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An in vitro drug release rate method for lipoidal materials

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Summary

A multiparticulate preparation of an osmotically mediated, controlled release system for lipoidal materials is described. Spherical beads containing a lipid carrier, an osmotic agent and a lipid soluble model drug were made and a microporous, polymeric coating applied. When placed in an aqueous medium, the coated beads controllably released first the lipid carrier (containing the model drug), then the osmotic agent. A technique is described for measuring the in vitro release rate profile of the lipoidal components of the beads using microporous polypropylene films. Sorption of the lipoidal components by the film occurred following release from the beads in an aqueous medium. Films were removed at specific times for analysis. The lipoidal components were extracted from the film with ethanol and the model drug content determined by spectrophotometry. This technique may be useful for other systems requiring release rate/dissolution testing of lipoidal agents in an aqueous medium.

Introduction

The in vitro release rate characteristics of a multiparticulate preparation have been investigated. The description of this osmotically mediated, controlled release system has been reported previously (Amidon et al., 1987; Haslam et al., 1989). Spherical beads containing a low melting lipid carrier, an osmotic agent and a lipid soluble model drug were made. The beads were surrounded by a microporous coating that controls the rate of lipid release. In operation, for the system to pump the lipid phase rather than the osmotic agent solution, the coating must be preferentially wetted by the lipoidal components.

It was necessary to develop an appropriate release rate test to determine the release rate profile of the lipid carrier/model drug in order to characterize the in vitro performance of the multiparticulate system. Several reports have described the use of surfactants in the dissolution medium to increase the solubility of poorly water-soluble compounds by micellar solubilization (Bates et al., 1966; Vaution et al., 1981; Gander et al., 1985). However, this approach may not be workable in the present system since a large amount of material (both the lipid carrier and model drug) would need to be solubilized. Walkling et al. (1979) used a partially organic dissolution medium to measure the release of griseofulvin from various dosage forms. Although this method permits testing un-

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der sink conditions, the use of this dissolution medium does represent a gross departure from the essentially aqueous medium encountered physiologically. Gibaldi and Feldman (1967) described a method to remove a dissolved drug from an aqueous dissolution medium by using an upper organic solvent phase so that sink conditions were maintained. A similar procedure was used to determine the in vitro performance of lipid osmotic tablets which released lipoidal components from two orifices (Haslam et al., 1989). When the coated beads were tested in a liquid-liquid two phase system such as these, build-up of lipoidal components on the surface of the dissolution vessel precluded accurate analysis of the material released. Thus, a new technique was developed to measure the release of the lipoidal components from the beads via sorption by microporous polypropylene films. The polypropylene film was removed at various times and the model drug taken up by the film was determined by ethanol extraction and spectrophotometric measurement.

Materials and Methods

Materials

Witepsol® H-35 (Dynamit Nobel Chemicals; Kay-Fries, Inc., distributor), a suppository base which melts at 35°C, was used as the lipid carrier. Reagent grade sodium chloride was used as the osmotic agent. Scarlet red, a lipid soluble dye, was used as a model drug to monitor lipid release and was obtained from Aldrich Chemical Co. Polyethylene glycol (PEG) 400, PEG 20000 and L-tartaric acid were purchased from Fisher Scientific Co.

Cellulose esters (cellulose acetate CA 436-80S and cellulose acetate propionate CAP 482-20) were obtained from Eastman Chemical Co. Reagent grade methanol and methylene chloride were used as the coating solvents. Absolute ethanol was obtained from Midwest Grain Co. The polypropylene film (grade 0.2A-3, 75% porosity, 0.007 inch thick, 0.5 μm maximum pore size) used for taking up the lipoidal components was obtained from Enka Industrial Products Inc., Accurel® Systems Division (Schaumburg, IL).

