PREPARATION AND IN VITRO EVALUATION OF SUSTAINED

RELEASE SUPPOSITORIES OF INDOMETHACINE

İNDOMETAZİNİN SÜREKLİ ETKİLİ SUPPOZİTUVARLARININ HAZIRLANMASI VE İNVİTRO DEĞERLENDİRİLMESİ

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ÖZET

İndometazinin sürekli etkili suppozituvarları suda çözünmeyen taşıyıcı olan selüloz asetat ftalat (CAP) ve Eudragit RL/RS kullanılarak hazırlandı. Witepsol H15 ve polietilen glikol (PEG) karışımları hidrofobik ve hidrofilik sıvağlar olarak seçildi. Formülasyonlar üzerinde dağılma zamanı, sertlik ve salım deneyleri yapıldı. Sonuçlar matriks materyali olarak Eudragit RL/RS (1:1) karışımının CAP'tan daha uygun olduğunu gösterdi. Salım deneylerinin kinetik değerlendirilmesinde en iyi uyum $Q\sqrt{t}$ kinetiği ile elde edildi.

Anahtar kelimeler: İndomethacin, Eudragit, CAP, sürekli etkili suppozituvar, in vitro salım hızı, kinetik değerlendirme.

SUMMARY

Indomethacin (IM) sustained release suppositories were prepared by using a solid matrix of cellulose acetate phythalate (CAP) and trimethylamonium methacrylate chloride's (Eudragit RL and RS) as poorly soluble cariers. Witepsol H15 and polyethylene glycol (PEG) mixtures were used as examples of hydrophobic and hydrophilic bases, respectively. Disintegration time, fracture point and release experiments were conducted on the formulations. The results indicate that Eudragit RL/RS (1:1) combination was found more suitable than CAP as a matrix material. From the kinetic assesment of release data, the best fit was achieved with $Q\sqrt{t}$ kinetic.

Key words: indomethacin, Eudragit, CAP, sustained release suppository, invitro release rate, kinetic assessment.

INTRODUCTION

Indomethacin (IM) is a well established analgesic, anti-inflammatory and anti-arthritic agent (1). However, it causes a number of side effects including the most frequent gastrointestinal actions (2-4). Rectal administration of IM can be used as an alternative to the oral route. Besides the conventional form, sustained release suppositories can be prepared to achieve sustained-release medication. In the literature, there are several attempts to formulate sustained release suppository dosage forms and to enhance the bioavailability of different drugs (5-8).

Eudragit RS (5% trimethylammonium methacrylate chloride) and RL (10% trimethylamonium methacrylate chloride) are copolymers of acrylic and methacrylic acid esters containing some quarternary ammonium groups. Eudragit E RL/RS (1:1) dispersions are available for water insoluble film coatings for delayed release products. The permeability of the film depends on pH. Cellulose acetate phythalate (CAP) is also used as an enteric coated material for solid dosage forms. In this study, we examined the utility of CAP and Eudragid RL/RS (1:1) combination as poorly soluble carriers in IM sustained release suppositories.

MATERIAL AND METHODS

Materials

Indomethacin was supplied by Selecthemie A.G, PEG's (PEG-400, PEG-1000, PEG-2000, PEG-4000) by Merck, CAP by Kodak and Eudragit RLPM and RSPM (E RL/RS) by Röhm Pharma. All other chemicals were reagent grade.

Methods

Preparation of suppositories

Conventional suppositories (SWH, SP 21, SP 141, SP 441) were prepared by the fusion method at either 38°C (Witepsol H15) or 48°C (PEG mixtures) depending on the base used.

