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Surface wetting effects in the lipid osmotic pump

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Summary

An osmotically driven system for the controlled release of lipoidal drugs is described. The system consists of a solid, low melting core surrounded by a semipermeable membrane that controls the rate of drug release. The core contains the drug, a lipid carrier, and an osmotic agent. In operation, water passes through the semipermeable membrane, interacts with the osmotic agent, and increases the pressure within the system, which forces the lipid carrier and drug through orifices in the coating. For this system to pump the lipid carrier rather than the osmotic agent solution, the semipermeable membrane must be preferentially wetted by the lipid phase rather than the aqueous phase containing the osmotic agent. A technique is described for measuring contact angles as an indication of the surface wetting properties of cellulose acetate films in order to predict which membranes might selectively pump the lipid phase in a coated tablet. The results from the contact angle measurements show good correlation with actual tablet performance.

Introduction

The first description of an oral osmotic drug delivery system occurred in the mid 1970's (Theeuwes, 1975). Since then, various systems have been developed which have extended the utility of osmotic pressure as the driving force for the controlled release of drugs (Higuchi and Leeper, 1976; Baker, 1976; Theeuwes, 1984; Zentner et al., 1985). Osmotic systems have been particularly successful in achieving constant release rates because of their lack of sensitivity to variations in the pH or motility of the gastrointestinal tract (Theeuwes, 1975; Zentner et al., 1985). The delivery rate from these systems is governed by the osmotic pressure of the formulation and the water permeability of the controlling membrane. Although earlier work largely focused on applications for water soluble drugs, a number of systems were later developed for release of water-insoluble drugs via the use of carrier vehicles and/or compartmentalized devices (Nakano et al., 1976; Cortese and Theeuwes, 1982).

The lipid osmotic pump (Amidon et al., 1987) has been designed for the controlled release of lipoidal drugs. The system consists of a solid, low melting core surrounded by a semipermeable membrane that controls the rate of drug release. The core consists of an osmotic agent and a lipid carrier containing the drug. For the system to pump the lipid carrier rather than the osmotic agent solution, the semipermeable membrane must

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be preferentially wetted by the lipid phase. This report describes a technique for measuring contact angles as an indication of the surface wetting properties of cellulose acetate films in order to predict which polymers might selectively pump the lipid solution in a coated tablet. The results from the contact angle measurements are compared with the in vitro performance of tablets coated with these membranes.

Materials and Methods

Materials

Witepsol® H-35 (melting point 33.5–35.5 °C) was used as the lipid carrier. Witepsol suppository bases are glycerol esters of mixtures of saturated vegetable fatty acids, in which lauric acid predominates (Dynamit Nobel Chemicals; Kay-Fries, Inc., distributor). Reagent grade sodium chloride was used as the osmotic agent. Scarlet red, a lipid soluble dye, was used to monitor lipid release and was obtained from Aldrich Chemical Co. Isopropyl myristate (IPM) was purchased from Sigma Chemical Co. or Croda and was used as received. Timolol free base was obtained from Merck & Co., Inc.

Cellulose esters (cellulose acetate CA 398-10, CA 436-80S, CA 320S, cellulose acetate butyrate CAB 553-0.4, and cellulose acetate propionate CAP 482-20) were obtained from Eastman Chemical Co. Reagent grade absolute methanol, methylene chloride, and acetone were used as the coating solvents. Polyethylene glycol 400 was purchased from Fisher Scientific Co.

Contact angle measurements

Two series of cellulosic ester films (containing 0 and 30% w/w PEG 400) were prepared by drawing 2–7% solutions of polymer in methylene chloride/methanol/acetone mixtures over a glass plate using a casting knife (Gardner Instruments, Co.) set at 0.5 mm. The solvents were allowed to evaporate slowly. The films were removed from the glass and allowed to air dry for a week or more before use to minimize residual solvents in the film.