Lipid beads

A mixture of 60 g Witepsol H-35, 40 g sodium chloride (80–140 mesh), 1 g PEG 20000 (less than 140 mesh) and 0.14 g scarlet red was added to a 250 ml stainless-steel beaker and heated to 45–50°C by means of heating tape. A mechanically driven stirrer was used to stir the molten mixture continuously and suspend the sodium chloride. The molten mixture was allowed to drip from a 0.76 mm orifice drilled in the bottom of the beaker into several liters of stirred liquid nitrogen forming spherical beads upon congealing. The liquid nitrogen was then decanted and the beads equilibrated to room temperature over several hours at 15–20% relative humidity. The diameter of the beads ranged from 2 to 3 mm.

Film coating

A microporous cellulose acetate coating was applied to the beads in a Uni-Glatt® fluidized bed coater equipped with a 4-inch Wurster coating column. Lipid beads (20 g) and white Celcon® filler beads (2–3 mm diameter, 500 ml) were initially coated with a solution prepared from 16 g CAP 482-20, 6.4 g PEG 400, 16 g tartaric acid, 100 ml methanol and 300 ml methylene chloride. The tartaric acid was first dissolved in methanol and then slowly added to a mixture of the other ingredients. This coating solution (100 ml) was applied at a flow rate of 17 ml/min with 25 lb/inch^2 (p.s.i.) of atomization air pressure to the spray gun. A second coating solution (1 l) prepared from 40 g CA 436-80S, 16 g PEG 400, 40 g tartaric acid, 250 ml methanol, and 750 ml of methylene chloride was then applied in the same manner as the first solution. The beads were maintained in a fluidized state in the coating column with a moderate flow of unheated, ambient air. After drying in the unit, the beads were collected and the lipid beads separated from the filler beads according to color. The lipid beads had a coating thickness of approx. 110 μm.

Release rate measurements

The in vitro release rate profile of scarlet red from coated beads was determined by placing the beads (700 mg) in an NFXIV dissolution bottle containing distilled water (60 ml) and a strip (2 × 7

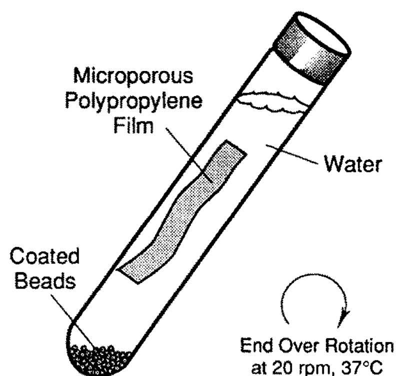

Fig. 1. Set-up for in vitro release rate testing of coated beads using a microporous polypropylene film.

mm) of a microporous polypropylene film (Fig. 1). The bottles were capped with teflon-lined lids and rotated end-over-end (20 rpm) in a water bath at 37°C. Sorption of the lipoidal material by the film occurred following release from the beads. The film was removed at specific intervals and placed in a dissolution bottle containing ethanol (5–50 ml) and rotated end-over-end at room temperature for approx. 30 min or until all the color was extracted. The amount of ethanol required varied depending on the amount of material on the film such that the absorbance of scarlet red at 515 nm was between 0.1 and 0.9 when measured using a Cary 14 spectrophotometer. The lipid beads were crushed at the end of the run and any remaining scarlet red was quantitated. The release of sodium chloride was monitored periodically using a conductance cell and meter (Extech Model 480). Initially, the release rate profile of the lipid carrier and scarlet red was also determined gravimetrically to confirm that scarlet red was a true indicator of lipid release. For these studies the films were weighed initially and before the ethanol extraction after drying for 30 min at 30°C.

The recovery of scarlet red and Witepsol H-35 after sorption by the polypropylene film was checked by adding known amounts of a molten Witepsol H-35/scarlet red mixture (40 g Witepsol H-35 and 92 mg scarlet red) to a dissolution bottle containing 60 ml water and a single preweighed polypropylene film. After rotating the bottles end-over-end for 30 min at 37°C, the film was removed, dried at 30°C, and then weighed to determine the amount of Witepsol and scarlet red that the film had taken up. The scarlet red was then extracted from the film with ethanol and quantitated spectrophotometrically. An equivalent amount of the molten mixture was added directly to ethanol and the recovery of scarlet red from water was determined by comparison with this standard. The time required for complete sorption of the lipoidal components by the film was also determined.