Matrix suppositories (SP 22, SP 23, SP 24, SP 25, SP 142, SP143, SP 144, SP 145, SP 442, SP 443, SP 444, P 445) were prepared by the fusion method as follows. Physical mixtures of specified proportions of CAP and PEG mixtures, E RL/RS(1:1) and PEG mixtures were prepared. CAP and E RL/RS(1:1) were added to the bases in two different ratios, of 5 and 10%. These mixtures were heated at 80°C in a thermostated oven with occasional stirrings until clear homogeneous fused mixtures were formed. Then, IM was melted in the fused mixtures and the fusion were quickly poured into steel moulds and allowed to solidify at room temperature. After then they were wrapped in

aluminium foil and stored in a desiccator in the refrigerator at +4°C until use. The formulations are given in Table 1. The content of IM in all suppositories was 100 mg.

Table !: Code and Constituents of Suppositdries

CODES	Substances (mg)								
	IM	Witepsol H15	PEG-400	PEG-1000	PEG-2000	PEG-4000	CAP	Eudragit RLPM	Eudragit RSPM
SWH	0.100	1.889							
SP 21	0 100				234				
SP 22	0 100				2.23		0.117		
SP 23	0 100				2.11		0.234		
SP 24	0 100				2.23			0.0585	0.0585
SP 25	0 100				2.11			0.117	0,117
SP 141	0 100			2.29		0,0468			
SP 142	0 100			2.19		0.0446	0.117		
SP 143	0 100			2.07		0.0422	0.234		
SP 144	0 100			2.19		0,0446		0.0585	0,0585
SP 145	0 100			2.07		0,0422		0,117	0,117
SP 441	0 100		1.17			1.17			
SP 442	0 100		1.12			1.12	0.117		
SP 443	0 100		1.05			1.05	0.234		
SP 444	0 100		1.12			1.12		0.0585	00585
SP 445	0 100		1.0S			1.05		0.117	0,117

Disintegration time and Fracture Point Determinations

The disintegration tests were performed according to the BP 1993 (9) at 37°C.

For evaluation the resistance of the formulations to deformation under the effect of increasing weight, the Erweka Apparatus (Type:SBT) was utilised.

In vitro release study

In vitro release tests were carried out according to the USP XXII basket method (10). Each suppository was placed in the basket and lowered into a flask containing 500 ml of phosphate buffer solution (pH 7.2). The basket was rotated at 50 rpm at a constant temperature of 37+0.5°C. 2 ml of samples were withdrawn at appropriate time intervals and assayed to obtain a dissolution profile. 2 ml phosphate buffer was immediately added to dissolution medium to compensate for sampling. The release of IM from different bases was assayed spectrophotometrically at 264 nm. (Pye-Unicam SP 1025). The results were the mean of three determinations. The release data obtained for sustained-release suppositories were also evaluated kinetically.

RESULTS AND DISCUSSION

Disintegration time and Fracture point

The results of disintegration time and fracture point tests are given in Table 2. The BP 1993 disintegration test uses three suppositories and specifies a disintegration time not more than 30 minutes for fatty-base suppositories and not more than 60 minutes for water-soluble suppositories. All the formulated conventional suppositories (SWH, SP 21, SP 141, SP 441) met these requirements. On the other hand, BP 1993 disintegration test is also met by all of the sustained release suppositories investigated in this study except SP 23. It is also observed that the samples containing E RL/RS except the samples coded as SP 22 to 25 disintegrate in a time longer than those of the formulations which contain CAP as inert matrix material.

Table 2 : Disintegration Time and Fracture point
Values of Suppositories

Codes	Disintegration	Time (min)	Fracture	Point (kg)
	X	SD	X	SD
SWH	4.69	0.012	2.20	0,184
SP 21	20.40	0.078	6.8>	-
SP 22	48.60	0.052	6,8>	-
SP 23	87.20	0.063	6.8>	-
SP 24	30.40	0.587	6.8>	-
SP 25	80.00	0.003	6.8>	-
SP 141	9.25	0.006	0.60	0.112
SP 142	14.70	0.377	0.80	0.273
SP 143	33.10	0.072	1.00	0,054
SP 144	23,30	0.002	0.84	0.147
SP 145	43.20	0,064	1.46	0.087
SP 441	9.60	0.010	2.40	0.014
SP 442	17.50	0.082	2.16	0.101
SP 443	22.50	0,057	2.24	0.023
SP 444	18.40	0.093	2.20	0.129
SP 445	28.40	0.079	2.40	0.078

SD : Standart deviation

The prepared suppositories exhibited a reasonable degree of hardness ranging between 0.80 and above 6.80 kg. However, SP 141- SP 145 coded series prepared by PEG 1000:4000 (98%: 2%) mixture as suppository bases were found to have lower fracture points than those of the others. The implications of these factors on drug release will be discussed later.

