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Influence of fat composition on the melting behaviour and on the in vitro release of indomethacin suppositories

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Summary

Thermal analysis was used to determine the influence of monoglycerides, a fatty acid-fatty acid methyl ester blend, fatty acid polyethylene glycol esters and indomethacin on the melting behaviour and hardening of triglyceride suppository bases. The influence of these additives on the in vitro release of indomethacin was also investigated. A correlation was seen between the melting point of the monoglycerides and the increase in melting point of the added triglyceride. The addition of indomethacin always resulted in higher melting temperatures. No important influence of the additives and the drug was observed on the hardening behaviour of the suppository bases. Indomethacin release, in vitro, was higher for polyethylene glycol and Suppocire AP formulations than for all other bases. The chemical composition and melting point of the monoglycerides added to the triglyceride can influence the in vitro release of indomethacin. Fatty acid-fatty acid methyl ester blends increased the release of indomethacin only when they were added to a lauric triglyceride (Witepsol H 15).

Introduction

Triglyceride and polyethylene glycol (PEG) suppositories induce severe mucosal damage after sub-chronical application. This irritative effect could be reduced by addition of monoglycerides and fatty acid (derivatives) (De Muynck et al., 1991).

This study reports on the influence of monoglycerides, a fatty acid-fatty acid methyl ester blend and fatty acid polyethylene glycol esters on the melting behaviour of triglyceride suppository bases. The hardening or aging phenomenon was investigated, since this is a major reason for changes in in vitro release profile and differences in pharmacokinetic behaviour of the active ingredient (Möes and Jaminet, 1976; De Blaey and Rutten-Kingma, 1977; Krowczynski et al., 1977; Voigt et al., 1982; Tukker and De Blaey, 1984).

Using the dialysis tubing method (Aoyagi et al., 1988), the in vitro release profiles of indomethacin from two commercial formulations were compared to triglyceride formulations with and without different additives. Indomethacin, an anti-inflammatory drug often used in suppository formulations was used as drug substance.

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Materials and Methods

Materials

Two commercially available indomethacin suppository formulations were used: Indocid® (Merck, Sharp and Dohme, Brussels, Belgium) and Dolcidium® (Galephar, Brussels, Belgium). Polyethylene glycol (PEG), a hydrophillic base, is used as the excipient in Indocid®, while a synthetic lauric triglyceride (Suppocire AP (Gattefossé, St Priest, France) mainly containing C_{12}–C_{18} saturated fatty acids supplemented with a non-ionic surfactant (polyethylene glycol fatty acid esters)) is used as the excipient in Dolcidium®. Each suppository contained 100 mg indomethacin.

Other suppository formulations were based on two triglyceride compositions: Witepsol H 15 (Hüls AG, Witten, Germany), a lauric triglyceride (mainly containing C_{12} and C_{14} saturated fatty acids) and Mesuro PS (Vandemoortele N.V., Izegem, Belgium) a non-lauric triglyceride (mainly C_{16}–C_{18} saturated and unsaturated fatty acids). These triglycerides were used as such or were supplemented with monoglycerides or fatty acids and fatty acid methyl esters. The monoglycerides (Dimodan®) were provided by Grindsted N.V. (Antwerpen, Belgium); the fatty acids and their methyl esters had an identical composition to that of the glyceride fatty acids from Mesuro PS (Vandemoortele, Izegem, Belgium) and were added at a 9:1 w/w ratio to Mesuro PS and Witepsol H 15, respectively. All monoglycerides were added at a concentration of 5% w/w to Mesuro PS. Only Dimodan® LS and P were added at the same concentration to Witepsol H 15.

Micronized indomethacin (< 10 μm micronized powder; Esteve Quimica, Barcelona, Spain) was used in all experiments where a drug substance was incorporated in the suppository bases.

