IN VITRO SURVEY OF KETOPROFEN RELEASE FROM EMULGELS

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ABSTRACT

In the past years emulgels have been developed as one of the most interesting medicinal forms for the delivery of hydrophobic drugs through the skin. They are emulsions, included in gel bases.

The objective of the present research is *an in vitro* study of the processes of release of ketoprofen, included in an emulgel for skin application. Sample variants with different quantity of oil phase- 5 %, 6 %, 7.5 % Light liquid paraffin (LLP) were researched, and for a gelling agent was used Carbopol 940. The resulting emulgels are of excellent appearance, homogeneous, with suitable consistency and PH for skin application. The object of the study was the influence of the oil phase quantity on *the in vitro* release of Ketoprofen from the emulgels.

The results show that the increase of the quantity of the oil phase raises the amount of released Ketoprofen.

Key words*: emulgel, Ketoprofen, Carbopol 940®*

1. INTRODUCTION

Products for dermal application depending on their composition and texture may range from liquids, semisolids to powders. Most popular are the semisolid preparations, which include ointments, creams, gels, pastes, medical plasters. In recent years a new drugdelivery system for local application is being developed - the emulgel. Emulgels are emulsions, included in gel bases. In fact, the addition of a gelling agent to the aqueous phase of the emulsion turns it into an emulgel and leads to its stabilisation [1]. Most often used as gelling agents are Carbopol 940 [2], Carbopol 934 and methylcellulose (MC) [3], hydroxypropylmethylcellulose (HPMC) [4].

The oil phase of emulsions for external application is most frequently liquid paraffin [5]. The most popular emulgel available on the pharmaceutical market is Voltaren emulgel (Novartis Pharma, Basle, Switzerland), which contains diclofenac diethylamine. There are literary data for developed experimental emulgel preparations with other drugs - ketoconazole [6], clotrimazole [3], pyroxicam [7], claritromicine [8], calcipotriol [9]. Emulgels for dermal application are easily spread, well adhere to the skin and are easily cleaned. They can be used as emollients and have long shelf life [10].

Ketoprofen (KP; 2- (3-benzoylphenyl-propionic acid)) is a non-steroid anti-inflammatory drug, most often used for the treatment of muscular-skeletal aches [11]. It possesses perfect physico-chemical properties - a suitable distribution coefficient, low molecular weight and high permeability. Although KP has a short half life of 1.5 -4 hours after oral administration [12], its plasma levels are kept relatively constant for approximately 24 hours after transdermal application [[13]. Various medicinal forms for dermal application have been developed, such as gels [14, 15], creams [16], ointments [17], plasters [18], microemulsions [19].

The objective of the present research is to study the influence of the oil phase (LLP) concentration on the processes of the release of KP from emulgel preparations for dermal application.

2. MATERIALS AND METHODS

2.1 Materials

Ketoprofen (Sigma Aldrich), Carbopol 940 - Ph.Eur., Light liquid paraffin - Ph.Eur. [0240], Span 65 (Sigma Aldrich), Tween 60 (Sigma Aldrich), Propylene glycol (Sigma Aldrich), Ethanol - 95 % -v/v Ph.Eur., Methyl parabene and Propyl parabene (Fluka), Purified water.

2.2 Preparation of emulgels

Emulgels with KP were prepared by the method of Mohamed (2004) with minor modifications. The gel basis was prepared by dispersing the Carbopol 940 in purified water by continuous stirring with a mechanical stirrer. pH was adjusted in the range of 6-6,5 with the aid of triethanolamine.
The oil phase of the emulsion was prepared by dissolving Span 65 in liquid paraffin, and the aqueous phase by dissolving Tween 60 in purified water. KP was dissolved in ethanol and the methyl- and propyl parabenes - in propylene glycol. The two liquids were mixed with the aqueous phase. Both phases of the emulsion were heated individually to 70°C - 80°C, after which the oil phase was added to the aqueous one, stirring continuously until reaching room temperature. The resulting emulsion was mixed with the gel basis in a ratio of 1:1 by stirring till the formation of an emulgel. The separate ingredients are presented in table 1.