Release of IM from suppositories in vitro

The in vitro release behaviour of IM from the conventional suppositories is shown in Fig 1. It is seen from this figure that nearly 90% of drug released from all conventional suppositories with PEG mixtures in 45 minutes whereas that from W-H15 was about 13% of theoretical at most. The lower and slower release associated with the W-H15 could be due to the lipophilicity of IM manifested in its relatively high partition coefficient ($C_{octanol}$ / C_{water}=16.09) (11). The results have shown that the lipophilic bases are not suitable for sustained-release suppository formulations. However, PEG mixtures as hydrophilic bases are convenient for the formulation of sustained release suppositories of IM as similar findings were reported in the literature (12-14).
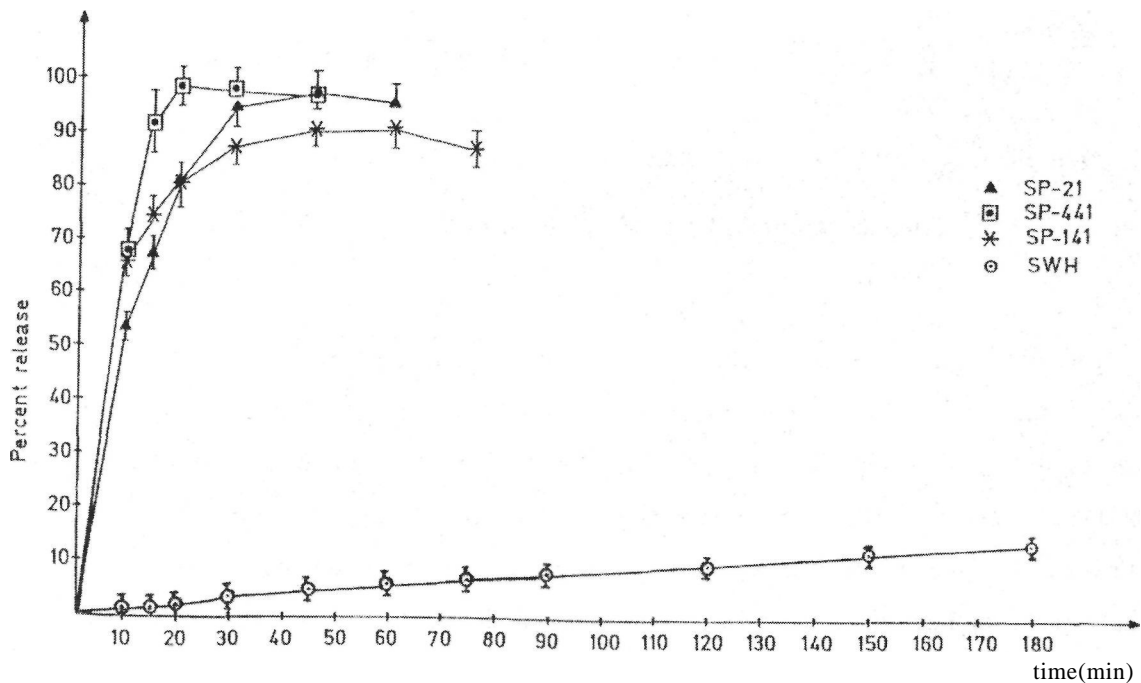

