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IN VITRO DIFFUSION STUDIES OF KETOPROFEN TRANSDERMAL THERAPEUTIC SYSTEMS

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ABSTRACT

The release of Ketoprofen from the matrix model of TTS were studied. It may be concluded that the pharmaceutical availability of the drug can be regulated by the type and thickness of the matrix.
Quantitation of the active agent in the dissolution medium was done by UV-spectroscopy.
The results obtained by the rotating cylinder method were compared to another method utilizing a modified Stricker cell.

INTRODUCTION

Oral administration of Ketoprofen **1** is very effective for the treatment of rheumatoid arthritis (1) but it has a side-effect concerning gastro-intestinal mucosa. There are reports on the effects of administration of Ketoprofen externa (gels, ointments) on the percutaneous absorption (2, 3)but no reports about transdermal therapeutic systems.

MATERIALS AND METHODS

Materials: **1**=Ketoprofen (Sigma, St.Louis, USA), **2**=Eudragit NE-30D according to "Polyacrylate dispersion 30 per cent" Ph.Eur.; **3**=Eudragit Rl 30 D according to "Ammonio Methacrylate Copolymer, Type A" USP/NF, **4**=Eudragit RS 30 D according to "Ammonio Methacrylate Copolymer, Type B", Plastoid E 35 L (Röhm; Darmstadt, Germany) Hydroxypropylmethylcellulose HPMC according to Metolose 60 SH-4000 USP/NF; Triethylcitrat (Merck; Darmstadt, Germany), Silicium diox.disp. (Pharm.Eur.). Back foil: Polypropylen 0,030 mm/aluminium 0,012 mm

TABLE 1
Composition of TTS with Ketoprofen using **2** as matrix

	Ketoprofen mg/cm^2	Eudragit NE 30 D mg/cm^2	HPMC mg/cm^2	Plastoid E 35 L thickness in µm	Matrix thickness in µm
TTS 1	4,6	53,4	3,2	250	160
TTS 2	9,9	53,4	3,2	250	160
TTS 3	9,9	100	3,2	250	300
TTS 4	9,9	33,3	3,2	250	100
TTS 5	9,9	53,4	3,2	100	160
TTS 6	9,9	100	3,2	100	300
TTS 7	9,9	33,3	3,2	100	100

TABLE 2
Composition of TTS with Ketoprofen using **3** and **4** as matrix

	Keto-profen mg/cm^2	Eudragit RS 30 D mg/cm^2	Eudragit RL 30 D mg/cm^2	Aerosil mg/cm2	Tween 80 mg/cm^2	Triethyl -citrat mg/cm^2	Plastoid E 35 L thickness µm	Matrix thickness in µm
TTS 8	9,9	66,6	-----	1,5	1,6	5,0	100	160
TTS 9	9,9	------	48,8	1,5	1,6	5,0	100	120
TTS 10	9,9	33,2	33,2	1,5	1,6	5,0	100	160
TTS 11	13,2	------	48,8	1,5	1,6	5,0	100	120
TTS 12	9,9	------	33,2	1,5	1,6	5,0	100	80

pigmented in skin tone; supporting foil: aluminium 0,038 mm (Tscheulin, Teningen, Germany).

Preparation of matrices:

In order to prepare matrices, **1** was suspended in Eudragit NE 30 D and then the thickener HPMC-gel was added (Tab.1). The patches with Eudragit RS 30 D and Eudragit RL 30 D needed a plasticizer (Tab.2) like triethylcitrat. The preparations in laboratory scale were made according to ref.4. The polymer dispersion was applied by using a raquele. Drying led to flexible films. After application of the adhesive the supporting foil was fixed. Then the TTS were blanked out in a suitable size (r=2,2; 1,5 cm).

Determination of in vitro release rates from TTS:

Method 1: diffusion studies with the Stricker cell (3). Originary this apparatus was developed to study the diffusion of drugs through lipid membranes. Instead of the lipid membran the TTS was applied and there was only one direction of the circulation of the acceptor medium .

