DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 16(4), 707-717 (1990)

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RELEASE OF INDOMETHACIN FROM SUPPOSITORY BASES

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ABSTRACT

The in vitro release of indomethacin from different suppository bases was investigated using the USP rotating basket dissolution method. Suppositories containing 100 mg of indomethacin were prepared by the fusion method using theobroma oil, Witepsol, polyethylene glycols, and glycerinated gelatin. The percent released was found to be in the order PEG 3 = PEG 4 = PEG 5 = glycerinated gelatin > theobroma oil = Witepsol. The addition of polysorbate 80 resulted in a significant increase in the percent indomethacin released in the case of fatty bases and a small increase in the case of water-soluble bases.

INTRODUCTION

Indomethacin is a nonsteroid with anti-inflammatory and analgesic properties[1]. However, it causes a number of adverse effects including the most frequent gastroitestinal reactions[2-5], mouth ulcers[6], and oesophageal ulceration[7]. Consequently, the rectal administration of indomethacin in suppository-form may offer an advantage over its administration in capsules- or tablet-form in eliminating such reactions.

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The release of a drug from a suppository is greatly dependent on the suppository formulation[8]. The in vitro release of indomethacin was found to be greater with a polyethylene glycol base[9]. On the other hand, the release rate of indomethacin was reported to decrease as the percentage of polyethylene glycol 4000 or 6000 increased[10]. More recentrly the release of indomethacin was found to be higher from oily bases with low hydroxyl values[11].

Drug release from a suppository is also influenced by the presence of surfactants in the suppository formulation[11-14]. Increase in the release of indomethacin as a result of inclusion of dioctyl sodium sulphosuccinate was reported by Othman and Muti[11]. In contrast, the same authors reported a marked decrease in indomethacin release as a result of inclusion of polysorbate 80. The influence of inclusion of surfactant on drug release was found to depend on the nature and concentration of surfactants[11-15].

In view of the above variable results, this study was undertaken to investigate the in vitro release of indomethacin from different suppository bases. In addition, the effect of inclusion of a nonionic surfactant such as polysorbate 80 on the release rate was examined.

MATERIALS AND METHODS

Materials

Polyethylene glycols (PEG) 400, 1540, 4000, and 6000, and gelatin (B.D.H Chemicals, Ltd,. Poole, England); disodium hydrogen ortho-phosphate, potassium dihydrogen ortho-phosphate (Koch-Light Lab., Ltd., Buckinghamshire, England); glycerin (Searle Co., Chadwell Wealth, Essex, England); Polysorbate 80 (Sigma Chemical Co., Poole, England); theobroma oil (cocao butter) and Witepsol H15 (Dynamit Nobel Chemicals, Troisdorf-Oberlat, West Germany). Indomethacin was provided as a gift from the Jordan Pharma-

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TABLE 1
The Composition of Suppository Bases.

Constituent	Suppository Base.					
	1	2	3	4	5	6
Theobroma Oil	100%					
Witepsol H15		100%				
PEG 400					20%	18%
PEG 1540			75%	70%	33%	
PEG 4000			25%			
PEG 6000				30%	47%	
Gelatin						25%
Glycerin						20%
Water						37%

ceutical Co., Na'ur, Jordan. All chemicals were analytical or reagent grade purity except indomethacin which was pharmaceutic grade.

Methods

Preparation of Suppositories

The displacement values for all suppository bases (Table 1) were first determined[16], and then the required amount of base was calculated. All suppositories, containing 100 mg indomethacin each, were prepared by the fusion method[17] using a metal mold of 24 cavities. Suppositories having an additional 0.5, and 5% polysorbate 80 were also prepared. All suppositories were stored in a dessicator at room temperature for 24 h before use.

Uniformity of Weight

Twenty suppositories were randomly selected from each base and weighed individually. The average weight and percent deviation of each suppository was calculated.

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Disintegration Test

The USP tablet disintegration apparatus (DT4, Erweka, West Germany) was used to determine the disintegration of the prepared suppositories using 100 ml of water as the immersion fluid. A suppository was placed in each of three tubes of the basket, and was covered with a disk. The time required for each suppository to completely disintegrate at 37±5°C was determined.