Gas chromatography

The fatty acid composition of the suppository bases was determined by gas chromatography after hydrolysis of the mono-, di- and triglycerides with subsequent derivatisation of the fatty acids into fatty acid methyl esters. Therefore, 0.2 g of fat was dissolved in 2 ml diethyl ether. After addition of 2 ml of a methanolic KOH solution (3%) the solution was shaken and allowed to stand for 3 min at room temperature. Next, 10 ml pentane and 2 ml of water were added and the mixture was again shaken. The upper layer was twice washed with water and after adding Na_2SO_4, 2–3 μl was injected via an on-column injector in a GC (Chrompack Packard Type 438A, Delft, The Netherlands) equipped with a 15% diethylene glycol succinate on Chromosorb HP (Bio-Rad, Eke, Belgium) packed column (length 2 m, internal diameter 4 mm). Nitrogen was used as a carrier gas (inlet pressure $\pm$0.9 kg). The oven temperature was 185°C; injector and detector temperature was 200°C in both cases and detection was performed by FID. Relative peak areas were calculated and used to determine the amount of each fatty acid.

For the analysis of mono-, di- and triglyceride composition, approx. 10 mg of fat was heated with 2 ml pyridine to 60°C. Hexamethyl disilozane (0.5 ml) and trimethylchlorosilane were added and the organic solvent was removed by evaporation under N_2. The residue was redissolved in 10 ml iso-octane and 0.5–1 μl was injected on the column in a GC (Chrompack Packard Type 438A, Delft, The Netherlands) equipped with a Chrompack-Sil 5 (film thickness 0.12 μm on WCOT fused silica, length 7 m, internal diameter 0.32 mm; Chrompack International B.V., Delft, The Netherlands). The injector temperature was ambient, the detector temperature was 350°C and the oven temperature was increased from 50 to 350°C at a rate of 25°C/min. The carrier gas was helium and detection was carried out using FID. Relative peak area was used to calculate the percentages of mono-, di- and triglycerides.

Solidification curve

The solidification curves were determined for Witepsol H 15 and Mesuro PS using NMR (Brucker Minispec, Brucker Spectrospin N.V., Brussels, Belgium). The suppository bases were melted in capillary tubes and kept molten for 1 h at 60°C and next put at 10, 20 and 25°C. The

percentage solid was measured after 15, 30, 60, 90, 180, 240, and 300 min.

Production and content uniformity of indomethacin suppositories

2 g suppositories were made, each containing 100 mg micronized indomethacin in suspension. The displacement factor was found to be 0.83 for both Witepsol H 15 and Mesuro PS. 50 suppositories were prepared for each composition by melting the base at 40–45°C before adding the micronized indomethacin to the melt. The suspension was then poured into stainless-steel suppository molds previously cooled to 7°C and the molds were placed in a refrigerator for at least 5 h. A weight variation and a content uniformity test was performed according to the USP XXII (1989).

The time between production and in vitro dissolution never exceeded 5 days. During that period the suppositories were stored at 7°C.

Thermal analysis

The suppository base was molten before being placed in the DSC cup. 6–10 mg were weighed accurately in a cup cooled to 7°C to prevent sedimentation of the suspended indomethacin. The samples were put into hermetically sealed cups (part no. 900790.901 for the upper part and 900796.901 for the bottom part). The cups were closed and the samples were kept at 7°C for 24 h before the first analysis was performed. Thermal analysis was then performed on samples stored at 25 ± 0.2°C, after 55, 140 and 260 days. An empty cup was always used as a reference cell. The analysis were performed on a 9900 Computer/Thermal Analyzer system (E.I. du Pont de Nemours & Co Inc., Wilmington, DE, U.S.A.). During analysis the samples were equilibrated at 15.0°C, kept isothermal for 2 min and subsequently heated at 2.00°C/min until a temperature of 50.00°C was reached.

For the determination of the melting points of the monoglycerides, the samples were equilibrated at −15.0°C and kept isothermal for 2 min before being heated at 5.00°C/min until attaining a temperature of 80.00°C.

