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Effects of surfactant characteristics on drug availability from suppositories

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The addition of surfactants to suppository formulations is referred to in the scientific literature, but their effects on drug availability remain uncertain. Surfactants are reported to improve drug dispersion into hard fatty excipients, to increase the spreading of the melted suppository on the rectal *mucosa* leading to a greater contact surface, to reduce the viscosity of the molten mass and to reduce the pathway of drug particles to the interface. In the present study a systematic investigation based on tensiometric and rheological methods was carried out to evaluate the effects of nonionic surfactants with different HLBs (hydrophilic-lipophilic-balance) on drug availability and to clarify the possible mechanisms involved in the release process. The relationship between the melted suppositories and a membrane simulating the rectal barrier were investigated in the course of the *in vitro* release test by measuring their energy characteristics. At the same time, the potential influences of such interactions on drug release were investigated in suppositories formulated with different kinds and concentrations of surfactant additives. Drug availability was influenced not only by the interaction between the suppository and the rectal membrane but also by the interaction between surfactant, lipophilic excipient and suspended drug particles. Such interactions appear to greatly influence drug release from suppositories, which, in turn, is the main parameter determining drug availability.

1. Introduction

Adeps solidus, or hard fats, consist of mixtures of triglyceride esters with varying proportions of mono- and diglycerides. They have different physicochemical properties, such as melting point, hydroxyl value and saponification value. They are available as commercial bases and are widely used in suppositories as vehicles for a variety of drugs, either to exert local effects or to achieve systemic absorption.

In suppository formulations, drugs are usually dispersed as a suspension into the molten mass and their availability after application is conditioned by particle movement in this molten mass, by diffusion through the *interfacia* of the suppository and by dissolution into rectal fluids.

Due to this complex path, a series of chemical and physical properties of the mass, such as its melting range and melting rate, the rheological and hydrolipophilic properties of the base and hence the presence of a surfactant, can influence drug release from suppositories, producing varied therapeutic responses after administration of different formulations containing the same amount of active compound (Yoshioka et al. 1982; De Boer et al. 1990; Fontan et al. 1991; Ogiso et al. 1991; Al Gohary et al. 1993; Lindmark et al. 1997; Tamaka et al. 1998; Onyeji et al. 1999).

Drug availability is greatly influenced by its dissolution rate under rectal pH and temperature conditions. In addition, the drug concentration achieved in rectal fluids can regulate the release rate from suppositories and the gradient sustaining diffusion across the rectal barrier, thus conditioning all steps in the complex path of drug availability (Realdon et al. 2000).

The addition of surfactants to suppository formulations has been investigated, but their effects on drug availability remain uncertain. Surfactants are reported to improve drug dispersion in hard fatty excipients by modifying the surface properties of drug particles, thus influencing their migration into the rectal water phase. Surfactants may also increase the spreading of the melted suppository on the rectal *mucosa*, leading to a greater contact surface with the *mucosa*, a reduced viscosity of the molten mass and a shorter pathway of drug particles to the interface. Surfactants have been reported to improve the mobility of drug particles to the *interfacia* of suppositories thanks to a decrease in mass viscosity (Regdon et al. 1998).

In the present study a systematic investigation based on tensiometric and rheological methods was carried out to evaluate the effects of nonionic surfactants with different HLBs (hydrophilic-lipophilic-balance) on drug availability and to clarify the possible mechanisms involved in the release process.

2. Investigations, results and discussion

A series of bases were obtained by adding nonionic surfactants of the homologous series Span and Tween to a hard fatty excipient (Witepsol H 15). The Span series consists of sorbitan esters with fatty acids of differing lengths

and structures. Their HLBs are low (less than 10) and inversely related to the length of the fatty chain (C number). The Tween series, called polysorbates, consists of polyoxyethilene sorbitan esters of fatty acids differing in length and structure of the fatty chain. Due to the presence of polyoxyethilene chains, they are mainly hydrophilic, and have higher HLBs, over 10.