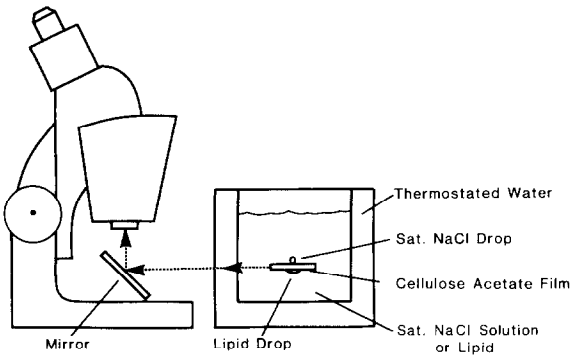

Fig. 1. Apparatus used to measure the contact angle made between a lipid drop or a drop of a saturated solution of sodium chloride on a cellulose acetate film. Relative positions of a lipid drop and a drop of a saturated solution of sodium chloride on the film are shown.

The apparatus shown in Fig. 1 was utilized for measurement of contact angles between either a drop of lipid or a drop of a saturated sodium chloride solution and the polymer film. A section of a cellulose acetate film was attached to a microscope slide with double-sided adhesive tape. The slide was then immersed into a saturated sodium chloride solution at 37 °C. Small drops (less than 2 μl) of Witepsol H-35 were allowed to rise to the surface of the film. The contact angle of the lipid drop (Fig. 2) was calculated as previously described (Bargeman, 1972) by measuring the diameter of the droplet and its height using a stereoscopic microscope fitted with a filar micrometer eyepiece (Bausch & Lomb). The measurement of the contact angle for a drop of a saturated sodium chloride solution was carried out in a similar manner except the film was equilibrated with lipid, the reservoir also contained lipid, and the saturated sodium chloride drops were allowed to descend onto the film. The contact angle made by several

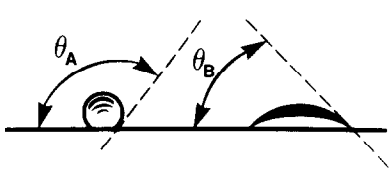

Fig. 2. The measurement of the contact angle (θ) of a liquid drop on a solid surface. A large contact angle (θ_A) indicated poor wetting while a small contact angle (θ_B) indicated good wetting and spreading of the drop on the solid surface.

TABLE 1

Lipid osmotic tablet composition

Tablet preparation	Inner coating [a]	Thickness (μm)	Outer coating [a]	Thickness (μm)	%PEG 400 [b]
A	CAB 553-0.4 [c]	20	CA 398-10	70	25
B	CA 436-80S	60	CA 398-10	90	40
C	None	–	CA 320S	115	25

[a] 2% (w/v) polymer solutions.
[b] Amount of PEG in inner and outer coating as a percentage of polymer weight.
[c] 0.5% (w/v) polymer solution.

drops on the film was measured and the average angle determined. The reproducibility for separate measurements was within 5%.

Lipid cores

Lipid cores were made from 60 g Witepsol H-35, 40 g sodium chloride (40–60 mesh), 2 g timolol and 0.14 g Scarlet red. This mixture was heated to melt the triglycerides and dissolve the drug. Vigorous stirring was used to suspend the osmotic agent as the molten material was poured into a beaker of liquid nitrogen causing rapid solidification. The resultant material was made into granules by forcing the material through a series of cooled screens of decreasing size to a final 25 mesh screen. The sieved material was warmed to room temperature and compressed into tablets (400 mg) using cooled 3/8 inch extra deep concave or ball-shaped punches in a Carver® press under about 900 kg. These lipid tablets were left to harden at room temperature for at least a day before being coated.

Film coating

The coating solutions were sprayed onto the lipid tablets utilizing a baffled pan coating unit (Freund Hi-Coater Model HCT-MINI, Tokyo, Japan). The pan was loaded with 6–50 lipid tablets and about 600 ml of 0.8 mm filler tablets (Avicel® pH 101, lactose, cornstarch and magnesium stearate) to make up bulk in the pan coating unit. Coating conditions were set using only the filler tablets. A solution spray rate of 6–10 ml/min with an atomizing air pressure of 0.9 kg/cm^2 was used. The inlet air temperature (35–50 °C) was adjusted so that the outlet air temperature stayed between 26–29 °C. Under these conditions the tablet bed remained cool enough so that the coated lipid tablets did not melt.