The sample size (6–10 mg) as well as the heating rate (2°C/min) were chosen in order to detect the maximum number of transitions in the melting pattern (Liversidge et al., 1981). The melting points (defined by Liversidge et al., 1981) as the temperature of the last peak maximum during thermal analysis) of monoglycerides and of freshly prepared and stored formulations of triglycerides (Witepsol H 15 and Mesuro PS) with and without additives (monoglycerides or fatty acid-fatty acid methyl ester blends) with and without indomethacin were determined.

The influence of storage time and temperature on the melting behaviour of suppository bases was investigated for the following samples: without Mesuro PS additions, Mesuro PS supplemented with Dimodan® LS, Dimodan® P and the fatty acid-fatty acid methyl ester blend, with and without indomethacin.

The reproducibility of the DSC method was determined by measuring the melting temperature of five samples of Mesuro PS stored under the same conditions as for the freshly prepared samples. The day-by-day variation was assessed by recording the melting profile for freshly prepared Mesuro PS samples. The DSC equipment was calibrated using indium and mercury at a heating rate of 5°C/min. Melting temperatures (onset temperatures) were 157.11 ± 0.40°C ($n = 4$) for indium (theoretical 156.6°C) and -36.31 ± 0.20 ($n = 4$) for mercury (theoretical −38.9°C). The DSC equipment was adjusted using the resulting values. Recalibration was performed every 2 months.

In vitro dissolution

A dialysis method was used as described by Aoyagi et al. (1988). It consisted of a dialysis tubing (Visking, size 7-30/32 inch, Medicell International Ltd, London, U.K.) washed with boiling water and next with distilled water each for 5 min at room temperature. Before use, the remaining water was removed and the tubing was tied at one end. The suppository was inserted into the dialysis tubing and the system closed at the other end, leaving a distance of 5 cm between the two knots. After connecting an 8 g weight to

the tied end, the tubing was immersed in the dissolution fluid. This fluid was stored in a USP dissolution vessel equipped with a paddle, rotating at 50 rpm at a height of 1.5 cm above the bottom of the vessel. The dialysis tubing was placed in such a way that the lowest knot was at 3 cm above the paddle and 2 cm from the side wall of the dissolution vessel. 900 ml of 0.1 M buffer solution pH 7.2 (USP XXII) heated to 37 ± 0.2°C was used as dissolution fluid. The indomethacin release was measured spectrophotometrically (λ = 320 nm) (Beckman DU 65 spectrophotometer, Beckman Instruments, Inc., Fullerton CA, U.S.A.) at 20-min intervals over an 8 h time period. Six suppositories of every composition were tested. Dissolution profiles were recorded for suppositories made of Mesuro PS without additives and with fatty acid-fatty acid methyl ester or monoglycerides, for Witepsol H 15 without additive or supplemented with Dimodan® LS or fatty acid-fatty acid methyl ester and for the Indocid® and Dolcidium® suppositories.

A statistical evaluation of the in vitro results was performed using independent *t*-test.

TABLE 1

Chemical composition of suppository bases and additives used: amount of free fatty acids, mono-, di-, triglycerides, fatty acid derivatives and chemical composition according to chain length

	LS	CP	S	BP	PM 300	PM	PV	P
Dimodan® monoglycerides (percentage amount (w/w) of mono-, diglycerides and free fatty acids)								
Free fatty acid	3.35	3.80	0	0	0	0.50	0.28	0.34
Monoglyceride	91.00	85.90	92.40	86.10	100	96.80	97.50	97.30
Diglyceride	5.65	10.10	7.60	13.90	0	2.70	1.61	2.32
Composition of Dimodan® monoglycerides (percentage amount (w/w) of glyceride fatty acid according to its chain length)								
C8:0–C15:0	2.10	0.75	1.60	1.30	3.60	2.15	0.42	2.18
C16:0	10.20	21.80	29.10	42.70	29.00	28.09	12.00	26.90
C16:1	0.12	0.18	2.50	0.30	1.20	0.29	–	0.13
C17	0.12	0.07	0.40	0.10	1.50	1.00	0.21	0.67
C18:0	11.50	4.64	20.30	5.60	62.70	66.30	86.70	67.50
C18:1	15.00	29.00	37.10	39.70	0.30	0.23	0.04	0.16
C18:2	59.20	41.60	7.30	9.40	–	–	–	–
C20:0–C22:0	1.76	1.96	1.70	0.90	1.70	2.03	0.63	2.46