Two types of Span and two from the Tween series were chosen: Span 60 (sorbitan stearate ester), Span 20 (sorbitan laurate), Tween 60 (polyoxyethylene sorbitan stearate) and Tween 20 (polyoxyethylene sorbitan laurate). Two different concentrations of each surfactant, 1 and 5% (w/w) respectively, were added to Witepsol H 15.

Rheological tests performed on the bases showed that the viscosity of the molten masses at 37 °C was about 35 mPa.s and was independent of the type and concentration of surfactant added.

The tensiometric properties, expressed as surface free energy (SFE), polar (PC) and dispersed (DC) components, were calculated for the masses containing the tested surfactants and the results obtained are compared in Table 1.

As can be seen, the tensiometric properties of the lipophilic masses were modified by the added surfactant, depending on its concentration and its hydrolipophilic properties. In the presence of Tween 20 (HLB 16.7) the PC increased progressively with increased concentration and was higher than in the presence of Tween 60 (HLB 14.9). The addition of Span 20 (HLB 8.6) also increased the PC, but to a different extent compared with the Tween derivates. On the other hand, the addition of Span 60 (HLB 4.7) slightly reduced SFE with no relevant effect on PC.

The influence of paracetamol on the tensiometric properties was also investigated. Two masses were formulated containing 500 mg and 250 mg *per* dosage unit of paracetamol in Witepsol H15. The tensiometric properties were similar to Witepsol H15; however, the presence of paracetamol suspended in the molten mass produced a slight increase in PC, depending on its concentration, without modifying SFE. This effect may be ascribed to the arrangement of drug particles with polar characteristics at the surface of the mass, thus suggesting a higher preference of suppositories containing the drug for the hydrophilic mucous membrane in the rectal environment.

Masses containing the same amounts of drug (250 mg and 500 mg *per* dosage unit) were then formulated by adding 1% or 5% of surfactants of the homologous Span and Tween series to Witepsol H15. The tensiometric properties were mainly influenced by the chemical structure of the additive, particularly its hydro-lipophilic properties (Table 1). When the mainly lipophilic Span 60 (HLB 4.7) and Span 20 (HLB 8.6) were added, only slight reductions in SFE and PC were observed. This may be caused by the capacity of the lipophilic surfactant to interact with paracetamol particles, exposing its lipophilic portion to the excipient. In our formulations, only a minimal amount of Span 60 and Span 20 was applied to the molten mass with the hydrophilic portion exposed at the suppository-water interface.

The suppositories formulated with Tween derivatives showed unchanged SFE but an increased PC. When compared to Tween 60 (HLB 14.9), the addition of Tween 20 (HLB 16.7) produced higher PC values, in accordance with its higher HLB, at equivalent surfactant concentration.

This behavior can probably be ascribed to the structure of Tween molecules. Like the Span derivatives, the sorbitan ester structures allow interaction with drug particles, but the polyoxyethylene structures also permit simple interposing of drug particles between hydrophilic chains. In addition, the wider hydrophilic portion covers a larger surface area of the molten mass, giving it more polar properties.

Drug release from suppositories was expressed as AUC values of the release curves [mg vs radq(t)] over the three-hour test. The results obtained were then related to the viscosity and tensiometric properties monitored on the residues of suppositories during the test. As can be seen from the AUC data, drug release was generally influenced by the concentration and type of surfactant added.

The release of paracetamol decreased markedly in the presence of Span 60 (HLB 4.7), but increased with an increase in HLB. The addition of the most hydrophilic Tween 20 (HLB 16.7) produced an increase in drug release, independent of surfactant concentration (1 or 5%) and drug content (250 or 500 mg *per* unit).

The AUC values of the release curves are compared in Table 2 with the viscosity values of the suppository residues during the test.

For suppositories containing 500 mg paracetamol, the course of viscosity during the test was independent of the type of surfactant, but values were influenced by the characteristics of the additive and were related to paracetamol availability from the suppositories.

In the presence of Tween 20, at all concentrations tested, suppositories displayed the lowest viscosity values and highest paracetamol release at all times, and marked disintegration during the test. The high paracetamol availability and the low viscosity values are both related to the primary role played by the high HLB of Tween 20 on suppository disintegration and drug availability.

