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Preparation and evaluation of tolmetin sodium conventional and sustained-release suppositories

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Präparation und Auswertung von Tolmetin Natrium in konventionellen und Suppositorien mit verlängerter Wirkstofffreisetzung

ABSTRACT

Conventional suppositories of tolmetin sodium were prepared by using two different types of Witepsol as an oily base and two different ratios of polyethylene glycol 400: polyethylene glycol 4OOO as an water-soluble base. In addition, sustained- release suppositories were prepared by adding Eudragit L-100 to the suppositories. The effects of the suppository base and the ratios of the polyethylene glycol 4OO: polyethylene glycols 4OOO on the in vitro release characteristics were investigated. The release rate of tolmetin sodium from the conventional suppositories prepared with polyethylene glycol was slower than the other suppositories prepared with Witepsol. All of the suppositories with Eudragit L-100 showed slow-release profiles and the drug release rates clearly depended on the Eudragit L-100 content. When dissolution results were evaluated kinetically, zero order kinetic was observed with the sustained- release suppositories of tolmetin sodium prepared with polyethyleneglycol 4OO: polyethyleneglycol 4OOO by adding Eudragit L-100.

Key words: *suppository, suppository bases, sustained- released, Witepsol®, polyethylene glycol, tolmetin sodium*

INTRODUCTION

Suppositories are solid dosage forms of various weights and shapes, usually medicated, for insertion into rectum, vagina or the urethra. After insertion, suppositories soften, melt or dissolve in the cavity fluids. In addition to the local effects, rectal suppositories have systemic effects, such as analgesic, sedative, tranquilliser. They present many other advantages; it is easy to use for children and the drug bioavailability in an empty rectum is as good as the per oral route (1,2).

A number of factors affect the release rate of the drug from the suppositories such as pH, fluid content, surface area, suppository base, particle size and the solubility of the drug in the suppository base and in water (3-5).

Tolmetin sodium has anti-inflammatory, analgesic and antipyretic activities. The most frequent adverse effects are gastrointestinal and include, in descending order of frequency, epigastric or abdominal pain, nausea, vomiting (6). It is almost completely absorbed from the gastro-intestinal tract. It is commonly used in tablet form containing 200-400 mg tolmetin. It has also been formulated in capsule form (7). There is a paper to prepare microspheres of tolmetin sodium but no publication has been seen about tolmetin sodium suppository (8).

The aim of this study was to prepare tolmetin sodium suppositories and to investigate the influence of the suppository bases on the release of tolmetin sodium from the suppositories. There are various studies about sustained- release suppositories, so we also try to prepare sustained-release suppositories of tolmetin sodium by using Eudragit L-100. Eudragit L-100, an anionic polymer, synthesised from methacrylic acid and methacrylic acid methyl ester, provides sustained-release effects in suppository (9).

MATERIALS AND METHODS

Materials

Tolmetin sodium (TS) was supplied by Cilag AG. Witepsol S 55 and polyethylene glycol (PEG) 400, Witepsol H 15, PEG 4000, Eudragit L-100 were obtained from Fako AŞ, Deva AŞ, Sandoz, Röhm, respectively. The other materials used were of pharmaceutical grade.

Methods

Preparation of Suppositories

The content of TS in all suppositories was 10 %. They were prepared according to the fusion technique. The prepared suppositories were placed in refrigerator for 24 h and then stored at room temperature before testing.

Conventional suppositories: The various types of Witepsol and PEG are commonly used as suppository bases (10-14). In our study, TS suppositories were prepared using Witepsol H 15, Witepsol S 55 as an oily base, PEG 400: PEG 4OOO mixture as a water-soluble base. PEG 4000 wasn't used alone because of the hardness problem of the suppositories.

Sustained- release suppositories: Eudragit L-100 was added to melted suppository base and stirred until homogeneous fusions were formed.

All suppositories were poured into steel molds and allowed to solidify at room temperature. The formulae of suppositories prepared in this work are listed in Table 1.

Table 1: *The codes and the formulae of tolmetin sodium suppositories*

	S1	S2	S3	S4	S5	S6	S7	S8A	S8B
Witepsol H 15	2.205g	-	-	-	2.005g	-	-	-	-
Witepsol S 55	-	2.205g	-	-	-	2.005g	-	-	-
PEG 400	-	-	0.110g	0.220g	-	-	0.200g	0.100g	0.095g
PEG 4000	-	-	2.095g	1.985g	-	-	1.805g	1.905g	1.810g
Eudragit L-100	-	-	-	-	0.200g	0.200g	0.200g	0.200g	0.300g

Uniformity of weight, fracture point, disintegration tests and content uniformity controls were done according to the pharmacopoeia (15,16).