Figure 1. In vitro release profiles of IM from conventional suppositories

In vitro release profiles of IM from sustained release suppositories are as given in Figures 2 to 4. These results show that the use of CAP as the matrix material does not yield the desired sustained

release effects. The amounts of IM released especially from SP 22, SP 142 and SP 442 coded formulations in which the CAP ratio is 5%, are very close to those of conventional suppositories.
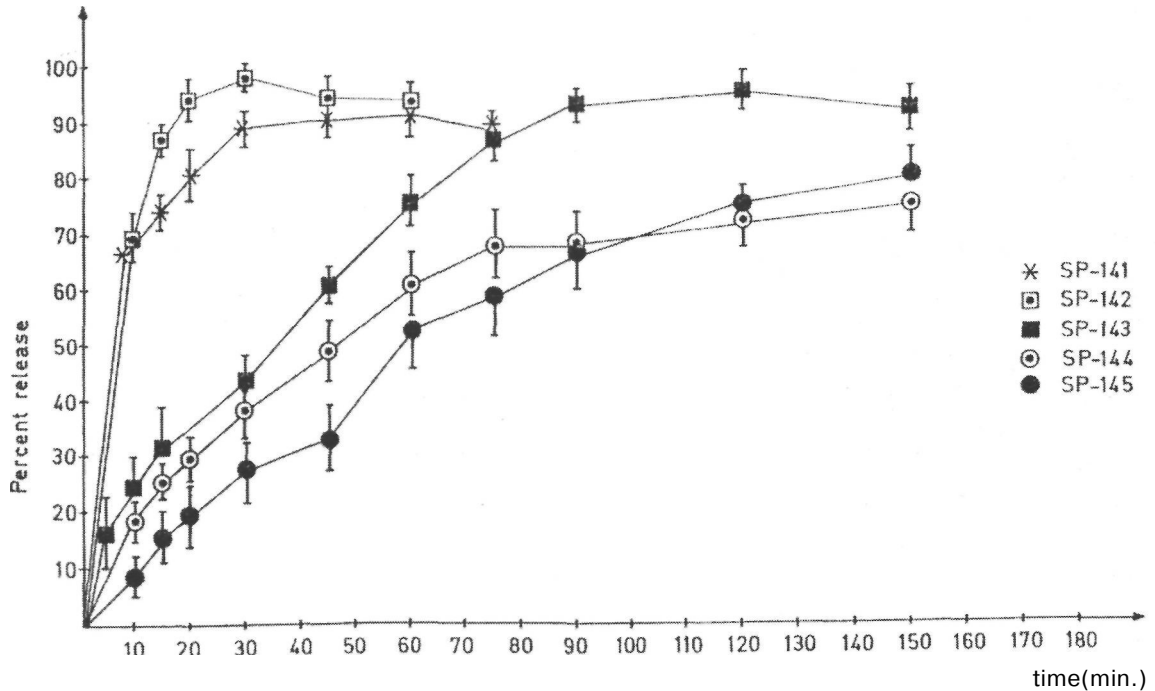

Figure 2. Effects of CAP and E RL/RS content on the release pattern of IM

from matrix suppositories. Base : PEG 1000 : 4000 (%98 : %2)