	Mesuro PS	Witepsol H15	Suppocire AP
Composition of triglyceride suppository bases (percentage amount (w/w) of mono-, di-, triglycerides and of PEG fatty acid esters)			
Monoglycerides	–	0.3	2.5
Diglycerides	2.9	10.7	28.0
Triglycerides	97.1	89.0	55–60
PEG-fatty acid esters	–	–	10–15
Lauric/Non-lauric base	Non-lauric	Lauric	Lauric
Percentage amount (w/w) of glyceride fatty acid according to its chain length.			
C8:0–C10:0	–	1.5	–
C12:0	0.1	54.3	46.9
C14:0	0.3	19.7	20.0
C16:0	17.5	11.5	16.3
C18:0	6.5	12.8	16.8
C18:1	68.0	0.1	–
C18:2	6.2	–	–
C20:0–C22:0	1.4	0.1	–

Results and Discussion

The mono-, di- and triglyceride content and fatty acid compositions for all fat substances used as determined by gas chromatography are listed in Table 1.

Production and content uniformity of indomethacin suppositories

The requirements of the USP XXII were met for both weight variation and content uniformity. All values were within the range of 85.0 and 115.0% of the labeled claim and the coefficient of variation (C.V.) was less than 6.0%.

Solidification curves

Solidification profiles for Witepsol H 15 and Mesuro PS were obtained to determine the temperature at which the molten base should be treated to prevent sedimentation of the suspended indomethacin after transferring the molten base into the molds. As can be seen from Fig. 1, the triglycerides solidified quickly when stored at 10°C. After 15 min, 86.0% of Mesuro PS and 96.4% of the Witepsol H 15 were in the solid state. At higher temperatures (20 and 25°C), the difference between both triglycerides was more pronounced. More time was needed before Mesuro PS reached a high solid fraction. For Witepsol H 15, at 20°C, 91.1% solid fraction was present after 30 min while with Mesuro PS only 69.6% was in the solid state; at 25°C, 67.8% of the Witepsol base was solid after 90 min compared to only 5.4% for Mesuro PS. The difference in solidification behavior is due to the difference in chemical composition of both fat bases. Witepsol H 15 mainly contains C12:0 and C14:0 fatty acids while Mesuro PS fatty acids are of the C16:0 and the C18:1 type. According to these observations the molds were cooled at 7°C before suppositories were moulded. Afterwards the molds were further cooled at 7°C.

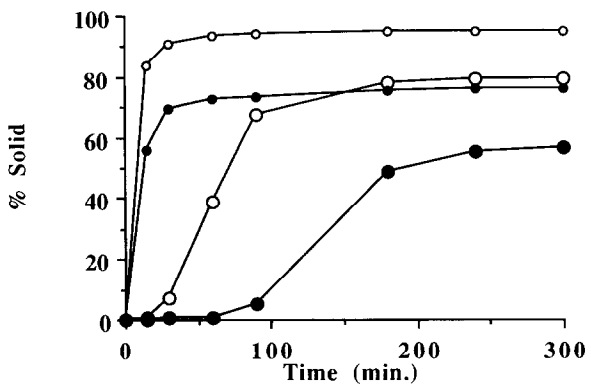

Fig. 1. Solidification profile for Mesuro PS and Witepsol H 15 at 20 and 25°C. (∘———∘) Witepsol H 15 (20°C), (○———○) Witepsol H 15 (25°C), (·———·) Mesuro PS (20°C), (●———●) Mesuro PS (25°C).