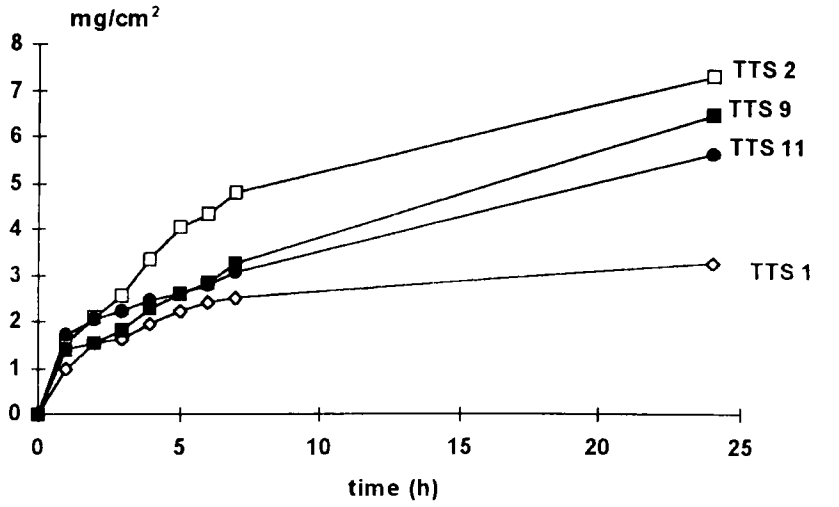

FIGURE 1
Liberation of **1** as a function of time, content of the drug and matrix polymer type, TTS 1,TTS2=**2** (matrix); TTS 11, TTS 9=**3/4** (matrix); points indicate average of three experiments

Temperature: 32± 0,5° C; Acceptor phase: Phosphate buffer pH 7,5 (0,33 M; Ph.Eur.), 24 hours.

Method 2: diffusion studies with rotating cylinder according to USP XXII; paddle speed: 100 rpm at 32 ± 0,5°C.

The TTS were gently pressed to a dry, unused square piece of Cuprophane membrane (Enka Ag), an inert porous cellulose material with the adhesive side against the membrane. The TTS was attached to a stainless steel holder.

Assay procedure:

The amount of **1** released from the matrix was determined spectrophotometrically

λ=260 nm; Photometer: Perkin Elmer Lambda 16UV/VIS). Each liberation process was carried out for 24 h in triplicate runs. Patches prepared in the same way without drug were checked photometrically.

RESULTS AND DISCUSSIONS

The investigation was carried out in two ways. The first experiment was the evaluation of how pharmaceutical availability of **1** was influenced by the amount of **1,** the mass (thickness) of the matrix, thickness of adhesive and

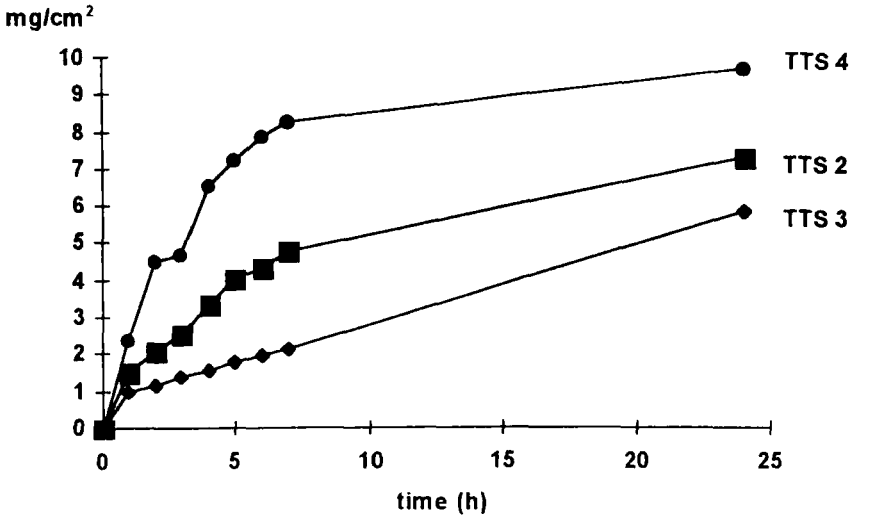

FIGURE 2
Liberation of **1** as a function of time and thickness of the matrix (**2**); TTS 2 (160 μm); TTS 3 (300 μm); TTS 4 (100 μm); points indicate the average of three experiments

variety of polymers (4). Second the results of two in vitro release methods (method1, 2) were compared.

First the influence of the amount of **1** (mg/cm^2) and polymer types on the release rates (Fig.1) was investigated.

Using **2** offers the possibility of controlling the releasing rates by the drug concentration but no significant differences between the releasing profiles were detected if applying **3, 4** in combination with different drug concentration. In case of using **2** as polymer matrix the releasing rates depend on the thickness of the matrix (Fig.2).

It is well known (5, 6) that **3** lead to films with high permeability and can be mixed in any proportion with **4** to reduce permeability therefore diffusion behaviour can be varied over a wide range.(Fig.3).

The thickness of the adhesive had no significant influence on the release of **1** (Fig.4).

In the next step the dissolution profiles of three optimized compositions with high diffusion rates delivered by a modified Stricker cell (7) were compared with the dissolution profiles obtained by the USP-method (rotating cylinder). The releasing rates of both methods were similar (Fig.5).