Figure 2 shows the release profiles of formulations prepared with the mixture of PEG 1000 and 4000 in the ratio of (98:2). Although the formulation SP-143 which is based on CAP in the ratio of 10%, exhibits sustained release effect, this effect is not considered to be satisfactory for sustained release EM formulations. This is because 90% of the IM content is found to be released from this formulation in 90 minutes time. As reported by Umeda et al in (15), sustained release formulation of Nifedipin yield similar results when CAP has been used as the matrix material. If CAP matrix material is replaced by E RL/RS(1:1) in the same base, the resulting formulations (SP-144 and SP-145) both give us satisfactory sustained release profiles. It is worth to note here that E RL/RS(1:1) concentration in these formulations (5% in SP-144 and 10% in SP-145) does not play a significant role on both the sustained release profiles and the amount of IM released from suppositories at the end of the experiment (nearly 70% of IM content in 150 minutes time).
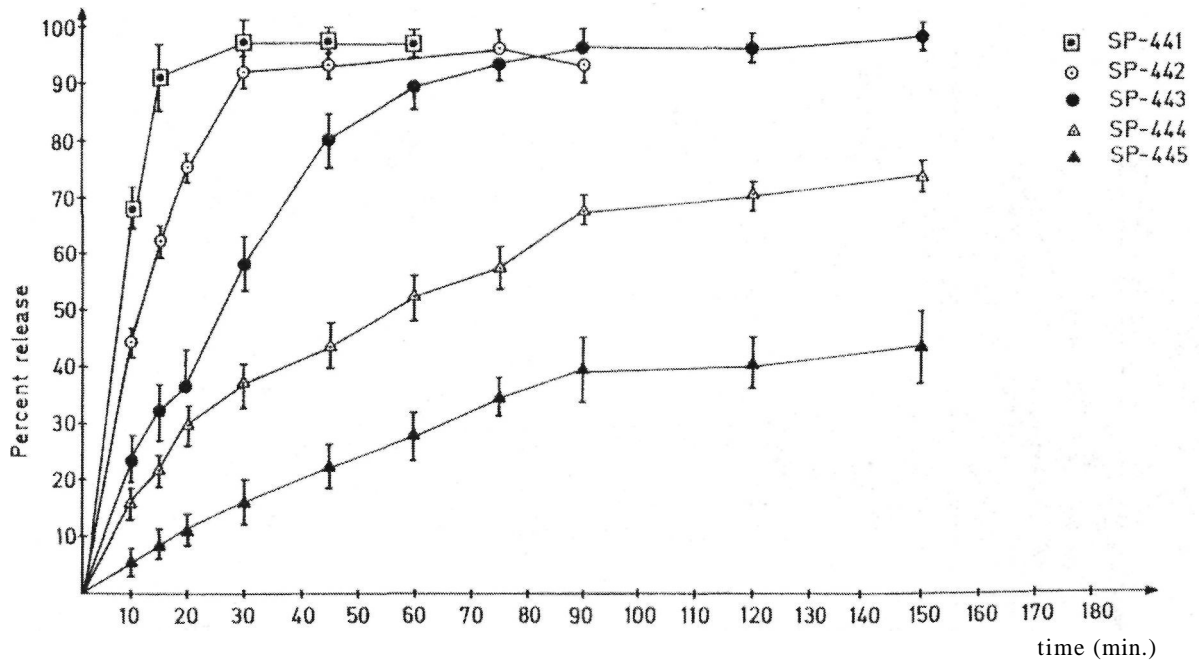
Figure 3. Effect of CAP and E RL/RS content on the release pattern of IM

from matrix supporitories. Base : PEG 400 : 4000 (%98:%2)

