Preparation and Evaluation of ketoprofen as Dermal Spray Film

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ABSRACT

Ketoprofen is one of the very potent and safe non steroidal anti-inflammatory drugs (NSAIDs) that belong to the propionic acid derivatives group. The aim of this study was to prepare spray film of ketoprofen and evaluate its properties as pH, viscosity, volume of solution delivered per each actuation, spray angle, evaporation time, content uniformity, and in vitro drug release. Different types of film forming polymer were investigated. The best formula containing mixture of 0.05% w/w poloxamer 407 and 0.05% w/w carbopol 940 was found to have pH, content uniformity, viscosity, drying time, volume per each actuation, and spray angle of 5.2, 100.6%, 1.5 mpse, 91sec., 0.09 ml, and 79.9^0 respectively. Drug release of the selected film was found to be 49.7% at 20 hrs with kinetic release of Higuchi model (R^2 of 0.9). Based on abstained results, it was concluded that ketoprofen can be prepared as dermal spray film using a mixture of 0.05% w/w for both poloxamer 407 and carbopol 940 as film forming polymer.

تحضير وتقييم الفلم الرذاذي الجلدي للكيتوبروفين

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مفتاح الكلمات: الفلم الرذاذي, كيتوبروفن, تحرير الدواء خارج الجسم و ميكانيكية تحرير الدواء.

الخلاصة

كيتوبروفين هو واحد من العقاقير المضادة للالتهابات غير الستيرودية قوية جدا التي تنتمي الى مجموعة مشتقات حامض البرويونك. ان الهدف من هذه الدراسة هو اعداد فيلم رذاذ من كيتوبروفين باستخدام عدد من البوليمر المكون للفلم وتقييم خصائصه كدرجة الحموضة , اللزوجة , حجم المحلول لكل جرعة , زاوية الرذاذ , وقت التبخر , وتجانس المحتوى بالأضافة الى نسبة تحرير الدواء خارج الجسم. وكانت افضل صيغة للفلم تحتوي على 0,05 نسبة مئوية (وزن/ وزن)من البولكسيمر 407 و0,05 نسبة مئوية (وزن/ وزن) من كاربابول 940 ولقد وجد ان لديها درجة حموضة , تجانس المحتوى , اللزوجة , وقت التبخر, حجم المحلول لكل جرعة , زاوية الرذاذ , , 5,2 , 100,6 , 1,5 , 91 ثانية , 0,09 مل , 79,9 درجةعلى التوالي. وكان نسبة تحرير الدواء من الصيغة المختارة 49,7 نسبة مئوية خلال 20 ساعة . واستنتج ان الكيتوبروفن يمكن تحضيره على شكل فلم جلدي رذاذي باستخدام خليط بنسبة 0.05 وزن/ وزن لكل من البولكسيمر407 و كاربابول 940.

INTRODUCTION

Spray film consists of active ingredient and film forming polymer in organic solvent. Sprayed onto the skin, film was formed, by evaporation of solvent and adhered to the skin [1, 2] .

Topical NSAIDs produce high drug concentration in dermis, muscle, synovium, and joint cartilage, while plasma drug concentrations are less than 10% of those obtained after oral administration. Tissue and synovial fluid concentrations obtained with NSAIDs approximate the concentration needed to inhibit 50% of enzyme activity (IC50) for prostaglandin synthetase in vitro. However, substantial inter-individual variability exists in transdermal drug penetration as individual skin and connective tissue differences may alter topical absorption of drugs [3].

Ketoprofen competitively inhibits both cyclooxygenase (COX) isoenzymes, COX-1 and COX-2, resulting in analgesic, antipyretic, and anti-inflammatory effects. The enzymes COX-1 and COX-2 catalyze the conversion of arachidonic acid to prostaglandins and thromboxanes that are involved in rapid physiological responses .
It has a good analgesic property that is widely used in the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and acute gouty arthritis [4].
is a white or almost white, crystalline powder, practically insoluble in water (1 part in more than 10000 parts), freely soluble in acetone, ethanol (96 %), methanol and methylene chloride . It is also soluble in ethyl acetate, chloroform and ether . It has been reported to have a melting point range 92 - 97 ºC . It is a weak carboxylic acid and has a dissociation constant value, pKa, of 4.5 and a partition coefficient, Log P (octanol/water), of 3.12 [5-7].
Hussain A., etal, developed novel ketoprofen transdermal patch using almond oil as penetration enhancers and Eudragit as polymer matrix. The result indicated that 3% concentration of almond oil was significantly increase the penetration of ketoprofen across rabbit skin[8] .

The aim of this study is to prepare ketoprofen as a dermal spray film using different types of polymers and evaluate its physicochemical properties and then select the most appropriated formula.