Release Tests of TS Suppositories

Release profiles of suppositories were determined at 37±0.1°C in 150 ml of phosphate buffer solution at pH 7.4* using rotating basket method (16).Basket rotation was controlled at constant 50 rpm. The samples were then assayed spectrophotometrically. The dissolution data for each suppository was treated by converting observed drug concentrations at each sampling time to amounts dissolved and in turn to percentage dissolved.

The results evaluated kinetically by zero, first order, Hixson-Crowell, RRSBW, Q$\sqrt{t}$, Modified Hixson- Crowell, Higuchi, Hopfenberg equations. The release constants (k), correlation coefficients (r^2) were calculated by means of a computer program (17).

**Phosphate buffer: Disodium hydrogen phosphate 8.05g, sodium dihydrogen phosphate 1.56g and water q.s .1000 ml.*

RESULTS AND DISCUSSION

The literature contains numerous reports of the effects of physicochemical properties of drug on the release of various medicaments from suppositories (18,19). The suppositories prepared exhibited good mechanical properties and were found to be in a good agreement with BP requirements. Table 2 shows that all the prepared suppositories comply with the requirements for weight variation (5%). The variation in drug content was less than 5% in all suppository bases.

The prepared suppositories exhibited a reasonable degree of hardness ranging between 1.6- 3.9 kg. The mechanical strength of conventional suppositories was less than the sustained-release suppositories. Eudragit L-100 led to an increase in mechanical strength. On the other hand, the results showed the effect of the suppository base on the mechanical strength. The fracture point of S1 and S2 was less than S3 and S4.

All the formulated suppositories including Witepsol as an oily base were disintegrated in a shorter time than the others, which contained PEG as a water-soluble base. In addition, the samples containing Eudragit L-100 disintegrated in a time longer than those of the conventional formulations.

Table 2: *Calculated physical parameters of tolmetin sodium suppositories*

Suppository	Weight of suppository (g±SD)	Drug content (mg±SD)	Fracture Point (kg± SD)	Disintegration Time (min±SD)
S1	2.46±0.03	197.65±6.00	1.9±0.1	15±2.4
S2	2.43±0.01	201.80±3.88	1.6±0.1	17±3.5
S3	2.53±0.04	199.10±3.55	3.1±0.1	102±5.4
S4	2.56±0.10	198.48±3.63	2.9±0.1	98±3.1
S5	3.37±0.01	200.60±1.98	2.4±0.1	54±3.1
S6	2.67±0.01	202.01±7.51	2.2±0.1	48±2.6
S7	2.54±0.09	196.58±8.95	3.2±0.1	110±2.0
S8A	2.53±0.01	201.01±3.56	3.9±0.1	111±1.7
S8B	2.57±0.11	200.10±1.61	3.9±0.1	116±6.0

SD: Standard Deviation

In vitro release of TS from conventional suppositories prepared with Witepsol H 15, Witepsol S 55 and PEG 400:PEG 4000 (5:95; 10:90) mixture is presented in Fig.1 where the drug release takes place according to the following sequence. S1 > S2 > S4 > S3.

The release sequence was found to be directly proportional to the disintegration time of the suppositories. The oily bases increased the release rate more than water-soluble bases. The results showed that the lipophilic bases were not suitable for suppository formulations. In addition, the efficiency of S3 and S4 for delivery of TS was compared with the PEG 400 content. S4 gave higher drug release when compared to S3, also indicating that a relationship exists between the PEG 400 content of the base and the release of TS. It showed the importance of the ratio of the PEG4OO: PEG4OOO mixture on the release pattern of suppositories likes molecular weight of PEG (20,21).