Thermal analysis

In order to eliminate thermal history, the DSC samples were prepared from completely molten fat bases. Thermal analysis of mono-, di- and triglyceride mixtures shows overlap of exothermic and endothermic peaks. Therefore, melting profiles rather than sharp melting peaks are obtained for these products (Müller, 1984). According to the work of Liversidge et al. (1981), the melting point of the formulations was taken as the temperature of the last peak maximum on the thermal analysis pattern. This temperature was in accordance (±1°C) with the melting point of the highest melting component under the hot stage microscope (Liversidge et al., 1981). A storage temperature of 25°C was chosen because temperatures higher than room temperature allowed a quicker response to variations in melting behaviour. Nevertheless, storage temperatures above 25°C would counteract the hardening phenomenon due to partial melting of the fat base (Müller, 1984; Thoma, 1984).

As a validation of the DSC equipment, the within-day and the day-by-day variations were calculated. The within-day variation determined on five Mesuro PS samples was low. The mean melting temperature was 34.93°C with a C.V. of 0.28%. The day-by-day variation was determined on four different days during the storage period of the samples. The mean melting temperature of Mesuro PS calculated from these samples was 34.95°C with a C.V. of 0.20%. Because of these very low coefficients of variation it was decided to perform the DSC analysis on only one sample for each formulation at every sampling time.

The melting temperature of samples from a molten base directly put in a DSC cup or of samples scraped off from the fracture in the middle of the suppository and put in a DSC cup was determined for Mesuro PS. This experiment was also performed on samples of Mesuro PS stored for 16 and 38 days at 25°C. Variations of less than 1% in melting temperature between both preparation methods were observed (results not shown) and allowed storage of the samples of the different formulations directly in the DSC cups. The melting points of the monoglycerides are listed in Table 2. They vary between 13.35 and 75.72°C. One monoglyceride, Dimodan® PV, contained two fractions melting at 40.45 and at 74.99°C, respectively, with a corresponding enthalpy of 17.6 and 59.7 J/g. After addition of the monoglycerides at a concentration of 5% (w/w) to Mesuro PS, a proportional relationship was seen between the melting point of the monoglyceride and the melting point of the added triglyceride (Fig. 2 and Table 2). Compared to the melting temperature of the Mesuro PS without additions, higher melting temperatures were achieved using Dimodan® PM300, PM, PV or P (Fig. 2). The lower melting fraction of Dimodan® PV had apparently no major influence on the melting behaviour of the mixture. Adding indomethacin to the formulations induced higher melting temperatures in all cases. With Dimodan®, LS, CP and S no proportional relationship between the melting point of the monoglyceride and the mixture was observed. For all other formulations, with or without indomethacin, the proportional relationship was observed (Fig. 2).

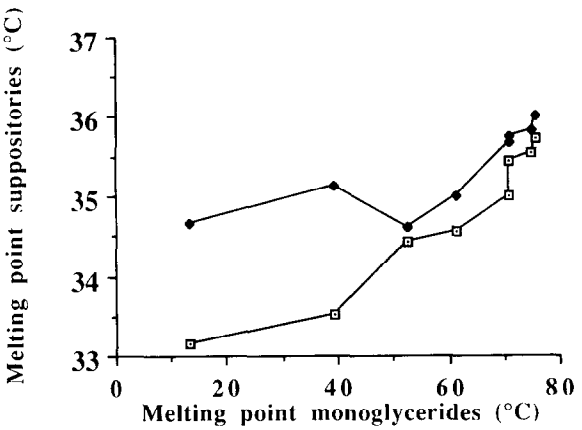

Fig. 2. Relation between melting point of the monoglycerides and the melting point of the suppositories (triglycerides added supplemented with monoglycerides. (⊡ ——— ⊡) Without indomethacin, (◆ ——— ◆) with indomethacin.