MATERIALS AND METHODS

MATERIALS

Ketoprofen (3Bpharmachem,China), poloxamer 407 **(**Sybronics ,Actico,Jordan), Carbopol 940(HiMedia lab.,Pvt Ltd,Mumdai,India), propylene glygol PG (Hopkins and Williams Ltd England), Sodium dihydrogen phosphate(Avonchem Cheshire UK), ethanol and acetone (GCC Analytical reagents, UK).

METHOD

Preparation of topical spray film formulas

Preformulation studies indicated that solvent system consisting of ethanol: acetone at a ratio of 20:80 exhibited desired spray patterns and high dispersibility of the polymers. The polymeric spray film formulas (F2-F8) were prepared by dissolving the polymers and PG (plasticizer) into the solvent system at 50 rpm for 15 min. The drug was accurately weighed in specially designed glass bottles and the total weight of the system

was adjusted with the polymeric solvents in such a way that desired amount of drug could be obtained after each actuation. The resulting solution was filled in refillable container containing plastic dip tube of 72.5mm length and 1.88 mm internal diameter [9].

Evaluation of the preparation topical spray film formulas

pH

The pH of the prepared solution was measured at room temperature using microprocessor pH meter.

Content uniformity

The content of ketoprofen in the prepared formulas was determined using a method from BP for assay of capsules with simple modification in that an equivalent weight of 20 mg of ketoprofen from each formula was measured using UV spectrophotometer at 260 nm after suitable dilution [10] .

Viscosity

The viscosity of solution was measured at room temperature utilizing Haake falling ball viscometer [11] . The spindle 2 was rotated at 60 rpm.

Volume of solution delivered per each actuation

The volume of solution delivered per each actuation was calculated using the following eq. [9]

$$A_L = (W_t - W_0) / D_a$$

Where A_L is volume of solution delivered per each actuation

W_t is weight of formulation after actuation

W_0 is initial weight of formulation before actuation

Spray angle

The sprays were actuated in horizontal direction onto activated form of TLC aluminium sheet polyamide 11 F -254 mounted at distance of 15 cm from the nozzle. The diameter of the circle were observed and measured under UV light [9].

Spray angle (Θ) = $\tan^{-1}$ (l / r)

Where l is the distance of sheet from nozzle, and r is the average radius of the circle.

Drying time

Evaporation time is the time required for the spray film to dry and it was estimated by spraying the formulation on filter paper and noting down the drying time [2].

***In vitro* dissolution test**

Studies of drug release from the prepared spray formulations (figure 1) were performed using the in vitro dialyzing method in which glass flask closed at one end and the open end covered by a 1.8 cm cap of dialysis membrane36/32 (soaked for 1 h. before the test in the phosphate buffer) this glass apparatus was fixed on the paddle with cable ties, in dissolution apparatus typeII. 5ml of the prepared spray formulation was placed into the glass cell and 500ml phosphate buffer pH 7.4 was used as a dissolution medium, within a period of 20 hs and 50 rpm at 37 °C. Samples (5ml) were taken at regular intervals and analyzed spectrophotometerically at 260nm [12] .

All experiments were carried out in triplicate and average values taken.

Release kinetics

To analyze the mechanism of release and release rate kinetics of the dosage form , the results obtained were fitted in to zero order , first order , higuchi matrix and korsmeyer-peppas and based on the R^2 value the best fit model was selected .[13]

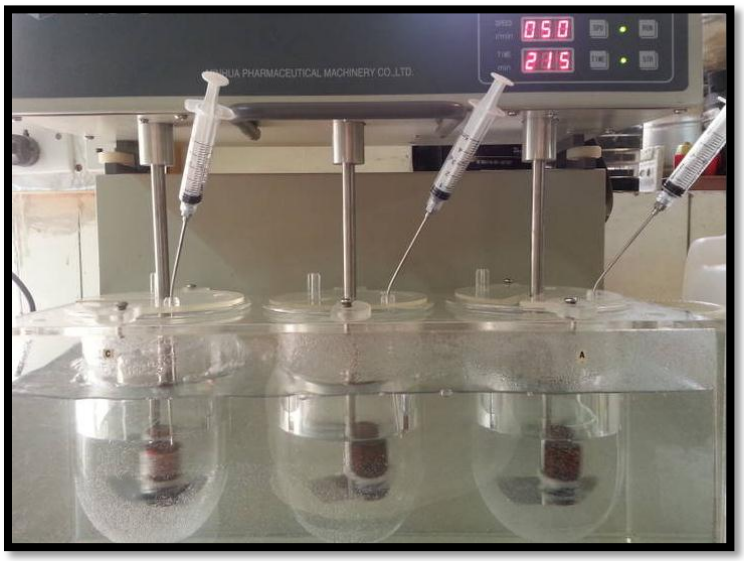

Figure1. Photograph of the in- vitro release test, dialysis membrane covered the glass vial which is attached to the dissolution paddle by a cable tie.