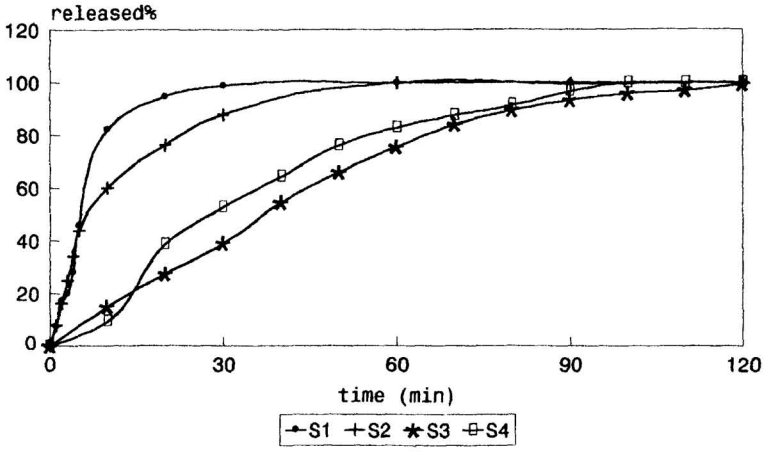

Figure 1: Dissolution release profiles of conventional suppositories of tolmetin sodium

On the other hand, all the other suppositories gave much slower release than the conventional suppositories (Fig.2).

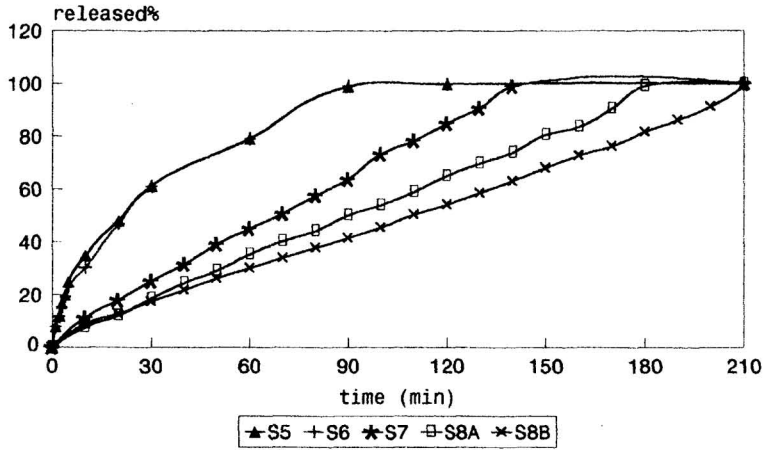

Figure 2: Dissolution release profiles of and sustained-release suppositories of tolmetin sodium

S5 and S6 gave complete drug release in 90 minutes from the beginning of the dissolution test and their release profiles were similar to each other.

There was an effect of Eudragit L-100 on the release behaviour of S7 and S8 suppositories. The tolmetin sodium release profiles of the S7, S8A and S8B formulations were also shown in Fig. 2. A linear relationship was observed between the released amount of the drug and the time. Similar dissolution profile was obtained from the sustained-released suppositories of progesterone prepared with sodium caprate in previous paper (14). The percent of TS released at 120 min in S7, S8A and S8B was approximately 85.0, 65.0 and 54.3%, respectively and they showed a sustained- release property. The release rate of TS from S7, S8A and S8B were lower than S3 and S4 suppositories. S8A and S8B contained 200 and 300 mg of Eudragit L-100, respectively.

When the release profiles of S8A and S8B were compared, increasing in the quantity of Eudragit L 100 caused the decreasing in the release amount of TS as it was expected (22). As a result S8B gave the slowest release because of the 300mg of Eudragit L-100. It was considered that pore formation and the development of a network structure were attributable to difference of dissolution rates of formulations. First, PEG dissolved faster than Eudragit L-100 at the surface of the suppository. Secondly a network structure of Eudragit L-100 appeared at the surface. This phenomenon continued until the suppository was completely dissolved.

Kinetic Assessment: When the kinetic data of S1 and S2 formulations were examined, it was found out that the determination coefficients were very low. For the conventional formulations Modified Hixson- Crowell and RRSBW kinetics were obtained. The data better fit Modified Hixson- Crowell kinetic for S5, S6 formulations and the zero order and Hopfenberg kinetics were obtained with S7, S8A and S8B suppositories. Table 3 showed the kinetic assessment of release data for the tolmetin sodium suppositories

