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In vitro drug liberation and kinetics of sustained release indomethacin suppository

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Abstract

The aim of this study was to formulate sustained release (SR) suppositories containing indomethacin (IND) microspheres. In the first part of the study, IND microspheres were prepared by solvent evaporation method. Ethyl cellulose was used as polymer. Shape and surface charactheristics, particle size and size distribution of microspheres were determined. The effect of drug: polymer ratio and stirring rate on microsphere formation, average particle size, drug loading capacity and in vitro IND release were investigated. The highest drug loading capacity was found with 1:1 drug–polymer ratio. Stirring rate caused insignificant effect on drug loading capacity but particle size. Increase in stirring rate resulted in a decrease in particle size. In the second part, SR suppositories were formulated by incorporating IND microspheres having the highest drug loaded. The bases used were PEG mixtures (400:1500:4000) and Witepsol H15. Qualitative controls and IND assay on the suppositories were carried out. The drugs released were evaluated by in vitro dissolution tests. Comparative results of SR suppositories containing IND microspheres with that of conventional ones showed that the former has sustained effect up to 480 min in vitro. Release results were evaluated kinetically and the data was fitted (Bt)[a] kinetics.

Keywords: Indomethacin; Microsphere; Suppository; Sustained release; Rectal administration

1. Introduction

The advantages of suppositories over other dosage forms are reduction of side effects namely gastrointestinal irritation and the avoidance of both disagreable taste and first pass effect. The general aim in designing sustained release (SR) suppositories is to obtain a desirable blood concentration of the drug, to maintain such a concentration at a roughly constant level for a suitable period of time. Furthermore, the formulation of a new dosage form as SR suppositories, obviously gives a new vision and increases the therapeutic possibilities [1–3]. SR suppositories can also be preferred to achieve sustained action medication clinically which alleviates the pain during sleep being often helpful in reducing anxiety.

Indomethacin (IND), a non-steroidal anti-inflammatory drug is commonly used for relief of pain and stiffness in rheumatoid diseases [4]. It is often administered orally. Since IND produce gastrointestinal side effects, rectal administration is used as an alternative to oral route. There are several reports on formulation of SR suppositories but none subjected SR suppositories composed of microspheres [1,2,5–11].

The aim of this study was to formulate SR suppositories containing IND microspheres. Release of IND from SR suppositories were evaluated by in vitro dissolution tests and the data was compared with that of conventional suppositories.

2. Experimental

2.1. Materials

IND gift from Nobel Drug Co., Turkey, ethyl cellulose N 22 NF purchased Hercules GMBH, Ger-

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many and all other reagents and chemicals were of analytical grade.

2.2. Procedure

2.2.1. Preparation of IND microspheres

IND microspheres were prepared by solvent evaporation technique. The organic layer consisted of IND dissolved in a mixture of ethyl cellulose and acetone (2:75) was emulsified with the addition of the oil phase which is a mixture of solid and liquid paraffin (2:100). Tween® 80 was used as the emulsifying agent. The microspheres formed were filtered, washed with cyclohexane and finally dried an overnight at room temperature.

The influence of process variables, such as drug:polymer ratio (1:1, 1:1.5, 1:2) and stirring rate (1000, 1500, 2000 rpm) were investigated on microsphere formation, average particle size, drug loading capacity and in vitro drug release.

2.2.2. Morphology and size distribution of IND microspheres

Shape and surface charactheristics of the IND microspheres were investigated and photographed using Scanning Electron Microscope (SEM, Jeol 840 AJXA, Japan). Microspheres were also subjected to combined sieving set analysis to determine particle size characteristics.

2.2.3. Drug loading capacity of IND microspheres

IND microspheres were completely dissolved in a mixture of 0.1 N HCl and methanol (1:9) and the content of IND loaded was assayed spectrophotometrically (Shimadzu spectrophotometer, model UV-1601) at 318 nm.

2.2.4. Dissolution of IND microspeheres

Dissolution of IND from the microspheres was carried out using USP XXII basket method. Microspheres containing 25 mg of IND were dispersed in the dissolution medium (900 ml, 0.2 M pH 7.2 phosphate buffer solution, 37 °C ± 0.5, 100 rpm). At appropriate times, 5 ml of the test solution was removed and 5 ml of the same fresh fluid was added to maintain the constant volume. The amount of IND was assayed spectrophotometrically at 318 nm.