Two percent (w/v) polymer solutions in methylene chloride/methanol (3 : 1) were used unless noted otherwise. The coated tablets were dried at room temperature for at least 24 h before release rate studies were conducted. All tablets used for dissolution studies were examined by 70 × light microscopy and judged to be free of visible de-

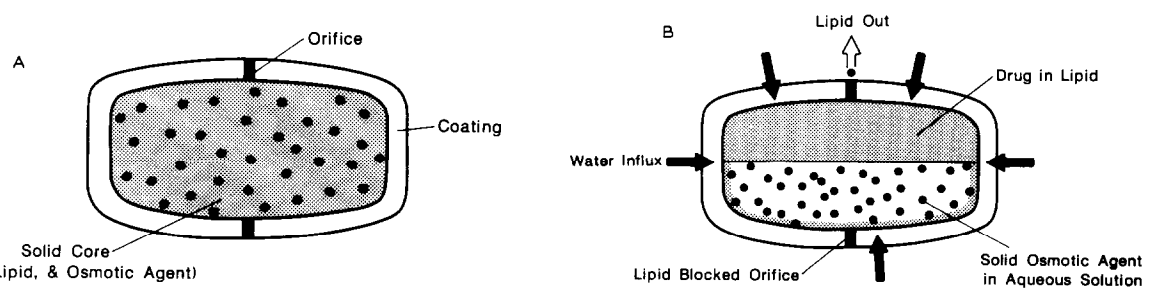

Fig. 3. Schematic drawing of the lipid osmotic pump at room temperature (A), and at 37 °C (B). See text for further description.

fects. Table 1 lists the different tablet preparations which were made.

Release rate measurements

An orifice, approximately 100 μm in diameter, was made in each tablet face with a fine needle before the release rate measurements were conducted. The apparatus shown in Fig. 3 was developed as a way to monitor both the release of lipid and osmotic agent at 37°C. A coated tablet was attached to a rubber wheel via a small stainless-steel spring clip. The shaft was then turned (8 rpm) so the wheel rode on the bottom of the dissolution flask rotating the tablet at about 10 rpm. The released lipid drops floated to the top of the distilled water layer (900 ml) where a layer of IPM (100 ml) dissolved the lipid and drug contained within the lipid drop. The IPM layer was continuously monitored by pumping through a flow cell in a spectrophotometer (Beckman Model DU-7). A lipid soluble dye, scarlet red, was used as a marker substance for release of lipid; its absorption was followed at 515 nm. The release of sodium chloride was monitored conductometrically using a conductance cell, meter (Extech Model 480) and recorder. Typically, 2–6 coated tablets from each preparation were tested in the release studies.

Results and Discussion

Contact angle measurements

The use of contact angles to characterize the wettability of a liquid drop on a solid surface is well documented (Lucassen-Reynders, 1963; Zisman, 1964). The smaller the contact angle (θ) the greater the wetting and spreading of the drop over the polymer surface (Fig. 2). Table 2 lists the degree of acylation and the free hydroxyl content of the cellulose esters which were screened. The contact angle made between a lipid drop and the more hydrophobic polymers (CAB 553-0.4 and CAP 482-20) was smaller than those formed when the more hydrophilic polymers were used (Table 3). Likewise, the hydrophilic polymers showed smaller contact angles for the sodium chloride solution than the hydrophobic polymers although the differences tended to be more pronounced for the films without PEG. In general, the inclusion of PEG in the films tended to improve the wetting of both the lipid and saturated sodium chloride solution drops. Overall, CA 320S is not preferentially wetted by the lipid; however, CA 398-10 and polymers listed above it in Table 3 are preferentially wetted by the lipid.

TABLE 2

Composition of cellulose esters [a]

Polymer	Hydroxyl content (wt%)	Propionyl or butyryl content (wt%)	Acetyl content (wt%)	Total esterification (wt%)
CAP 482-20	2.1	46.3	2.5	48.8
CAB 553-0.4	4.7	47.0	2.0	49.0
CA 436-80S	0.82	–	43.6	43.6
CA 398-10	3.5	–	39.8	39.8
CA 320S	9.0	–	32.0	32.0

[a] Data obtained from Eastman Chemical Co., Kingsport, TN.

