is related to nonsteroidal anti-inflammatory drugs. The aim of this study is to investigate use of almond oil as enhancer to increase drug skin penetration. Five selected formulas of flurbiprofen gel with five different concentration of almond oil were prepared. Only one formula was prepared without almond oil. The prepared gels were evaluated for several physico-chemical parameters to justify their suitability for topical use. The *in vitro* drug release studies were carried out by using Franz cell diffusion apparatus across synthetic membrane. The permeation profile of various formulations also showed that the adding an enhancer in individual formula affected the permeation of the drug. Drug permeation increased with increased concentration of almond oil.

keywords : flurbiprofen, almond oil, transdermal, hydrogel, kinetics release.

الخلاصة

فلوربايبروفن يعود الى الادوية المضاد للالتهاب الغير ستيرويدي . الهدف من هذه الدراسة هو معرفة تاثير زيت اللوز كماده محفزة على زيادة نفاذية الدواء للجلد. حضرت خمسة صيغ من مستحضر جل الفلوربايبروفن مع مختلف النسب من زيت اللوز. كما حضرت صيغه واحد من الجل بدون زيت اللوز. جميع الصيغ المستحضرة فحصة من الناحية الفيزياوية والكيمايوة لمعرفة ثباتية وملائمة المستحضر للجلد. دراسة التحرر الدوائي في المختبر قد تمت من خلال استعمال الفرانز سل باستعمال الغشاء المصنوع. وضع النفاذية لمختلف الصيغ تظهر تأثير المحفز على نفاذية الدواء. نفاذية الدواء قد ازدادت كلما زاد تركيز زيت اللوز المستعمل .

1. Introduction

The transdermal route, as a drug delivery system, is frequently regarded as a safe rout of drug administration. This rout is characterized by a low bioavailability of drugs because of the skin barrier functions (1). This route also can provide constant drug release and avoid the first past metabolism by GIT (2). Flurbibrofen when administered orally exhibits poor bioavailability, due to low aqueous solubility and slow dissolution in water (3). Therefore to improve its bioavailability, an attempt was made to develop transdermal flurbibrofen gel. The amount of drug required for therapeutic effect in transdermal drug delivery system is less bio available as compared to oral route of administration, but the absorbed drug appears to be adequate for therapeutic uses (3). It has poor water bioavailability due to its poor water solubility (10.45 ± 3.2µg/ml). Gels are semisolid dosage form that has a three-dimensional polymeric matrix in which a liquid phase is constrained in which a high degree of physical (or sometimes chemical) cross-linking has been introduced. The way to improve the penetration of certain drugs via transdermal route could be achieved by the use of penetration enhancers (4). Olive and almond oil as skin penetration enhancer in various

concentrations significantly enhances the penetration of drug from transdermal gels and patch across synthetic membrane/rabbit skin (4, 5, 6).

Drugs can be concentrated or trapped within the polymer and released through diffusion mechanisms based on zero-order kinetics. The intrinsic properties of the hydrogel, the drug-polymer interactions, amount of entrapped drug, and drug solubility determine the diffusion kinetics, duration, and rate of solute release from the hydrogel(7)

Transdermal drug delivery has many advantages among them providing a controlled release of drug which provides a steady blood level profile, avoiding first-pass hepatic metabolism, potentially decrease side effects and the rapid termination of therapy in problematic cases(8).

The aim of this study is to develop a stable and suitable flurbiprofen hydrogel. And to investigate the penetration effect of almond oil as skin enhancer.

2. Experimental

2.1. Material

Flurbiprofen (FDC limited India), carbapol (Sigma Chemicals, USA), almond oil (Hemani live natural, Pakistan), Potassium di-hydrogen phosphate, Sodium hydroxide (Merck, Germany).

2.2. Equipment

UV spectroscopy (SCO-Tech model: SPUV-26 Germany), Magnetic stirrer, pH meter (Hanna USA), Weighing balance, synthetic membrane, Franz cell (SES GmbH, Germany).