The addition of the fatty acid-fatty acid methyl ester blend resulted in lower melting tempera-

TABLE 2

Melting point of monoglyceride, triglyceride without and with indomethacin and percentage indomethacin dissolved after 8 h (±C.V.) (n = 6)

	Melting point monoglyceride (°C)	Melting point without indomethacin	Melting point with indomethacin	% dissolved after 8 h (±S.D.)
Suppocire AP (Dolcidium®)	–	33.88	34.43	43.77 ± 3.13
PEG (Indocid®)	–	–	–	41.28 ± 4.31
Mesuro PS	–	34.93	35.31	31.59 ± 3.59
Mesuro PS + Dimodan® LS	13.35	33.16	34.65	30.66 ± 2.43
Mesuro PS + Dimodan® CP	39.22	33.53	35.14	31.24 ± 2.79
Mesuro PS + Dimodan® S	52.48	34.42	34.61	29.91 ± 3.40
Mesuro PS + Dimodan® BP	61.43	34.57	35.00	32.16 ± 3.26
Mesuro PS + Dimodan® PM 300	70.87	35.00	35.67	20.43 ± 1.73
Mesuro PS + Dimodan® PM	70.98	35.43	35.75	23.31 ± 2.88
Mesuro PS + Dimodan® PV	40.45/74.99	35.54	35.84	14.15 ± 2.70
Mesuro PS + Dimodan® P	75.72	35.72	36.01	14.23 ± 2.36
Mesuro PS + FA/FAME	–	33.79	34.30	27.28 ± 2.44
Witepsol H 15	–	35.00	35.02	32.54 ± 1.97
Witepsol H 15 + Dimodan® LS	13.35	31.71	31.77	34.86 ± 2.59
Witepsol H 15 + FA/FAME	–	31.73	32.07	34.73 ± 2.69

tures compared to the pure Mesuro PS and the addition of indomethacin did not influence this decrease (Table 2).

Dimodan® LS and the fatty acid-fatty acid methyl ester blends were also added to Witepsol H 15. In these formulations, with and without indomethacin, the additions induced a decrease in melting point (Table 2).

The different triglyceride bases showed melting point from 33.5 to 35.0°C. Due to the addition of indomethacin the melting temperature increased to values ranging from 34.43 to 35.31°C. The storage of these samples induced a substantial increase in melting temperature over the 260 day period. As can be seen from Table 3, the fastest increase was observed during the first 55 days except for the Witepsol H 15 formulation supplemented with indomethacin where a delay in hardening was observed (Table 3). The presence of indomethacin did not dramatically affect the hardening of the fat bases. Formulations of Mesuro PS supplemented with monoglycerides (Dimodan® LS and P) and with the fatty acid-fatty acid methyl ester blend were also submitted to storage tests. The increase in melting point was comparable to that seen for Mesuro PS. From these data it can be concluded that the additives did not change the hardening behaviour of the bases.

The literature is not consistent on this subject. Blending mono- and diglycerides or surface-active agents in the triglycerides has been shown to prevent recrystallisation to fat polymorphs with higher melting points (Müller, 1984). Thoma and Serno (1983) did not find a clear relationship between the hydroxyl value (the hydroxyl value of the excipients is affected by the presence of mono- and diglycerides, free fatty acids, fat alcohols and free glycerol and the hardening of a fat base. Eckert et al. (1979) demonstrated the influence of a higher amount of diglycerides on the increase in melting temperature of suppositories.