Release of Indomethacin from Suppository Bases.

The USP rotating basket dissolution apparatus (DT-D6, Erweka, West Germany) was used for the determination of release rates of indomethacin from the various suppository bases. Each suppository was placed in the basket and lowered into a flask containing 500 ml of phosphate buffer solution (pH 7.8). The basket was rotated at 120 rpm at a constant temperature (37±0.5°C). 5-ml samples were withdrawn at appropriate time intervals and assayed to obtain a dissolution profile. 5-ml of phosphate buffer were immediately added to the dissolution medium to compensate for sampling. The absorbances of the withdrawn solution were measured at 319 nm on a spectrophotometer (Shimadzu UV-240, Shimadzu Corporation, Kyoto, Japan) against blanks consisted of the corresponding plain suppository bases. Concentrations were then determined with references to a standard curve.

RESULTS AND DISCUSSION

The uniformity of weight of the prepared indomethacin suppositories was determined according to the B.P. method[18]. The average weight was found to be 1.113, 1.101, 1.356, 1.325, 1.343, and 1.335g for theobroma oil, Witepsol, PEG 3, PEG 4, PEG 5, and glycerinated gelatin, respectively. All the suppositories prepared met the uniformity of weight test of the B.P.

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TABLE 2
Disintegration Time of Suppository Bases

Suppository base	Distigration time (min)
Theobroma oil	3.0
Witepsol H15	2.5
PEG 3	13.5
PEG 4	14.8
PEG 5	15.6
Base 6	18.6

The disintegration times of the prepared indomethacin suppositories are shown in Table 2. The B.P.disintigration test uses three suppositories and requires not more than 30 min. for the disintegration of fat-based suppositories and not more than 60 min. for water-soluble suppositories. All the formulated suppositories met these requirments. However, the glycerinated gelatin-based suppositories required the longest time for complete disolution followed by PEG-based suppositories. Moreover, within the PEG-indomethacin suppositories, it was found that as the percentage of PEG 6000 increased, the disintegration time increased. The fat-based suppositories, theobroma oil and witepsol, which melt at body temperature, exhibited the lowest disintegration times.

The percent indomethacin released from the fat-based suppositories is depicted in Fig. 1. The amounts released at 15 and 30 min. intervals are shown in Table 3. The data indicate that there is no significant differences in the percent of indomethacin released during the first half hour or the cumulative amount released after one hour. In both

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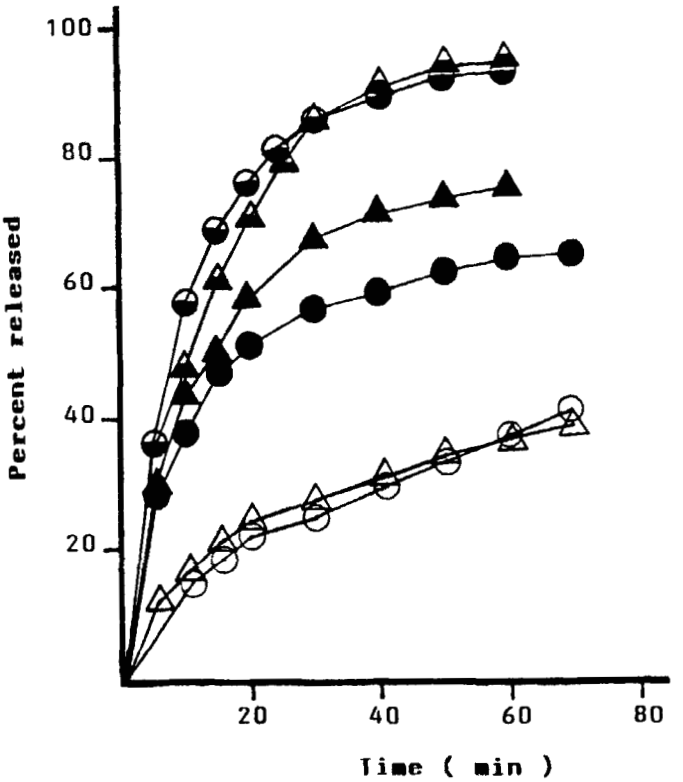

FIGURE 1

Percent released of indomethacin from the fatty bases: ○ *Theobroma* oil; ◒ *Theobroma* oil + 0.5% polysorbate 80; ● Theobroma oil + 5% polysorbate 80; △ Witepsol; ▲ Witepsol + 0.5% polysorbate 80%; ▲ Witepsol % 5% polysorbate 80.