2.3. Standard calibration curve of flurbiprofen

The standard calibration curve of flurbiprofen was constructed by plotting of absorbance values against different dilutions of flurbiprofen (2.5, 5, 10, 15 and 20 µg/ml) in phosphate buffer solution at pH 7.4. All the samples were analyzed for drug absorbance through UV spectrophotometer at 247 nm.

2.4. Preparation method of drug hydrogel

Flurbiprofen hydrogel was developed by dispensing 0.5 g carbopol (940) in 35 ml deionized water and was stirred with the help of magnetic stirrer until a homogeneous dispersion was obtained. In another step 0.5 g flurbiprofen was mixed in 3 ml 96% ethanol and sonicated to get a solution of complete dissolved drug. The drug solution was added separately to the each formula of carbopol (940) dispersion drop-wise with the help of syringe and was stirred continuously. An enhancer almond oil was added in different concentrations to 5 different formulas; one being blank ;without enhancer, and the others having different concentrations of enhancer i.e. 1%, 2%, 3%, 4% and 5% respectively as described in table 1. A solution of 1 ml of triethanolamine drop wise was added and mixed well for all formulas. The final volume was made up to 50 ml by adding sufficient quantity of deionized water and again stirred until a homogenous transparent gel was obtained.

Table 1. Formulation of 1% (w/v) flurbiprofen transdermal hydrogel

Formula no.	Flurbiprofen	Carbopol 940	TEA	Ethanol 96%	Almond oil	Deionized water
F1	1%	2%	0.5 mL	3 mL	0	to 50 mL
F2	1%	2%	0.5 mL	3 mL	1%	to 50 mL
F3	1%	2%	0.5 mL	3 mL	2%	to 50 mL
F4	1%	2%	0.5 mL	3 mL	3%	to 50 mL
F5	1%	2%	0.5 mL	3 mL	4%	to 50 mL
F6	1%	2%	0.5 mL	3 mL	5%	to 50 mL

2.5. Evaluation of gel properties

2.5.1. Organoleptic properties

The organoleptic properties of flurbiprofen hydrogel such as color, liquefaction, phase separation and homogeneity were investigated by visual inspection at various intervals such as 1st, 2nd, 5, 10, 20, 30, and 50 days.

2.5.2. pH changes

The pH value of the prepared flurbiprofen hydrogel formulas were determined by pH-meter. For all formulas, pH measurement were investigated at zero time and after 1, 5, 10, 20, 30, 40 and 50 days of preparation time.

2.5.3. Skin irritation test

Skin irritation test of flurbiprofen topical hydrogel was performed on human volunteers to find out any irritation problems which could reject its suitability for topical use. Approximately 1 gm from each formula of hydrogel was topically applied to deffernt groups of six volunteers. The gel application was on the hand of volunteer near the wrist to a 2 square inch area and were observed for any lesions or irritation or redness.

2.5.4. Drug content

A quantity of (100 mg) of the developed gel for each formula was separately dissolved in 100 ml of phosphate buffer pH 7.4. The mixture was stirred for sufficient time to get complete solubility of drug. The resultant mixture was filtered through membrane filter pore size 0.45 mm. The absorbance of each sample was determined at 247 nm. The concentration of flurbiprofen was evaluated from the regression equation of the calibration curve (9).

2.6. In vitro permeation and release kinetic study

The in-vitro drug penetration from gel formula across synthetic membrane was investigated by using Franz diffusion cell. The effective diffusional surface area of 0.8 cm^2 and a receptor cell volume of 5 ml. The receptor compartment was filled with phosphate buffer solution at pH 7.4. The synthetic membrane was fixed between the donor and receptor compartment of Franz cell. Approximately 1g of gel installed in the donor compartment. The temperature of the cell was maintained at 37 ^oC by surrounding water in jacket and the medium was stirred by magnetic stirrer at 100 rpm. The samples of 2 ml were collected from the receptor compartment at subsequent

intervals and replaced with equal volume of fresh buffer solution to keep the volume constant. The amount of flurbiprofen in the samples were analyzed in the comparison to their absorbance values at 247 nm.