Figure 3 shows the release profiles of suppositories for which the mixture of PEG 400 and 4000 are used in the ratio of 50%: 50%. E RL/RS(1:1) matrix material gives better results and sustained release profiles than CAP also for this base as in the case of PEG 1000-4000 (98% :2%) base (Fig. 2). In contrary to the previous case, E RL/RS(1:1) ratio plays here an important role on both the sustained release profile and the amount of IM released from suppositories at the end of the experiment. As the ratio of E RL/RS (1:1) matrix material increases, the active substance IM releases from suppositories more slowly resulting in prolonged sustained release period. IM released from suppositories in 150 minutes time for formulations SP 444 (the polymer ratio is 5%) and SP 445 (the polymer ratio is 10%) are nearly 75% and 40%, respectively (Figure 3).
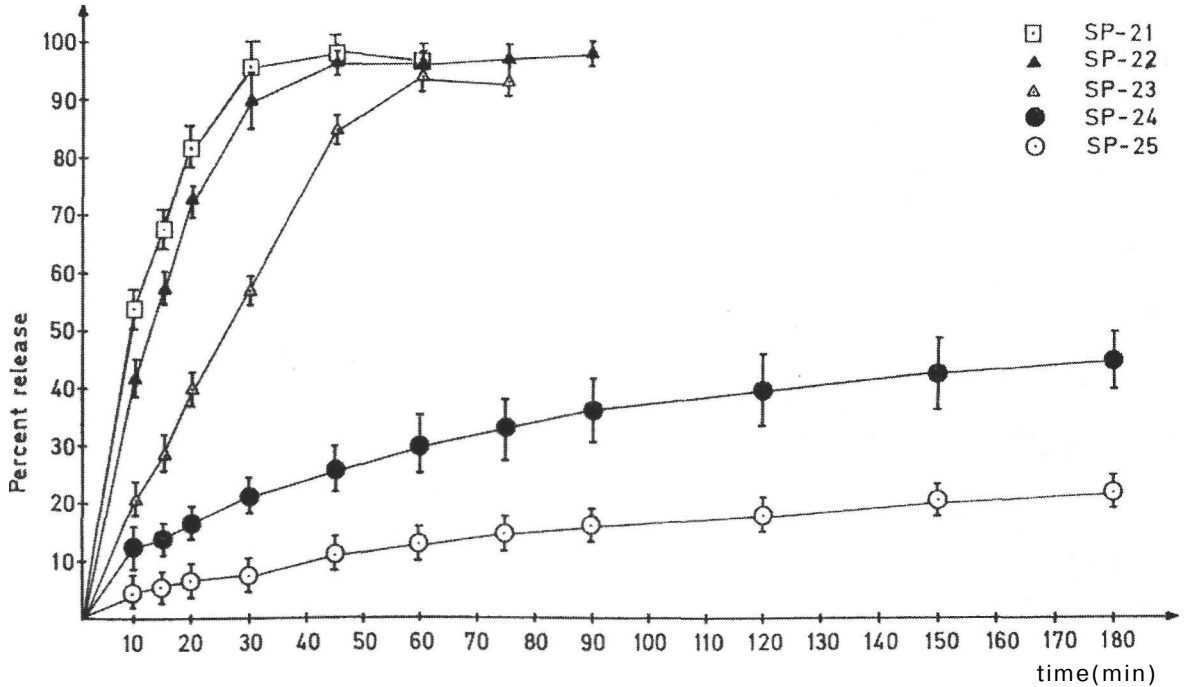
Figure 4. Effect of CAP and E RL/RS content on the release pattern of IM

from matrix suppositories. Base: PEG 2000

On the other hand, PEG 2000 base gives a slower release of IM as compared to other PEG mixtures (Figure 4). SP 21 - SP 25 coded samples prepared with PEG 2000 have also the highest disintegration time and fracture point. The above series of samples all disintegrate in a time longer than 30 minutes and are all being hard formulations. Since the fracture points for the above samples are all greater than 6.8 kg, the measurements can not be carried out. As a result of this, SP 24, SP 25 coded formulations which have E RL/RS (1:1) as matrix material in PEG 2000 base released the IM 43% and 18% respectively after 3 hours. Similar research was carried on by Ohnishi et al. (16), using PEG 2000 and Eudragit to prepare sustained release suppositories of IM and it was observed that as the amount of Eudragit L increased, the release rate of IM decreased from suppositories.

The results of the kinetic assesment of release data obtained for sustained release suppositories are given in Table 3-4. When we examined the results; the best fit was obtained for $Q \sqrt{t}$ kinetic for the samples prepared by E RL/RS (1:1). This is because E RL/RS has an inert matrix structure and hence forms a cage on the surface and in the suppositories. At first; the PEG-entrapped

IM at the surface of the suppository dissolves, than the pores and network structure would be appear, and the test solution is prevented from reaching the inner phase of the suppository. The phenomenon continue until the suppository is completely dissolved. This finding is similar to that from the suppositories containing HP55-PEG mixture matrix bases as discussed in a previous paper (12). However, when we examined the kinetic data of the suppositories prepared by CAP, it was found out that the determination coefficients were very low. When the evaluation of the same results were carried out according to SWSD(sum of the weighted square deviations) criterion, the best fit was obtained for $Q\sqrt{t}$ kinetic.