On addition of the two Span surfactants tested, drug release was reduced markedly at the highest surfactant concentration (5%), although the decreases in viscosity ob-

Table 1: Tensiometric data, expressed as surface free energy (SFE), related dispersed component (DC) and polar component (PC) values, of the suppositories obtained according to the different formulations

Paracetamol per unit (mg)	SFE, related DC and PC (mN/m) of the suppositories containing															
	Witepsol H15 surfactant free			Surfactant content (% w/w)	Witepsol H15 + Span 60 (HLB 4.7)			Witepsol H15 + Span 20 (HLB 8.6)			Witepsol H15 + Tween 60 (HLB 14.9)			Witepsol H15 + Tween 20 (HLB 16.7)		
	SFE	DC	PC		SFE	DC	PC	SFE	DC	PC	SFE	DC	PC	SFE	DC	PC
0	45.1	41.4	2.7	1	40.4	37.5	2.9	38.7	34.5	4.2	45.3	38.2	7.1	44.2	34.2	10.0
				5	41.5	38.8	2.7	39.7	35.3	4.4	45.5	38.0	7.5	47.5	33.3	14.2
250	41.7	36.3	5.4	1	33.6	30.0	3.6	35.8	31.7	4.1	42.5	31.0	11.5	42.0	23.0	19.0
				5	35.5	30.0	5.5	36.6	33.0	3.6	40.6	25.6	15.0	42.0	23.0	19.0
500	42.3	34.2	8.1	1	36.6	33.0	3.6	36.0	31.5	4.5	42.5	31.0	11.5	45.7	18.0	27.7
				5	35.4	32.0	3.4	36.0	31.0	5.0	43.5	28.5	15.0	39	18.0	21.0

Table 2: Course of viscosity at 37 °C of suppository residues collected during the release test compared with AUC values [mg vs. rad q(t)] obtained in the release test performed on the suppositories formulated with the different tested surfactants

	Paracetamol 500 mg					Paracetamol 250 mg				
	time	Surfactant 1%		Surfactant 5%		time	Surfactant 1%		Surfactant 5%	
		Viscosity (mPa · s)	AUC	Viscosity (mPa · s)	AUC		Viscosity (mPa · s)	AUC	Viscosity (mPa · s)	AUC
Span 60	0	73.3	840.96	71.3	105.84	0	60.3	675.00	61.3	93.00
	1	61.0		72.0		1	49.7		62.0	
	3	55.5		65.0		3	50.0		57.3	
Span 20	0	75.0	950.84	77.3	433.60	0	50.0	498.20	64.0	401.19
	1	55.0		69.0		1	48.8		57.0	
	3	50.0		60.0		3	47.0		56.7	
Tween 60	0	87.0	912.00	91.0	560.56	0	72.0	811.69	83.0	572.21
	1	77.0		88.0		1	66.0		78.0	
	3	65.0		70.0		3	57.0		72.0	
Tween 20	0	75.0	1160.46	81	943.00	0	75.0	803.81	81.0	572.00
	1	44.0		46		1	44.0		58.0	
	3	43.0		46		3	43.0		52.0	

served during the test were similar. The higher concentration of lipophilic surfactant allows a larger dose of drug to be trapped, thus impairing its dissolution in the medium. Suppositories containing 250 mg paracetamol *per* unit displayed analogous behavior, but with lower viscosity values due to the lower concentration of drug particles, thus confirming the obersevations previously expressed.

To evaluate the interaction taking place between the molten mass and rectal barrier, all the suppositories underwent tensiometric analysis during the release test.

The presence of paracetamol as the test drug produced slight polar properties in the lipophilic excipient.

The tensiometric measurements performed on suppository residues collected during the release test after 1, 2 and 3 h showed that as paracetamol was released, the PC of the mass decreased until it reached similar values to those of the excipient alone after 3 h.