Korsmeyer Pappas kinetic model was applied in order to find out the drug release mechanism (7). The in vitro drug release mechanism of flurbiprofen was determined by putting the in vitro penetration values in Korsmeyer Pappas equation:

$$Mt / M\infty = K\, t^n$$

Where Mt / M∞ represent the fractional drug release from formulation into the receptor solvent, K is a drug delivery constant and (n) is diffusion coefficient and its value in equation indicates the release mechanism of the drug in solvent. The value of (n) if equal to 0.5 indicates Quasi-Fickian diffusion mechanism, if (n>0.5) then anomalous or non-Fickian diffusion mechanism exists and if its value is (=1) then Zero order release mechanism exists.

3 Results and discussion

3.1 Calibration curve development

The standard calibration curve of flurbiprofen exhibited a linearity of the detector response for a range of flurbiprofen concentrations with a regression coefficient (R^2) of 0.9995 as shown in Figure (1)

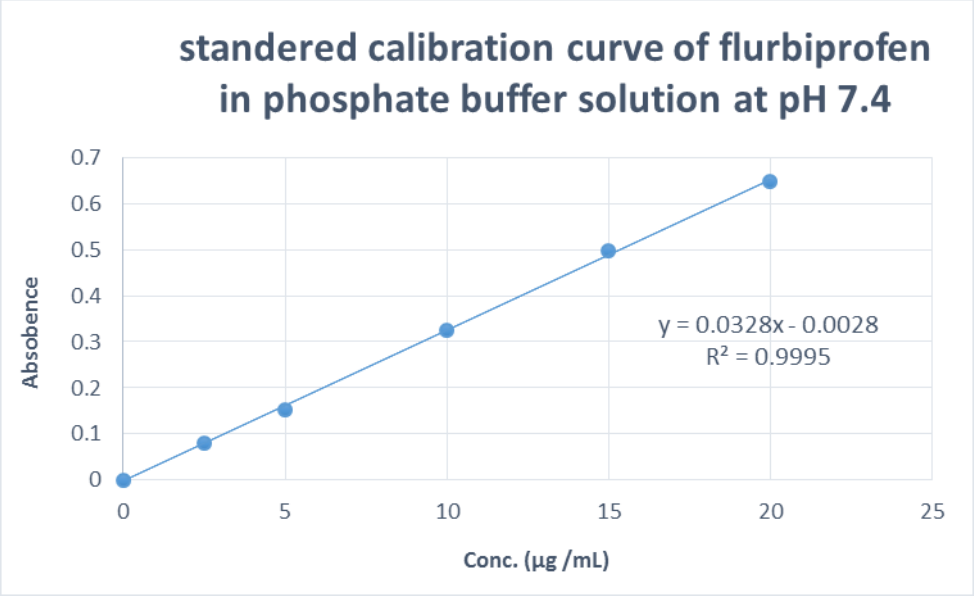

Figure (1) standard curve of flurbiprofen gel .

3.2 Evaluation of gel properties

Flurbiprofen topical gel in the presence almond oil was evaluated for various organoleptic properties to check its suitability and stability for transdermal use. All the formulas revealed no color change, liquefaction and phase separation along 50 days from beginning time of gel formulation as shown in table 2. This indicated that all formulas were stable.

The homogeneity of all formulas were investigated by visual inspection. The gels were filled into narrow transparent glass tubes and were checked in light for the presence of any particulate or lump (12). It showed no lump and has good homogeneity.

After the gel application to skin of human volunteers, there were no signs and symptoms of lesions, redness and itching found as shown in table 2. This result indicated that flurbiprofen hydrogel in the presence almond oil is suitable for human skin.

The drug content of each formula was fairly sufficient as shown in table 2. This indicated that all formulas have good content uniformity.