TABLE 3

Percentage of Indomethacin Released from the Fatty Bases at 15 and 30 min. Intervals

Suppository base	15 min.	30 min.
Theobroma oil	18.0	25.0
+0.5% polysorbate 80	69.0	85.0
+5.0%	46.9	56.7
Witepsol H15	21.0	27.5
+0.5% polysorbate 80	61.0	85.0
+5.0% polysorbate 80	50.0	67.0

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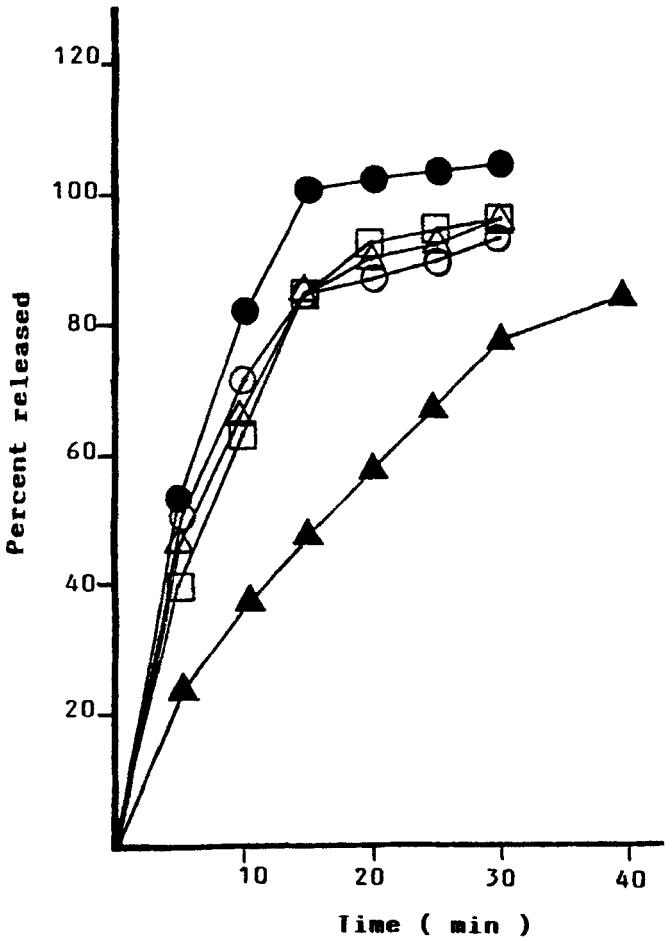

FIGURE 2

Percent released of indomethacin from the water-soluble bases: ○ PEG 3; ● PEG 3 + 0.5% Polysorbate 80; △ PEG 4; □ PEG 5; ▲ Base 6.

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TABLE 4
Percentage of Indomethacin Released from the Water Soluble Bases at 15 and 30 min. Intervals

Suppository base	15 min.	30 min.
PEG 3	84.5	93.0
+0.5% polysorbate 80	100.0	104.0
PEG 4	83.5	86.2
PEG 5	84.5	86.0
Base 6	46.8	76.9

cases, the addition of low concentration of polysorbate 80 (0.5%), resulted in an increase in the percent released. This might be due to the wetting action of the nonionic surfactant. On the other hand, the inclusion of higher percentages of polysorbate 80 (5%) in theobroma oil or Witepsol suppositories did not result in enhanced release over the low percentages. This is probably due to micellar solubilization which reduces the free concentration of the drug.