In vitro dissolution

In vitro dissolution tests for suppositories are of essential importance during the early stage of formulation development and in quality control (batch-by-batch uniformity) (Abdou, 1989). Several in vitro dissolution methods have been described (Bornschein et al., 1985; Zuber and Pellion, 1987), some of which have been used for indomethacin release studies, the rotating basket method (Suleiman and Najib, 1990), the flow-through system (Möller, 1984) and the dialysis tubing method (Othman and Muti, 1986; Aoyagi et al., 1988). Using these different dissolution systems, some in vitro/in vivo correlation was

TABLE 3

Increase of melting temperature of some suppository formulations during storage at 25°C

		1 day	55 days	140 days	260 days
Suppocire AP (Dolcidium®)	without indomethacin	33.88	37.33	37.79	38.17
	with indomethacin	34.43	37.90	38.14	38.39
Witepsol H 15	without indomethacin	33.55	36.87	37.11	37.89
	with indomethacin	35.00	34.84	36.54	37.70
Mesuro PS	without indomethacin	34.93	38.18	38.60	38.74
	with indomethacin	35.31	38.14	38.44	38.50
Mesuro PS + Dimodan® LS	without indomethacin	33.16	38.14	37.89	38.75
	with indomethacin	34.65	37.96	37.86	38.32
Mesuro PS + Dimodan® P	without indomethacin	35.14	36.97	38.54	39.55
	with indomethacin	36.01	39.43	39.79	39.98
Mesuro PS + FA/FAME	without indomethacin	33.79	36.03	37.25	37.93
	with indomethacin	34.30	36.97	37.06	37.55

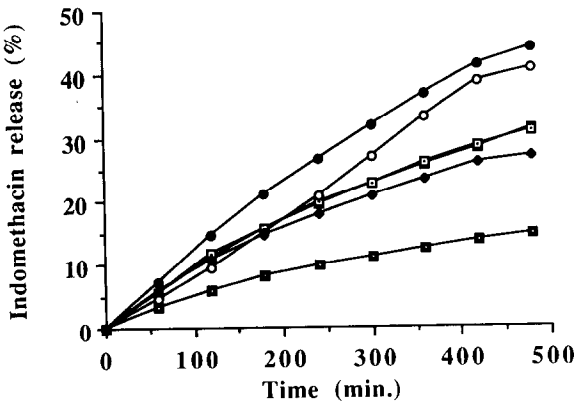

Fig. 3. In vitro indomethacin release for different suppository formulations using the dialysis tubing method ($n = 6$). (□——□) Mesuro PS, (⊡——⊡) Mesuro PS + Dimodan LS, (■——■), Mesuro PS + Dimodan P, (○——○) PEG, (●——●) Suppocire AP, (◆——◆) Mesuro PS + FA/FAME.

shown (Vidras et al., 1982; Möller, 1984; Aoyagi et al., 1988).

We used the dialysis tubing method as described by Aoyagi et al. (1988) because a good correlation between the in vitro method and the bioavailability in rabbits and pigs, as animal models, was found. The system seems to simulate quite well the small amount of water in the rectal compartment and the spreading after melting according to the surface-active properties. Typical dissolution patterns for some formulations are shown in Fig. 3.

The behaviour of the PEG suppositories (Indocid®) in the dialysis tubing was totally different from that of all other bases. Due to the osmotic effect of PEG, the dialysis tubing was filled with dissolution medium. In the mixture of dissolved PEG and dissolution medium indomethacin was completely dissolved. This phenomenon was not observed with the Suppocire AP formulations (Dolcidium®) although the indomethacin release profile was not significantly different from that of the PEG formulation after 480 min ($P > 0.05$) (Table 2). The indomethacin release from PEG and Suppocire AP was significantly higher than those obtained with all Mesuro PS and Witepsol H 15 compositions ($p < 0.01$). The faster indomethacin release from PEG suppositories compared to lipophilic formulations has been shown previously by several authors using different dissolution system (Kerckhoffs and Huizinga, 1967; Suleiman and Najib, 1990). The higher release rate from Suppocire AP suppositories must be attributed to the presence of the non-ionic surfactant. The presence of non-ionic surfactants may result in an increase (Gueurten et al., 1983) or a decrease in in vitro release depending on the type and concentration of the surfactant. The positive influence of the wetting action by 1% polysorbate 80 on the in vitro release of indomethacin was demonstrated by Archondikis and Papaioannou (1989) and Suleiman and Najib (1990). At higher concentrations (5% polysorbate 80), however, a decrease in indomethacin release was observed and micellar solubilization was suspected as being the reason. This concentration-dependent phenomenon was also demonstrated for meclozine HCl (Becirevic et al., 1984).