2.2.5. Preparation of SR suppositories

SR suppositories composed of IND microspheres were prepared by employing melting method. Witepsol H15 and a mixture of PEGs [(400:1500:4000) (7.5:30:62.5)] were used as two different suppository bases. Homogenous dispersions were formed in melted bases with microspheres of highest drug loading capacity (33.85%) within the particle size range of 125–212 μm. and then moulded. Comparative studies were run with conventional IND suppositories prepared. The codes and composition of all suppositories were listed in Table 1.

2.2.6. Physicochemical analysis of SR suppositories

SR suppositories of IND microspheres were analyzed for their weight variation, hardness, melting time and IND content.

2.2.7. Dissolution of SR suppositories

In vitro drug release from SR suppositories (S3, S4) compared with that of conventional ones (S1, S2) were determined using the USP XXII paddle method (900 ml, 0.2 M pH 7.2 phosphate buffer solution, 37 °C ± 0.5, 100 rpm) At appropriate intervals (0.5–8 h), 5 ml samples were taken and the content of IND was assayed spectrophotometrically at 318 nm. Results obtained were evaluated to determine the best-fitted kinetic model.

3. Results and discussion

Table 2 indicates the influence of process variables as drug:polymer ratio and stirring rate on average particle size and drug loading capacity. Increase in polymer ratio resulted in decrease in the amount of drug encapsulated. Variations in stirring rate caused no significant difference with respect to drug loading capacity. Higher mixing rate led to the formation of microspheres with smaller sizes (Table 2). These results are in agreement with Roy et al. and Babay et al. [12,13]. The highest loaded drug was found with 1:1 drug–polimer ratio. Insignificant effect was obtained between particle size and drug loading capacity (Table 2).

According to the morphological analysis IND microspheres were spherical and porous in respect to their shape and surface (Fig. 1).

Table 1
Formulation variables of conventional and SR suppositories of IND

Formulation	Constituents			
	S1	S2	S3	S4
IND	0.025	0.025	-	-
IND microspheres	-	-	0.074	0.074
PEG 400	-	0.200	-	0.195
PEG 1500	-	0.795	-	0.779
PEG 4000	-	1.656	-	1.624
Witepsol H15	2.105	-	2.081	-

S1: conventional suppositories with Witepsol H15; S2: conventional suppositories with mixed PEGs; S3: SR suppositories with Witepsol H15; S4: SR suppositories with mixed PEGs (the amounts are given in grams).

Table 2
Influence of process variables (drug:polymer ratio and stirring rate) on IND loading capacity and particle size

Drug:polymer ratio	Stirring rate (rpm/min)	Average particle size (μm)	Drug loading capacity (%) ±SD [a]
1:1	1000	300–710	33.18±0.19
	1500	212–300	33.98±0.43
	2000	125–212	33.85±0.54
1:1.5	1000	300–710	22.43±0.12
1:2	1000	300–710	20.70±0.26

[a] $n = 3$.

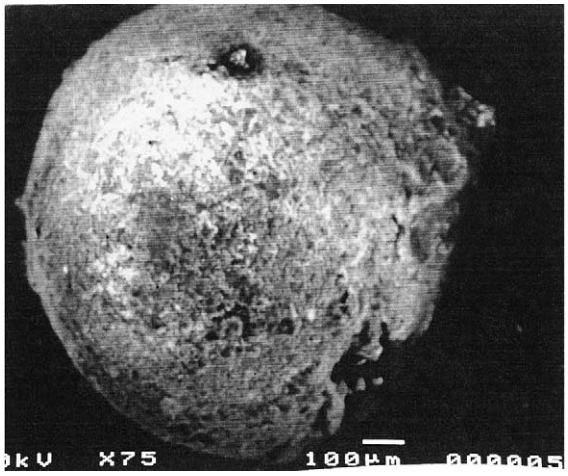

Fig. 1. Scanning electron micrographs of IND microspheres (125–212 μm) at magnification of ×75.

The results of released drug from IND microspheres with different particle sizes are shown in Fig. 2. SR behaviour was observed with all of the formulations examined. The percentage of IND released from microspheres within 8 h was approximately 94% (Fig. 2). No significant effect of particle size on released amount of IND was observed. These data are in agreement with those of Bodmeier et al. [14].