Table 3: Kinetic assesment of release data[a] for the samples contanied E RL/RS

Kinetics		SP 24	SP 25	SP 144	SP 145	SP 444	SP 445
Zero order	$kr°$	11.6	5.81	16.2	32.6	20.4	0.412
	r^2	0.921	0.944	0.741	0.937	0.853	0.874
	SSD	0.175	0.030	0.746	$9.21.10^{-2}$	0.422	0.119
	SWSD	0.206	$3.3.10^{-2}$	1.06	0.254	0.621	0.169
First order	kr	0.167	0.789	0.279	0.705	0.441	0,229
	r^2	0.949	0.957	0.821	0.988	0.921	0.895
	SSD	0.146	$2.69.10^{-2}$	0.503	$9.38.10^{-3}$	0.214	$4.82.10^{-2}$
	SWSD	0.175	$2.95.10^{-2}$	0.770	$1.78.10^{-2}$	0.337	$8.86.10^{-2}$
$Q\sqrt{t}$	k	0.580	0.118	1.77	1.83	1.78	0.668
	r^2	0.986	0.993	0.876	0.981	0.948	0.951
	SSD	$2.78.10^{-3}$	$7.6.10^{-4}$	$8.31.10^{-2}$	$5.72.10^{-2}$	$2.46.10^{-2}$	$3.01.10^{-2}$
	SWSD	$4.66.10^{-3}$	$8.3.10^{-4}$	0.441	$9.90.10^{-2}$	$9.98.10^{-2}$	$4.59.10^{-2}$

s : Summary of autput obtained from program DISSOL (17).
kr^0: Zero ordef release rate constant,
kr : First order rate constant,
k : The rate constant from the slope of the linear regression of cumulative amount release per unit area versus square root of time,
SSD: Sum of the square deviations,
SWSD : Sum of the weighted square derations.

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Table 4; Kinetic assesment of release data[a] for the
samples contanied CAP

Kinetics		SP 22	SP 23	SP 142	SP 143	SP 442	SP 443
Zero order		35.6	72.7	18.8	27.6	28.9	23.4
	r^2	0.664	0.911	0.343	0.735	0.577	0.596
	SSD	0.886	0.105	1.40	0.686	1.09	1.17
	SWSD	1.38	$-7.74.10^{-2}$	2.13	-0.347	1.4	1.22
First order	kr	2.40	2.58	139	1.03	1.58	1.11
	r^2	0.869	0.950	0.194	0.778	0.670	0.636
	SSD	0.111	0.118	1,25	$6.89.10^{-2}$	0.479	0.220
	SWSD	0.365	0.302	2.15	0.309	1.04	0.838
$Q\sqrt{t}$	k	7.06	5.24	11.5	3,07	6.90	3.59
	r^2	0.776	0.958	0.447	0.867	0.693	0.754
	SSD	0.153	$6.90.10^{-2}$	0.272	0.128	0.211	0.245
	SWSD	$-8.91.10^{-2}$	0.186	$-9.7.10^{-2}$	-0.674	$-4.44.10^{-2}$	-0.118

a : Summary of autput obtained from program DISSOL (17).
kr^0 : Zero order release rate constant,
kr First order rate constant,
k : The rate constant from the stope of the linear regression of cumulative amount release per unit area versus square root of time,
SSD : Sum of the square deviations,
SWSD : Sum of the weighted square devations.

In conclusion, E RL/RS (1:1) combination is a good matrix material for sustained released suppositories of IM.The SP 144 and SP 444 coded formulations appear to be suitable for development of a rectal drug-delivery preparation offering sustained release.

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