Other factors influencing the in vitro drug release are particle size of the suspended drug and the viscosity of the suppository base (Abdou, 1989). The influence of the particle size in our experiments should be minimized, since in all formulations indomethacin of the same particle size (< 10 μm) was used.

The difference in triglyceride fatty acid chain length, their degree of saturation and the amount of diglycerides did not influence the in vitro release of indomethacin as was proven by comparing the dissolution patterns of Mesuro PS and Witepsol H 15 ($p > 0.05$). The addition of the fatty acid-fatty acid methyl ester blend to Mesuro PS or Witepsol H 15 shows no significant influence on the amount of drug released compared to the triglycerides without additives ($p > 0.05$). However, the release rate from Witepsol H 15 supplemented with this adjuvant was significantly higher than from Mesuro PS with the same additives ($p < 0.05$).

Contradictory results on the influence of the hydroxyl value on the indomethacin release rate were reported by Othman and Muti (1986) and Möller (1984). In our experiments, the amount of indomethacin released from Witepsol H 15 base supplemented with Dimodan® LS was not signifi-

cantly different from that of the triglyceride without additions ($p > 0.05$). The effect of addition of monoglyceride at a 5% (w/w) level to Mesuro PS can be correlated to the melting point of the pure monoglyceride (Table 2 and Fig. 4). Using monoglycerides with melting temperatures ranging from 13.35 to 61.43°C no significant influence on the amount of indomethacin released (p values $>$ 0.05) was observed. With monoglycerides of higher melting temperatures (above 70°C), significantly lower releases were obtained compared to the formulations with lower melting monoglycerides ($p < 0.01$). Within the group of suppositories formulated with higher melting monoglycerides (> 70°C) significantly different drug releases were seen between Dimodan® PV and P (melting points 74.00 and 75.72°C) and Dimodan® PM 300 and PM (melting points 70.87 and 70.98°C, respectively) ($p < 0.01$). In addition to the fraction melting at 74.00°C Dimodan® PV also has a lower melting fraction (40.45°C). No significant difference ($p > 0.05$) was observed between the release from Dimodan® PV and P supplemented suppositories. We assume the release was being influenced by the higher melting fraction of the monoglyceride.

The same relationship was found between the melting point of the triglyceride (Mesuro PS) supplemented with monoglyceride and the indomethacin release (Fig. 4 and Table 2). However, the close relationship between the melting points of the suppositories and the amount released as reported by Aoyagi et al. (1988) was not confirmed here. Our study indicates that the hydroxyl value is important for the in vitro drug release rate from suppositories and is influenced by the chemical composition and the melting point of the monoglyceride and the triglyceride base (Fig. 4).

In conclusion, the weight variation and content uniformity tests met the requirements of the USP XXII for all formulations used. The difference in the monoglyceride melting point was reflected in the melting behaviour of the added triglyceride. Adding indomethacin resulted in higher melting temperatures. The hardening of the fatty bases was not dramatically influenced by the additives or by the presence of indomethacin.

The in vitro indomethacin release rate was higher for the PEG and Suppocire AP formulations in comparison to all other bases. The chemical composition and the melting point of the monoglyceride added to the triglycerides influenced the indomethacin release from the formulations. Fatty acid-fatty acid methyl esters increased the indomethacin release only when added to a lauric triglyceride (Witepsol H 15). In vivo experiments are currently in progress in order to show whether the in vitro model can be related to in vivo results.

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