Statistical analysis

The results of the experiments are given as a mean of three samples ± standard deviation and were analyzed according to the one-way analysis of variance (ANOVA) test at level of (P<0.05).

RESULTS AND DISCUSION

The best formula was selected depended on pH, viscosity, volume of solution delivered per each actuation, spray angle, evaporation time, content uniformity, and in vitro drug release. The organic solvent in the formulations evaporated quickly leaving behind a thin film that adhered to the skin for period up to 24 h.

pH

The surface of the skin has long been recognized to be acidic, with a pH of 4.2–5.6 measured in humans [14,15]. Table 2 shows that the pH all formulas ranged from 4.2 to 6.5. The formulations containing ethyl cellulose showed pH of 4.9 since this polymer is inert to alkalies and dilute acids [16], whereas pH of 6.5 and 4.6 were observed with formulation containing polyxamer and carbopole 940 respectively. While, F8 showed pH of 5.2 that is very closed to pH of human skin.

Content uniformity

The results of content uniformity indicated that average drug content per spray of the prepared formulas were 101.1±1.5, 99.5±1.2, 100.9±0.8, 102.1±0.6, 100.3±1.3 , 99.6±0.78, 105.1±1.9, and 100.6±0.8 for F1-F8 respectively, which are within acceptable rang .

Viscosity

Table 2 indicated that as the amount of polymer in the formula increase, the viscosity will be increased with viscosity of 1.5 mpse for F8.

Spray angle.

On the other hand, spray angle were found to be increased in the range of 78.7- 83.5, as volume per each was increased in the range of 0.09-0.14 ml.

Drying time

Drying time, this test indicated the effectiveness of the solvents in drying the film, of F1 was found to be 112 sec. as compare to selected one F1 (91 sec.) due to absence of film forming agent in F1.

Amount emitted per each actuation

There was no significant difference in the amount emitted per each actuation indicating the effectiveness of spray system in delivering reproducible amount of the formulation per each actuation.

***In vitro* Drug Release**

Different polymers were used to achieve the best pharmaceutically acceptable dermal film spray formula and according to above results, F5, F7, and F8 were chosen for further investigation of drug release. Figures (2) indicated that the percent of drug release from F 5 , F 7 , and F8 were 61.1% , 37.46%, and 49.7% respectively, this may be due to the fact that poloxamer are amphiphilic and surface properties that may enhance the release of ketoprofen [17,18], while C940 has high molecular weight and is chemically and physically cross-linked [19] .

Statistically (figure 3) F5 was significantly different from F7 with none significantly different from F8. Therefore, F8 was selected to be the best formula due to its pH (5.6) closed to pH of human skin.

Kinetics of Drug Release

As indicated in table (3), the correlation coefficient value (R^2) of zero-order and first –order model were low for the prepared formulas (0.305 - 0.784) indicated that the release kinetic is not zero or first order. While, were higher, around 0.9, by fitting the release data to Higuchi model indicated that the drug release follow this model.

On the other hand, korsmeyer – peppas model for the formulas show non fickian anomalous diffusion since n values range from 0.28 to 0.32 which is an indication of both diffusion/polymer relaxation controlled drug release [20-21].

Conclusion

According to the results of this study, the followings may be concluded: mixture of poloxamer 407 and carbopol 940 at 0.05 % w/w for both was the best film forming polymers showed the preferable pH to the skin of 5.2 (pH of human skin is 4.2–5.6)and acceptable drug release, in addition to the acceptable other evaluation properties. So, the overall results of these investigations indicate the possibility of utilizing the selected best formula (F_8) in the preparation of ketoprofen as dermal spray film.