Suppositories containing 500 mg paracetamol with the addition of Span 60 maintained high DC values in the course of the test due to the probable arrangement of surfactant molecules surrounding the suspended drug particles which are therefore trapped in the molten mass. The partition of paracetamol in the glyceride base is therefore enhanced, making its dissolution in the rectal medium difficult. This behavior was even more marked in the presence of Span 60 5% thus explaining the observed decrease in drug availability. The tensiometric properties of the suppositories formulated with Span 20, having a higher HLB, also showed a similar course, producing similar effects on drug release.

When more hydrophilic surfactants, such as Tween 60 and Tween 20, were added, different behavior was observed. In the course of the release test, the suppositories showed high values of PC, independently of the type of Tween and even though paracetamol was released, reducing its contribution to the polar properties of the mass. At the surface of the suppository residues, the hydrophilic surfactants may expose their polar fraction to the rectal phase.

The general behavior of tensiometric properties during the test as paracetamol was released followed the effect produced by the different surfactants on suppository properties. With an increase in the hydrophilic properties of the surfactant, from Span 60 (HLB 4.7) to Tween 20 (HLB 16.7), the suppository residues displayed an increase in SFE independently of surfactant concentration, and an increase of PC depending on the additive concentration.

Similar behavior was found for suppositories containing 250 mg paracetamol.

In the presence of the most hydrophilic surfactants, the general course of the tensiometric properties of residues demonstrates an increasing affinity of the suppository surface for the rectal water phase. This, in turn, displays a progressive decrease in its interfacial tension, probably due to the dissolution of an aliquot of the surfactant contained in the suppository. In particular, as reported in Table 3, in the presence of the Tween derivatives, the in-

Table 3: Course of interfacial tension (IFT) of the model rectal phase during the release test performed on the suppositories containing different tested surfactants

	IFT of model rectal phase (mN/m)							
		Time	Surfactant 1%	Surfactant 5%		Time	Surfactant 1%	Surfactant 5%
Paracetamol 500 mg	Span 60	0 h	78.2	78.2	Tween 60	0 h	78.2	78.2
		1 h	74.0	78.2		1 h	68.9	58.7
		3 h	72.0	77.6		3 h	57.3	54.7
	Span 20	0 h	78.2	78.2	Tween 20	0 h	78.2	78.2
		1 h	55.1	44.2		1 h	47.1	44.0
		3 h	57.3	44.0		3 h	42.9	38.5
paracetamol 250 mg	Span 60	0 h	78.2	78.2	Tween 60	0 h	78.2	78.2
		1 h	69.5	77.9		1 h	45.9	43.5
		3 h	70.5	79.7		3 h	49.0	42.8
	Span 20	0 h	78.2	78.2	Tween 20	0 h	78.2	78.2
		1 h	69.6	59.7		1 h	42.3	42.6
		3 h	72.0	59.6		3 h	43.2	43.0

terfacial tension of the phosphate buffer used as rectal phase decreased after the first hour of the test and thereafter remained unchanged.

In the presence of the Span derivatives, the decrease in the interfacial tension (IFT) of the water phase was lower, particularly at the 1% concentration of Span 60 and when the more lipophilic Span 20 was added. This behavior was in accordance with the lipophilic properties of the sorbitan esters which may influence their prevalent partition in the lipophilic glyceride excipient.

To complete the investigation, the tensiometric properties of the rectal membrane model were evaluated at different test times. The results obtained are reported in Table 4.

In the case of suppositories formulated with paracetamol, independently of drug content, the membrane collected during the release test showed high PC values, with only slight modifications of PC and DC during the test. When the release test was performed on suppositories containing lipophilic surfactant (Span series), no relevant modifications of PC and DC were shown in suppositories containing 250 and 500 mg of paracetamol. When the hydrophilic surfactants of the Tween series were used, the membranes collected during the test displayed a slight increase in DC, probably due to the interaction of the polyoxyethylene chains with the hydrophilic membrane and the consequent exposure of the hydrophobic portions on the membrane surface which could reduce the polar properties of the membrane itself.

Evaluation of the tensiometric properties of the suppository residues and membranes made it possible to clarify their relationship during the release test, and the influence of the additive on drug availability. In the course of the test, the surfactant-free suppositories did not modify their affinity for the membrane, independently of the quantity of drug. As a consequence, the suppositories maintained a high DC and the membranes maintained their high PC.