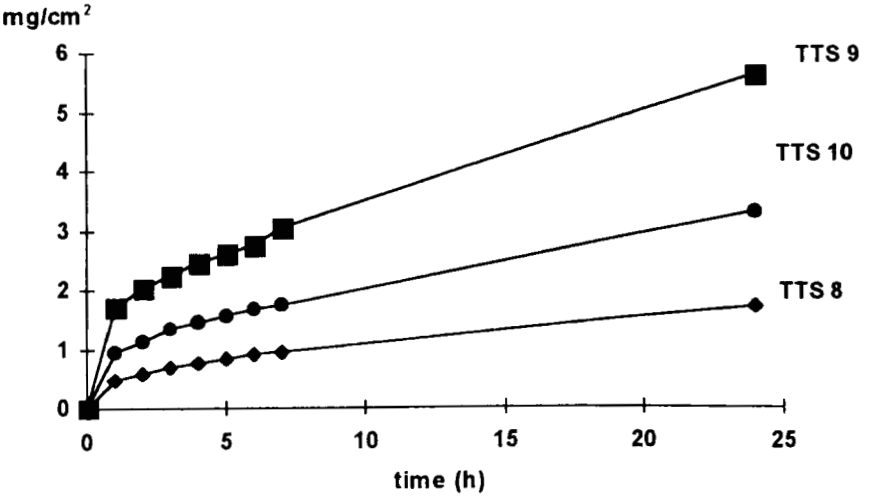

FIGURE 3
Liberation of **1** depending on the type of matrix, TTS 8: **4** (=matrix) TTS 10: **3** and **4,** 1:1 (=matrix); TTS 9: **3** (=matrix); points indicates average of three experiments

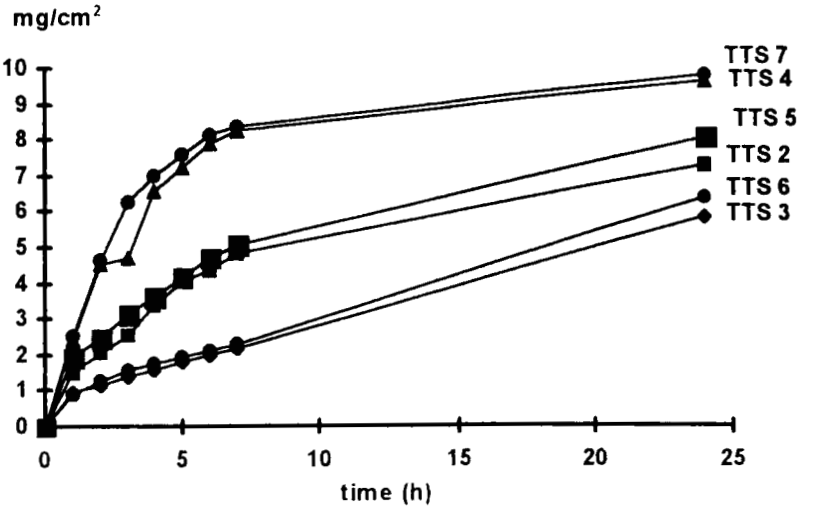

FIGURE 4
Liberation of Ketoprofen as a function of thickness of the matrix and thickness of the adhesive; points indicate average of three experiments

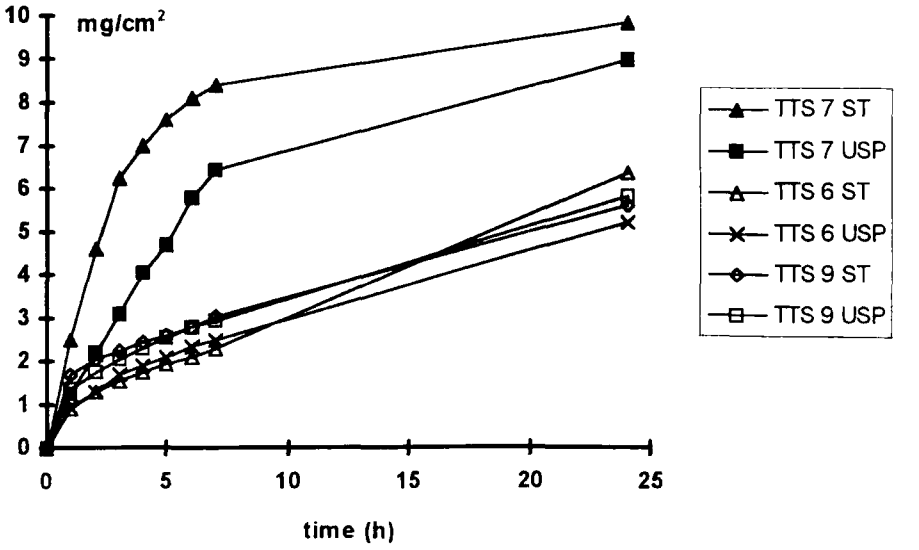

FIGURE 5
Comparison between the releasing rates of **1**; ST=method 1 USP=method 2 points indicate the average of three experiments

Further in vitro studies with native skins may lead to a successful formulation for **1** in a transdermal therapeutic system.

ACKNOWLEDGEMENTS

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