3.3 pH stability

The pH values of the flurbiprofen hydrogel are show in table (3) indicated no significant changes in the pH value of all formulas during 50 days of storage in ambient temperature. This indicated that all formulas demonstrated good stability. The range of pH value are suitable to the skin pH range which is normally between 5.5 to 6.5.

Table 2. Organoleptic properties of flurbiprofen gel

Parameters	F1	F2	F3	F4	F5	F6
Color	*W	W	W	W	W	W
Liquefaction	-	-	-	-	-	-
Phase separation	-	-	-	-	-	-
Homogeneity	good	good	Good	Good	Good	Good
Skin irritation test	No	No	No	No	No	No
Drug content	97%	95.8%	96%	96%	97%	96.4%

W* (weight color)

Table 3. pH stability of flurbiprofen during storage at ambient temperature

Time (day)	pH value					
	F1	F2	F3	F4	F5	F6
0	5.5	6.1	6.0	6.5	6.5	6.8
1	5.5	6.2	6.0	6.6	6.5	6.8
5	5.8	6.4	6.3	6.5	6.7	6.9
10	5.8	6.3	6.3	6.4	6.8	6.6
20	5.7	6.3	6.4	6.6	6.9	6.8
30	5.9	6.5	6.5	6.6	6.8	6.8
50	6.1	6.6	6.7	6.8	6.8	6.9

3.4In vitro drug penetration studies

The percent drug release of flurbiprofen from topical gel across synthetic membrane is shown in figure 2. Drug release percent from the formula, which is without almond oil enhancer, was very small and only up to 35% drug was penetrated across synthetic membrane into the receptor solvent in 24 hr. Significantly there was an increase drug penetration observed from all formulas having almond oil. The percent penetration was reached to a maximum 72% in the presence of 1% almond oil and the percent penetration of drug was increased by increasing the concentration of almond oil and a maximum 91% drug penetration was observed from the formula having 5% almond oil. This is significantly indicated that as almond oil concentration increase of almond oil

the drug diffusion increased. By modifying the barrier properties of stratum corneum when the amount of flurbiprofen penetrated was increased when the concentration of penetration enhancer was increased