Tablet performance

Fig. 3A represents a typical coated tablet at room temperature which has a solid core surrounded by a water-insoluble membrane while Fig. 3B represents the same tablet in an aqueous environment at 37°C. At a temperature higher than 35°C the lipid carrier melted. Water entered the tablet by diffusion through the semipermeable coating and dissolved the osmotic agent creating,

TABLE 3

Wettability of cellulose acetate films

Polymer [a]	Contact angle (°)			
	Saturated sodium chloride drop		Lipid drop (Witepsol H-35)	
PEG 400 (wt%)	0	30	0	30
CAP 482-20	150	120	51	44
CAB 553-0.4	146	122	54	45
CA 436-80S	121	121	82	79
CA 398-10	115	112	96	91
CA 320S	91	0 [b]	113	97

[a] Eastman Chemical Co., Kingsport, TN.
[b] Complete wetting.

in addition to the molten lipid phase, an aqueous osmotic agent phase within the tablet. As pressure increased within the tablet due to the influx of water, the lipid phase of the tablet was released through the orifices.

The apparatus shown in Fig. 4 was developed as a modification of the USP paddle dissolution method to monitor both the release of lipid and osmotic agent from coated tablets. When tablets were tested in this system without rotation, the released lipid drops became rather large before they would break from the surface of the tablet, resulting in stepwise release profiles. In this case, the initial wetting of the lipid at the lower hole was sufficient to cover the hole and prevent the aqueous phase from being pumped or drained from the tablet so that essentially all the lipid was pumped from the upper hole. When the tablets were slowly rotated (10 rpm), the lipid drops broke easily from the surface of the tablet leading to smooth release profiles which were similar in their overall profiles to those obtained for tablets tested without rotation.

The lipid release profile for tablet preparation A exhibited an initial burst due to the expansion of the lipid on melting, followed by a relatively constant rate of release for 12 h (Fig. 5). The inner

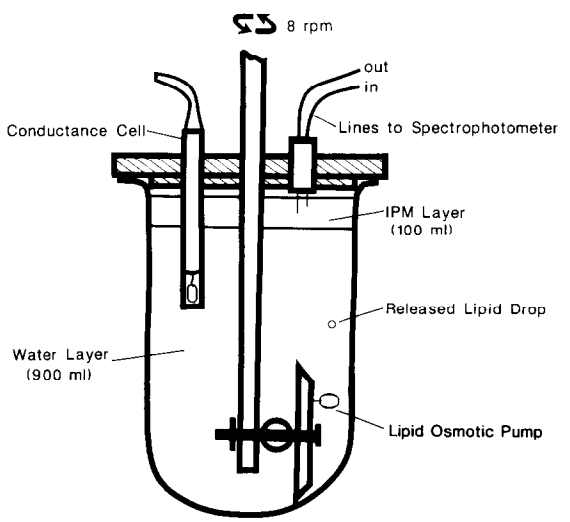

Fig. 4. A schematic representation of a modified USP dissolution apparatus used to monitor the release of lipid and osmotic agent at 37 °C (see text for further description).

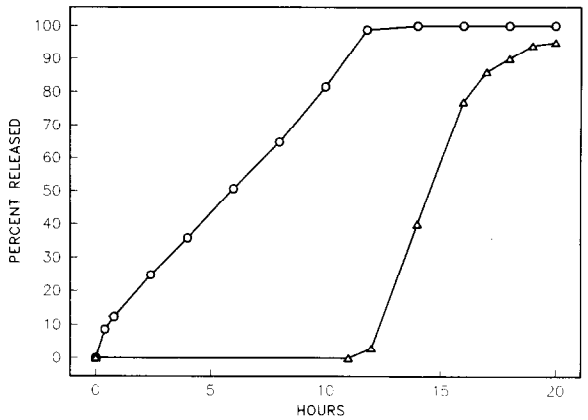

Fig. 5. Scarlet red (○) and sodium chloride (△) release from tablet preparation A.

coating for these tablets was a hydrophobic polymer (CAB 553-0.4) high in lipid wettability, and the second (outer) coating (CA 398-10) was less hydrophobic with a higher water permeability to increase the rate of lipid release. Virtually all of the lipid had been released before pumping of the aqueous salt solution began. Although timolol was also included in this formulation, its absorbance at 295 nm in the IPM layer could not be accurately measured since the IPM absorbed at this wavelength. However, the release of timolol was measured in an acidic medium (900 ml, pH 3 HCl) and it was identical to the release of Scarlet red in the IPM layer.