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Table 1: Composition of the Ketoprofen Dermal Spray Film Formulas

Composition Formula Number	Ketoprofen %(w/v)	PG %(v/v)	Eyhylcellulose %(w/v)	Poloxamer 407%(w/v)	Carbopol %(w/v)	Ethanol:acetone(80:20)
F1	2.5					q.s
F2	2.5	0.25	1			q.s
F3	2.5	0.25	0.1			q.s
F4	2.5	0.25		1		q.s
F5	2.5	0.25		0.1		q.s
F6	2.5	0.25			1	q.s
F7	2.5	0.25			0.1	q.s
F8	2.5	0.25		0.05	0.05	q.s

Table 2: Evaluation of the Prepared Formulas (n=3)

Formula No.	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
PH	4.2±0.1	4.9±0.5	4.9±0.2	6.5±0.7	6.5±0.3	4.6±0.7	4.6±0.4	5.6±0.2
Content uniformity (%)	101.1±1.5	99.5±1.2	100.9±0.8	102.1±0.6	100.3±1.3	99.6±0.78	105.1±1.9	100.6±0.8
Viscosity (mPs)	0.8±0.02	2.05±0.09	1.2±0.1	1.51±0.8	0.7±0.2	6.22±0.9	0.7±0.1	1.5±0.7
Drying time (sec)	112±5	91±3	88±6	90±0.6	89±0.9	90±1.6	88±2.2	91±0.8
Volume(ml) pereach actuation	0.10±0.021	0.10±0.011	0.11±0.012	0.11±0.030	0.09±0.013	0.09±0.031	0.14±0.022	0.09±0.023
Spray angle	82.2±0.3	82.0±0.5	82.4±0.1	81.8±0.2	78.7±0.4	79.8±0.5	83.5±0.3	79.9±0.1

Table3: The Release Models of the Prepared Spray Ketoprofen Formulas

Formula NO.	R^2 value			n(slop)
	Zero order	First order	Higuchi	Korsmyyer-Peppas
F5	0.527	0.381	0.866	0.29
F7	0.784	0.403	0.887	0.28
F8	0.678	0.305	0.902	0.32

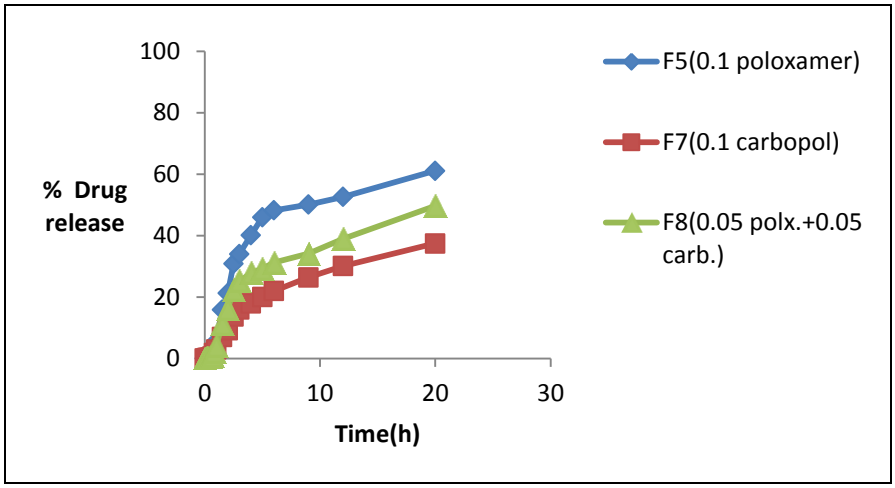

Figure (2): In-vitro drug release study of prepared ketoprofen dermal spray film (F5, F7, and F8) in phosphate buffer pH7.4 at 37°C±0.5°C.

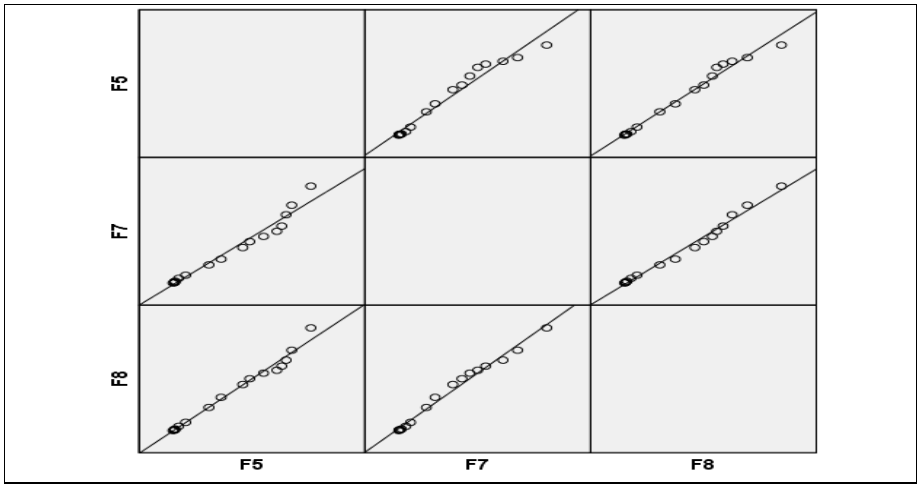

Figure (3): Statistical regression study of F5, F7, and F8.