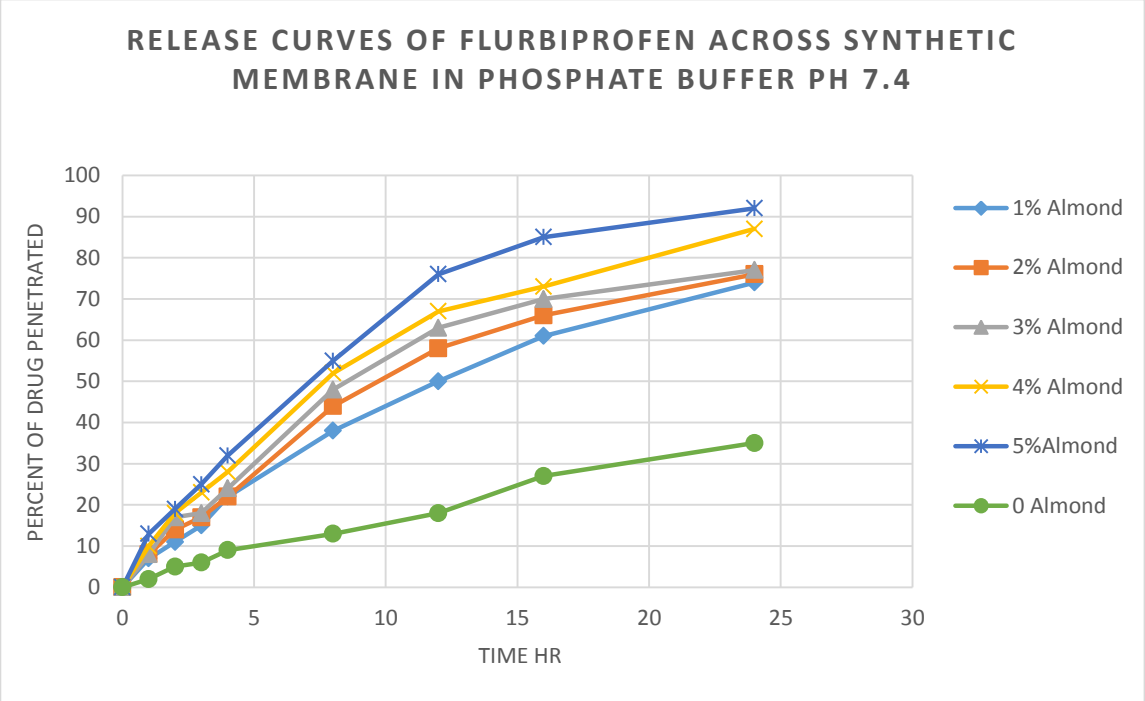

Figure 2. Release curves of flurbiprofen across synthetic membrane in phosphate buffer pH 7.4

3.5 Drug release kinetics

In order to investigate the mechanism involved in the release of flurbiprofen from topical gel, a kinetic approach was made by employing Korsmeyer Pappas kinetic model to the in vitro drug release profiles. As discussed earlier an (n) value in Korsmeyer Pappas equation represents the way by which the drug is released from the gel formulation across synthetic membrane/rabbit skin into the receptor solvent. By employing the kinetic model the values of (n) were (1<n>0.5) indicating that two release mechanism were involved in the release of flurbiprofen from transdermal gel, non-Fickian (anomalous) and super case II transport