The percent of indomethacin released from the water soluble bases is depicted in Fig. 2. The amounts released at 15 and 30 min. intervals are shown in Table 4. The data indicate that the PEG-based suppositories are superior to glycerinated gelatin-based suppositories with respect to the time of release and amount of indomethacin released. This could be due to the faster disintegration of the PEG-based suppositories (13.5-15.6 min.) compared to 18.6 min. for the glycerinated gelatin-based suppositories. Moreover, the data indicate that the addition of 0.5% polysorbate 80 to PEG 3 base resulted in an appreciably higher

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release of indomethacin. This finding is consistent with what was reported in the literature[14] in that polysorbates of high HLB values, like polysorbate 80, enhanced the release of chloramphenicol from PEG 1500 suppositories.

Comparing the fatty bases with the water-soluble bases used in this study with respect to the release of indomethacin, the data presented indicate that the water-soluble bases, with the exception of glycerinated gelatin, were superior to the fatty bases. These results are in good agreement with those reported in the literature[9]. The lower and slower release associated with the fatty bases could be due to the lipophilicity of indomethacin manifested in its relatively high partition coefficient (C octanol/C water = 16.09)[15] and complete solubility in these bases. Thus, the transport of the drug from the oil phase to the aqueous phase becomes the rate-limiting step.

In conclusion the various suppository bases used in this study may be ranked with respect to release of indomethacin in the following order: PEG 3 = PEG = PEG 5 > glycerinated gelatin > theobroma oil = Witepsol. The inclusion of 0.5% or 5% polysorbate 80 in the fatty bases resulted in a significant increase in the percent indomethacin released compared to a marginal increase upon the inclusion of 0.5% of the same surfactant in the PEG 3 base.

ACKNOWLEDGEMENTS

The authors are very grateful to Mr. Rabah J. Halman for his technical assistance.

REFERENCES

1. A. Osol, in "Remington's Pharmaceutical Sciences", Mack Publishing Co., Easton, Pennsylvania, 1985, p. 1118.

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2. R.T. Taylor, E.C. Huskiss, G.H. Whitehou, F.D. Hart, D.H. Trapnel, Br. Med. J., 4, 734 (1968).

3. J.H. Swallow, Br. Med. J., 1, 783 (1969).

4. M.R. Thompson, Br. Med. J., 280, 448 (1980).

5. A.N. Campbell, J.R. Beasley, A.P. Kenna, Lancet, 1, 1110 (1981).

6. J. Guggenheimer, Y.H. Ismail, J. Am. Dent. Ass., 90, 632 (1975).

7. F.W.H.M. Merkus, Pharm. Int., 1, II (1980).

8. A.T. Florence, D. Attwook, in "Physicochemical Principles in Pharmacy", The Mecmillan Press Ltd., London. Basingstoke. 1981, p. 391.

9. N.J. Vidras, V.E. Reid. N.R. Bohidar, F.M. Plakogiannis, J. Pharm. Sci., 71, 945 (1982).

10. E.H. Mills, J.A. Whileworth, J. Andrews, N.Z.J. Aust. Med., 12, 478 (1982).

11. S. Othman, H. Muti, Drug Develop. Ind. Pharm., 12, 1813 (1986).

12. N.A. Allawalla, S. Riegelman, J. Am. Pharm. Ass., Scient. edn., 42, 267 (1953).

13. M. Kata, Pharmazie, 24, 395 (1969).

14. J.M. Plaxco, C.B. Free, C.R. Rowlands, J. Pharm. Sci., 56, 609 (1967).

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15. S. Noro, Y. Komatsu, T. Uesugi, Chem. Pharm. Bull., 30, 2912 (1982).

16. S.J. Carter, in "Cooper and Gunn's Dispensing for Pharmaceutical Students", Pitman Medical Ltd., London 1976 pp. 238-239.

17. G.S. Banker, R.K. Chalmers, in "Pharmaceutics and Pharmacy Practice", J.B. Lippincoot Co., Philadelphia Pennsylvania pp. 416-417.

18. British Pharmacopoeia, University Printing House, Cambridge, 1980, pp. A118-A119.

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