Table 1: Composition of Ketoprofen Emulgel Formulations (%w/w)

Ingredients	F_1	F_2	F_3
Ketoprofen	1	1	1
Carbopol 940	1	1	1
Light liquid paraffin	5	6	7.5
Span 65	0.69	0.69	0.69
Tween 60	1.31	1.31	1.31
Propylene glycol	5	5	5
Ethanol	2.5	2.5	2.5
Methyl parabene	0.03	0.03	0.03
Propyl parabene	0.01	0.01	0.01
Purified water	q.s.	q.s.	q.s.

2.3 Evaluation of emulgel

2.3.1 Physical examination

The prepared emulgel formulations were inspected visually for their color, homogeneity, consistency and phase separation [6].

2.3.2 Determination of pH

The pH values of 1% aqueous solutions of the prepared emulgels were measured by a pH meter (inoLab pH 720).

2.3.3 In vitro release studies

In vitro survey of the release of KP from emulgel sample variants was carried out in a modified diffuse cell through a cellulose membrane. A definite quantity of the tested sample variants (~ 200 mg) was applied on the membrane and it was fixed on the acceptor phase of the system. A freshly prepared phosphate buffer with pH 5.5 and volume 175 ml was used as a medium for the release. The experiment was conducted at a temperature of 32°C±0.5°C. The acceptor phase was continuously homogenised with an electromagnetic stirrer. At appropriate for

the experiment time intervals, samples for analysis were taken. The quantity of released KP was determined spectrophotometrically at λ=260nm.

3. RESULTS AND DISCUSSION

3.1 Physical appearance

Emulgel formulations were white viscous creamy preparations with a smooth homogeneous texture and glossy appearance. Results have been discussed in Table 2.

3.2 pH determination

The pH of the emulgel formulations was in the range 6.0-6.5. Results have been discussed in Table 2.

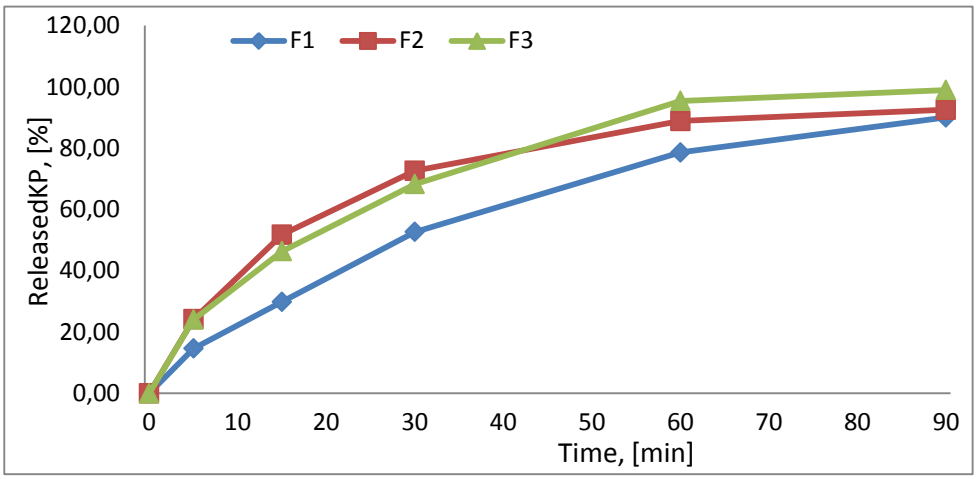
Table 2. Physical parameters and pH values.

Formulation	Color	Homogeneity	Consistency	Phase separation	pH
F1	White	Excellent	Excellent	-	6.02
F2	White	Excellent	Excellent	-	6.34
F3	White	Excellent	Excellent	-	6.15

3.3 In vitro release study

The release of KP from the emulgel was varied according to concentration of oil phase of emulsion. The release of the drugs from the emulsified gel formulation can be ranked in the following descending order: $F_3 > F_2 > F_1$. The amounts of the drug released after 90 min. were 99.02%, 92.52%, 90.15% respectively. It has been concluded that, if we increase the concentration of light liquid paraffin, the diffusion of drug through the membrane also increases. The results are shown in Figure 1.

Figure 1: *In vitro* released KP, [%] of formulations F_1-F_3.



4. CONCLUSION

The emulgels with ketoprofen developed by us are of excellent appearance, consistency and homogeneity. There is no separation of the phases. the pH of the obtained sample variants is in the range 6.0 -6.5. It was established that the increase of the oil phase concentration increases the amount of released KP by the emulgel. The most suitable concentration of Light Liquid Paraffin is 7.5 %.

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