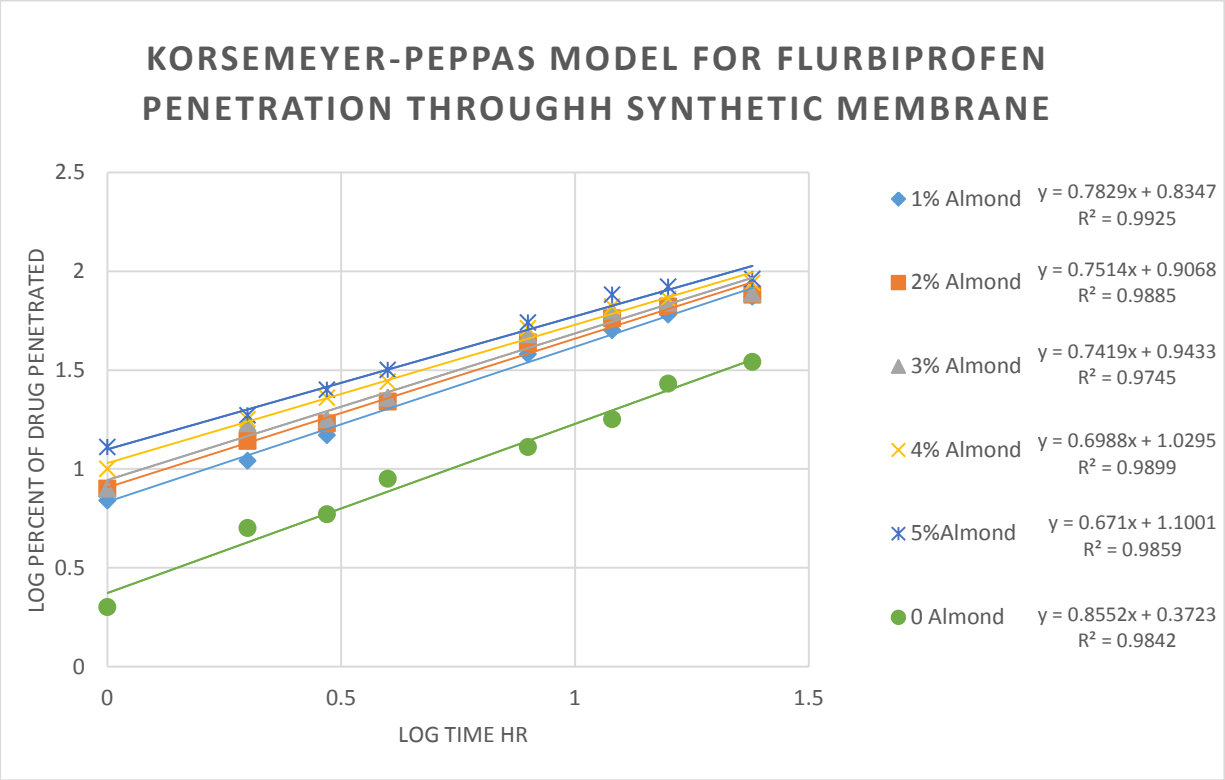

Figure 3. Korsemeyer-peppas model for Flurbiprofen penetration through synthetic membrane.

4 Conclusion

Developing of flurbiprofen gel in the presence of almond oil as an enhancer demonstrated a good stability and suitability to the human skin. Almond oil demonstrated penetration enhancement with all prepared formulas. The diffusion enhancement increases with increase the percent of almond oil

References

1. Francesco C, Paola M, Antonella C, Leila T, Stefania P and Luisa M (2005). Polymethacrylates as crystallization inhibitors in monolayer transdermal patches containing ibuprofen. *Eur. J. Pharm. Biopharm.*, **60**: 61-66.
2. Shubhika Kwatra*, Guncha Taneja, Nimisha Nasa. Alternative Routes of Drug Administration-Transdermal, Pulmonary & Parenteral. Indo Global Journal of Pharmaceutical Sciences, 2012; 2(4): 409-426
3. Dong Eli, Moy JH, Prabagar B, Yi Dong Y, Doon HO, Jung HJ et al. Enhanced oral bioavailability of flurbiprofen by combined use of micelle solution and inclusion compound. Arch Pharm Rev 2010; 33(1): 95-101.
4. Syed NHS, Mahboob R and Muhammad FA (2006).Study of percutaneous absorption of diclofenac diethylamine in the presence of cetrimide through hairless rabbit skin. J. Res. Science, 17(1): 45-51.
5. Hussain A, Khan GM, Shah SU and Rahim N, Development of a novel Ketoprofen transdermal patch: Effect of almond oil as penetration enhancer on in-vivo and ex- vivo penetration of Ketoprofen through rabbit skin Pak J pharm Sci,2012; 25(1): 227-32.
6. Hussain A[1], Khan GM, Jan SU, Shah S, Shah K, Akhlaq M, Rahim N, Nawaz A, Wahab A. Effect of olive oil on transdermal penetration of flurbiprofen from topical gel as enhancer. Pak J Pharm Sci. 2012 Apr;25(2):365-9.

7. Suvakanta dash1*, Padala narasimha murthy2, Lilakanta nath. Kinetic modeling on drug release from controlled drug delivery systems. Acta Poloniae Pharmaceutica ñ Drug Research, Vol. 67 No. 3 pp. 217ñ223, 2010
8. Donatella P, Cinzia A, Steven N, Giovanni P and Massimo F (2002). Lecithin microemulsions for the topical administration of ketoprofen: Percutaneous adsorption through human skin and in vivo human skin tolerability. Int. J. Pharm., 244: 21-31.
9. Singh MC, Naik AS, Sawant SD. Transdermal drug delivery systems with major emphasis on transdermal patches: a review. J Pharm Res. 2010 Oct;3(10) :2537-43.
10. Sera UV and Ramana MV (2006). *In vitro* skin absorption and drug release-a comparison of four commercial hydrophilic gel preparations for topical use. *The Indian Pharmacist*, **73**: 356-360.
11. Dash S1, Murthy PN, Nath L, Chowdhury P. Kinetic modeling on drug release from controlled drug delivery systems. Acta Pol Pharm. 2010 May-Jun;67(3):217-23.
12. Shivhare UD, Jain KB, Mathur VB, Bhusari KP, Roy AA and Sharad (2009). Formulation development and evaluation of diclofenac sodium gel using water soluble polyacrylamide polymer. Digest J. Nanomat. Biostruct., 4: 285-290.