The suppositories formulated with Span 60 and Span 20 displayed similar behavior with unaltered affinity for the rectal membrane. Conversely, in suppositories containing 500 mg and 250 mg paracetamol, the addition of Tween surfactants produced an increase in the affinity of the molten mass for the membrane, which was even more marked in the presence of Tween 20.

Both the hydrophilic Tween surfactants increased the affinity for the membrane during the release test and the increase was related to the hydrophilic properties and surfactant concentration.

3 Experimental

3.1. Materials

Paracetamol was supplied by Farmalabor (Canosa di Puglia, BA, Italia). Witepsol H 15 (Hüls, Werk Witten, Germany) was used as the suppository base. Tween 20, Tween 60, Span 20 and Span 60 from ACEF (Fiorenzuola d'Arda, PC, Italy) were used as surfactants.

3.2. Preparation of suppositories

2.5 ml suppositories containing 250 or 500 mg of paracetamol were prepared by the melting method. Witepsol H15, or Witepsol H15 with the addition of 1% or 5% (w/w) Tween 20, Tween 60, Span 20 or Span 60, were used as suppository bases. Witepsol H15 was melted and the surfactant and paracetamol were added at 40 °C; a homogeneous dispersion was obtained with the aid of a Silverson turbomixer (Waterside, Chesham, Bucks, UK). The molten mass was poured in PVC molds at 37 °C and allowed to cool to room temperature. Prepared suppositories were stored at 4 °C until use.

3.3. In vitro release study

Experiments were performed using the dynamic membrane diffusion method. The acceptor phase was phosphate buffer at pH 7.4 (modelling rectal pH). Six suppositories were individually enclosed with 5 ml phosphate buffer pH 7.4 in a kidney dialysis membrane (Visking® Dialysis Tubing 36/32, 12-14000 Da, Medicell International ltd, London, UK) and placed in 3 l of buffer in a vessel at body temperature (37 ± 0.5 °C), which was stirred constantly (100 rpm) with a paddle.

Samples of the acceptor phase (2 ml) were collected for each suppository after 15, 30, 45, 60, 90, 120, 150 and 180 min, which were then replaced, and the quantity of paracetamol released was determined spectrophotometrically (UV-Cary 50 Scan, Varian) in the samples of acceptor phase using the absorbance at $\lambda = 242$ nm. The mean values were calculated from parallel measurements on each occasion (± SEM).

Table 4: Course of tensiometric properties of the membranes used during the release test performed on suppositiories with different formulations

SFE related DC and PC (mN/m) of membranes during the test

			Time	DC	PC	SFE			Time	DC	PC	SFE
Paracetamol 500 mg	Span 60	1%	0 h	11.12	58.45	69.57	Tween 60	1%	0 h	11.12	58.45	69.57
			1 h	10.72	59.11	69.83			1 h	14.06	56.78	70.84
			3 h	10.67	59.32	69.99			3 h	15.01	57.14	72.15
		5%	0 h	11.12	58.45	69.57		5%	0 h	11.12	58.45	69.57
			1 h	12.47	56.21	68.68			1 h	15.50	59.40	74.90
			3 h	8.31	63.90	72.21			3 h	15.90	57.99	73.89
	Span 20	1%	0 h	11.12	58.45	69.57	Tween 20	1%	0 h	11.12	58.45	69.57
			1 h	11.45	57.55	69.00			1 h	15.55	51.40	66.95
			3 h	11.51	57.16	68.67			3 h	15.19	51.68	66.87
		5%	0 h	11.12	58.45	69.57		5%	0 h	11.12	58.45	69.57
			1 h	10.47	59.61	70.08			1 h	15.90	52.94	68.84
			3 h	10.47	59.58	70.05			3 h	16.30	53.43	69.73
Paracetamol 250 mg	Span 60	1%	0 h	11.12	58.45	69.57	Tween 60	1%	0 h	11.12	58.45	69.57
			1 h	7.34	65.96	73.30			1 h	10.73	59.07	69.80
			3 h	11.23	58.23	69.46			3 h	10.74	58.95	69.69
		5%	0 h	11.12	58.45	69.57		5%	0 h	11.12	58.45	69.57
			1 h	12.95	55.42	68.37			1 h	8.62	60.77	69.39
			3 h	12.03	57.00	69.03			3 h	10.15	58.75	68.90
	Span 20	1%	0 h	11.12	58.45	69.57	Tween 20	1%	0 h	11.12	58.45	69.57
			1 h	11.88	57.16	69.04			1 h	14.75	52.56	67.31
			3 h	12.40	56.36	68.76			3 h	15.39	51.62	67.01
		5%	0 h	11.12	58.45	69.57		5%	0 h	11.12	58.45	69.57
			1 h	10.20	59.95	70.15			1 h	13.77	53.60	67.37
			3 h	10.44	59.56	70.00			3 h	13.50	53.51	67.01