Table3: Kinetic parameters of dissolution data of all suppository formulations

Kinetics		S1	S2	S3	S4	S5	S6	S7	S8A	S8B
Zero order	r^2	0.360	0.673	0.927	0.949	0.920	0.905	0.999	0.987	0.997
	Kr^0	32.81	49.83	93.84	75.84	71.46	74.70	80.12	56.36	52.23
First order	r^2	0.840	0.917	0.944	0.645	0.937	0.939	0.723	0.703	0.510
	kr	3.015	3.620	2.354	5.926	3.522	3.591	1.456	1.510	1.015
$Q\sqrt{t}$	r^2	0.506	0.821	0.976	0.884	0.975	0.968	0.974	0.983	0.958
	k	611.2	547.9	340.2	426.9	401.8	397.0	194.5	147.3	117.6
Hopfenberg	r^2	0.360	0.873	0.926	0.764	0.920	0.905	0.999	0.987	0.997
(slab erosion)	k'''	0.003	0.004	0.008	0.006	0.006	0.006	0.007	0.005	0.004
Hopfenberg	r^2	0.549	0.815	0.991	0.945	0.974	0.969	0.948	0.971	0.909
(cylindrical erosion)	k''	0.005	0.006	0.008	0.008	0.007	0.008	0.006	0.004	0.004
Hopfenberg	r^2	0.643	0.855	0.996	0.978	0.976	0.973	0.896	0.918	0.818
(spherical erosion)	k'	0.004	0.006	0.007	0.008	0.008	0.008	0.005	0.004	0.003
RRSBW	r^2	0.915	0.974	0.987	0.932	0.934	0.948	0.919	0.915	0.875
	τ	5.83	10.73	43.87	24.66	27.00	28.245	75.517	97.00	121.4
	β	0.718	0.847	1.365	1.310	1.115	1.179	1.243	1.362	1.174
Hixson-Crowell	r^2	0.643	0.855	0.996	0.978	0.976	0.973	0.896	0.918	0.818
Modified	r^2	0.825	0.977	0.997	0.979	0.974	0.983	0.961	0.972	0.941
Hixson-Crowell	A	0.447	0.548	1.118	0.938	0.789	0.845	1.079	1.149	1.025
	B	0.01	0.009	6.779	0.009	0.006	0.007	0.004	0.003	0.002
Higuchi	r^2	0.587	0.839	0.986	0.984	0.961	0..956	0.812	0.862	0.733
(heterogen pellet)										

r^2, determination coefficient; kr^0(mg/hour); kr($hour^{-1}$);k ,k', k'', k''' , release rate constants; β, the shape factor; τ, the value stads for the time 63.2% release of the drug;
a, parameter is associated with the shape of the dissolution curve; b, parameter is the apparent dissolution rate constant

The graph, belonged to the sustained- released suppositories, was shown in Fig.3.

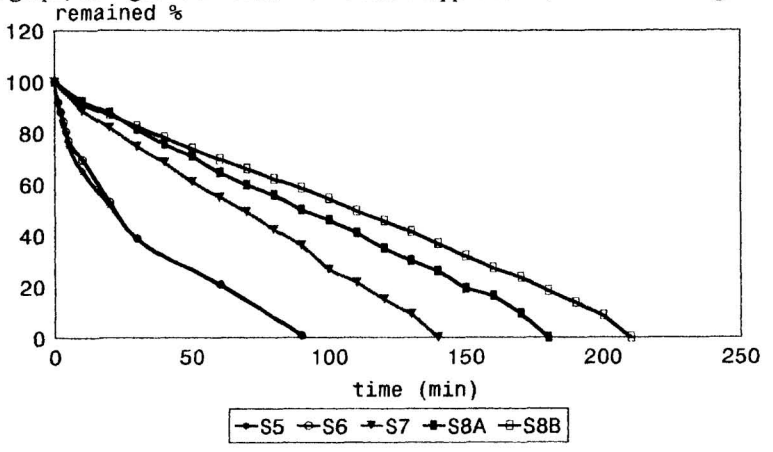

Figure 3: Zero order plots of tolmetin sodium suppositories included Eudragit L-100

In conclusion, TS suppository formulations were developed using Witepsol as an oleaginous and PEG as water-soluble bases. Effect of the suppository base on the release rate was investigated. The use of PEG 400:PEG 4000 mixtures is preferable to prepare TS suppositories. In addition, Eudragit L-100 provides sustained- release action for TS when it is used with PEG 400: PEG 4000 (5:95) mixture. This action of Eudragit L-100 is in accordance with the literature (9).

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I am remembering my dear colleague Ozan Kırkağaçlıoğlu that I lost unexpectedly after completing our study and I owe this paper to his unforgettable memory.

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