A specific experiment was conducted to demonstrate that the release of lipid from these tablets was osmotic pressure dependent. The rate of lipid release from tablet preparation A was measured using a saturated sodium chloride solution instead of water as the aqueous medium surrounding the tablet. An initial, rapid release of 11.5% lipid was observed with no further release of lipid over the next 18 h. The tablet was removed and placed in a second flask containing water as the dissolution medium. Lipid was then released from the tablet with a release rate profile essentially the same as seen for tablets which had been placed in distilled water only. The osmotic agent was released subsequent to complete release of the lipid.

Tablet preparation B was similar to tablet preparation A except that CA 436-80S was used for

the inner coating instead of CAB 553-0.4 (Table 1). The lipid solution was pumped at constant rate over a 7 h period although about 5% of the sodium chloride solution was also released (Fig. 6). Both the lipid wettability and water permeability of the cellulose esters are important variables which determine the rate and extent of lipid release since water permeability generally decreases with increasing lipid wettability. The lipid release rate for tablet preparation B is faster than for tablet preparation A because CA 436-80S was more hydrophilic than CAB 553-0.4 (Table 2) and thus had a higher water permeability (Batt, 1985).

Tablet preparation C which was coated with CA 320S released about 20% of the lipid as result of thermal expansion and initial pumping (Fig. 7). Sodium chloride was then pumped from the tablet with no further release of lipid. These results support the findings from the contact angle measurements which indicated that a CA 320S film would be better wetted by a saturated solution of sodium chloride over lipid (Table 3). Thus, a coating as hydrophilic as CA 320S is not sufficiently wetted by the lipid carrier to allow preferential pumping of the lipid solution over the aqueous sodium chloride solution.

The critical requirement of the lipid osmotic pump relates to the wetting of the membrane preferentially by the lipid carrier over the aqueous phase. Although the effects of timolol and/or Scarlet red on lipid wetting were not considered,

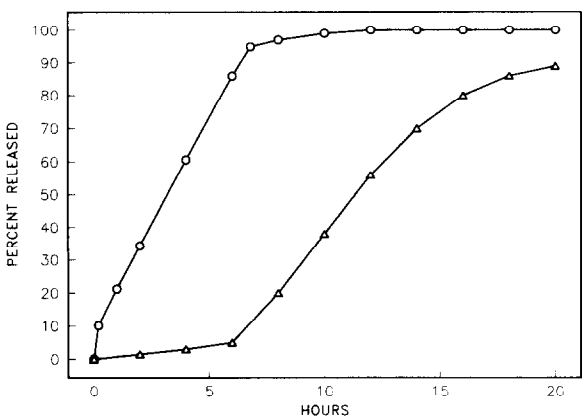

Fig. 6. Scarlet red (○) and sodium chloride (△) release from tablet preparation B.

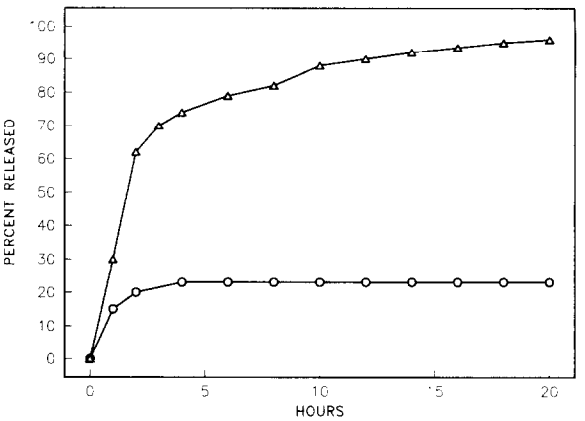

Fig. 7. Scarlet red (○) and sodium chloride (△) release from tablet preparation C.

the contact angle measurements were good indicators of tablet performance. Most compounds suited for this system have a low melting temperature and high lipid solubility and would not be expected to strongly affect wetting by the lipid carrier. However, some active agents may significantly change the wetting characteristics of the lipid carrier due to their charge distribution or dose. In such cases, the compound of interest would need to be considered in the initial screening process.

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