The test was performed simultaneously on a total of 18 suppositories placed in three vessels and was stopped in each vessel after 1, 2 and 3 h. Rheological and tensiometric tests were performed on the residues collected.

3.4. Determination of suppository viscosity

The viscosity of the suppositories was evaluated using a Rotovisco RV 20 viscosimeter (Haake, Karlsruhe, Germany) with a RC 20 rheocontroller programmer and NV measurement equipment. The rheological determinations were carried out at 37 ± 0.1 °C on the mass of 6 suppositories stored at 37 °C for 20 h. The same determination was performed on suppositories during the drug release test, as described in a previous article (Realdon et al. 1997). After interrupting the drug release test at 1 h time intervals, the suppositories were first cooled to 5 °C and subsequently incubated at 37 °C for 20 h, and then tested for viscosity.

3.5. Tensiometric methods

The tensiometric characterization of dialysis membranes, suppositories and liquids was carried out using a G40 tensiometer (Kruss GmbH, Hamburg) equipped with a G211 camera and Haake C/F3 thermostat (Fowkes et al. 1964; Owens et al. 1969; Wu 1971; Neumann et al. 1979; Girault et al. 1984; Gaydos et al. 1987; Hansen et al. 1991).
During the release test, six samples were taken from each vessel after 1, 2 and 3 h. The membranes, suppository residues, and the liquid simulating rectal fluids were measured for their tensiometric characteristics. Similar measurements were performed on the suppositories and the membranes soaked with phosphate buffer.

3.5.1. Tensiometric characteristics of the membranes during the release test

The tensiometric measurements were performed on both membranes soaked with phosphate buffer (pre-test standard) and membranes collected after 1, 2 and 3 h during the release test. The contact angle method and *sessile drop* software were used.
The dialysis tubes containing the suppository and rectal phase were emptied and opened to obtain a flat sheet suitable for characterization. The outer side of the membrane was fastened to a suitable device. Ethylene glycol and didiodomethane were used as standard liquids.
A drop of standard liquid (diameter 2–6 mm) was applied to the surface of the sample and the contact angle was measured. The angles determined were used in the Owens method to obtain the polar (PC) and dispersed component (DC), the sum of which expresses the surface free energy (SFE).

3.5.2. Tensiometric measurements of the suppositories

The tensiometric characteristics of the suppositories were determined both in pre-test conditions and after 1, 2 and 3 h during the release test.
The mass of six suppositories was poured at 38 °C under constant stirring in to a Perspex® cell. After 24 h, a solid mass was collected which had a smooth lower surface on which tensiometric evaluation was performed at 37 °C using the *sessile drop analysis* calculation program. The results were expressed as the mean value of the contact angle of three determinations with each standard liquid.

3.5.3. Surface tension of the rectal fluids

The surface tension was calculated on the phosphate buffer under pre-test conditions, and on the rectal phase collected from the dialysis tubes during the release test after 1, 2 and 3 h. The pendant drop method and the *pendant drop* calculation program were used. A 0.5 mm diameter needle was used. A mean value of surface tension was calculated from 5 determinations of the pendant drop profile for each liquid examined.

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