Weight variation, hardness, and melting time of SR suppositories prepared from IND microspheres were similar to those of the standards (Table 3). Content

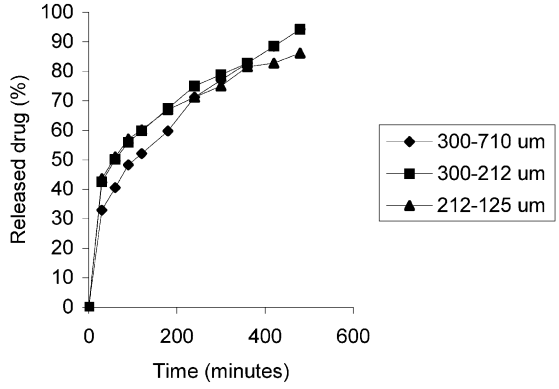

Fig. 2. Release profiles of IND microspheres with different particle sizes. (0.2 M phosphate buffer solution, pH 7.2).

Table 3
Weight variation, hardness, and melting time of conventional and SR suppositories

Parameters	S1±SD [a]	S2±SD [a]	S3±SD [a]	S4±SD [a]
Weight variation (g)	2.14±0.01	2.65±0.02	2.15±0.01	2.63±0.01
Hardness (kg)	3.16±0.15	3.62±0.15	2.80±0.16	3.42±0.19
Melting time (min)	19.00±1.00	14.17±0.76	15.67±1.53	14.00±1.00

[a] $n = 20$.

uniformity was found within the expected values (Table 4).

In vitro dissolution tests showed that SR suppositories prepared with Witepsol H15 and mixed PEGs have SR effect (Fig. 3). The percentage of the drug dissolved within 8 hours was 85.02±0.01% in SR suppositories composed of IND microspheres based Witepsol H15 (S3). On the other hand 94.21±0.01% of drug released in 4 hours from Witepsol H15 based IND suppositories examined as control (S1). Suppositories containing IND microspheres prepared with the base consisting of PEG's mixture (S4) released 86.55±0.01% of drug in 8 h while corresponding control with conventional suppositories (S2) gave 98.43±0.01% and 30 min, respectively. Hence the rate of drug released from S3, S4 were slower than S1, S2.

In vitro release charactheristics of SR suppositories were evaluated to determine the best-fitted kinetic model (Table 5). The data obtained were in agreement with (Bt)[a] kinetics.

Suppositories prepared with IND loaded microspheres using Witepsol H15 and PEG bases [(400:1500:4000) (7.5:30:62.5)] showed SR effect up to

Table 4
Content uniformity of conventional and SR suppositories

Formulations	IND (%) ±SD [a]
S1	99.28±0.25
S2	97.92±0.19
S3	101.88±0.54
S4	101.52±0.41

[a] $n = 3$.

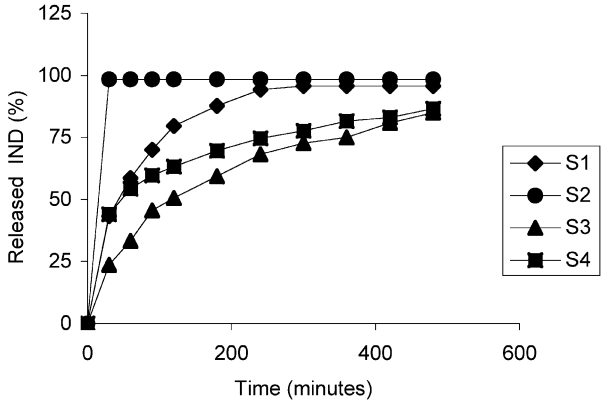

Fig. 3. Release profiles of IND from the suppositories prepared with Witepsol H15 (S1, S3) and mixed PEGs (S2, S4).

Table 5
Kinetical assessment of the SR suppositories of IND microspheres

Kinetical model	Parameters	S3	S4
(Bt)[a]	r^2	0.9945	0.9974
	b	5.9×10^{-4}	2.5×10^{-4}
	a	0.6015	0.3567
RRSBW	r^2	0.9839	0.9943
	β	0.7159	0.4339
	t_d	196.165	110.626
Zero-order	r^2	0.9146	0.9107
	k_1	0.31×10^{-1}	0.21×10^{-1}
First-order	r^2	0.8017	0.8492
	k_2	0.23×10^{-2}	0.12×10^{-2}
Higuchi model	r^2	0.9790	0.9777
	k_3	0.9087	0.6095

k_1, mg/min^{-1}; k_2, min^{-1}; k_3, mg/cm^{-2}/min$^{-0.5}$; t_d, min; S3, SR suppositories with Witepsol H15 base; S4, SR suppositories prepared with mixed PEGs.

480 min in vitro. From these results, it was concluded that reducing the frequency of drug administration provides more convenient therapy and less risk of side effects. Thus, the SR suppositories composed of IND microspheres can be suggested as an alternative way to conventional dosage forms.

Acknowledgements

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