Results and Discussion

Sorption of lipoidal components

A technique for measuring the rate of release of lipoidal components from 2–3 mm coated beads containing scarlet red has been devised. A strip of a microporous polypropylene film added to an aqueous medium will take up both the released lipid carrier and scarlet red. The recovery of scarlet red from water as a function of concentration was determined by comparison with direct addition to ethanol. The recovery of scarlet red was 96% or greater when 20–150 mg of a molten Witepsol H-35/scarlet red mixture (in the same proportion as in the beads) was added to a dissolution bottle containing 60 ml of water and a single polypropylene film (Table 1). The recovery of the lipid carrier and scarlet red as determined gravimetrically was very close to the percent recovery of scarlet red as shown by the paired data in Table 1. The capacity of the film was approx.

TABLE 1

Recovery of scarlet red and Witepsol H-35

Witepsol H-35 and scarlet red [a] (mg)	Ethanol (ml)	Scarlet red recovery (%)	Scarlet red and Witepsol recovery (%)
20	20	100, 98.1	97.1, 97.7
50	30	100, 100.3	99.2, 99.0
100	30	99.8, 99.2	98.9, 97.9
150	50	98.2, 94.5	94.6, 92.5
200 [b]	50	83.4, 85.6, 82.8	83.7, 85.4, 86.9

[a] Witepsol H-35 containing 0.23% scarlet red.
[b] Polypropylene film removed after 60 min.

TABLE 2

Time dependency of scarlet red [a] recovery

Sorption time (min)	Recovery (%)
5	89.4
10	98.1
20	104
30	100
60	104

[a] 100 mg of Witepsol H-35 containing 0.23% scarlet red.

12 mg/cm^2 since the film was clearly saturated once 200 mg of the molten mixture was added, even allowing longer time for sorption (Table 1). When the release rate studies were conducted, the film was removed at frequent intervals to give an accurate assessment of the release profile such that no more than 15% of the lipoidal components was released in any sampling period. This represented about one-third of the saturation capacity of the film. The time required for complete sorption of the lipid carrier/scarlet red (100 mg) onto the polypropylene film was 10–20 min (Table 2). The release rate profile of the lipid phase from the coated beads as determined gravimetrically was found to be identical to the release rate pattern of scarlet red.

System performance

Spherical lipid beads were prepared and coated initially with a thin layer of a hydrophobic polymer (CAP 482-20) high in lipid wettability followed by an outer coating (CA 436-80S) higher in water permeability (Batt, 1985; Haslam et al., 1989). A typical microporous coated bead is shown in Fig. 2A; Fig. 2B represents the same bead in operation in an aqueous environment at 37°C. As previously described (Haslam et al., 1989), water entered the bead by diffusion through the semipermeable coating and dissolved the osmotic agent creating, in addition to the molten lipid phase, an aqueous osmotic agent phase within the bead. As pressure increased within the bead due to the influx of water, the lipoidal components were released through numerous pores in the coating. Tartaric acid and PEG 400 were used as soluble components that would leach out in an aqueous environment creating voids in the coating (Donbrow and Friedman, 1975; Samuelov et al., 1979). Tartaric acid was chosen since it had a high melting point (m.p. 168–170°C) and was soluble in the methanol/methylene chloride solution used as the coating solvent. The beads released about 90% of the lipoidal components at a fairly constant rate over a 15 h period followed by release of the salt solution (Fig. 3). The data in Fig. 3 represent multiple sampling times for a single sample of beads. The values at a given time point were generally reproducible within 5%.

The present technique provided a facile method for measurement of the in vitro release rate of lipoidal components from a multiparticulate pre-

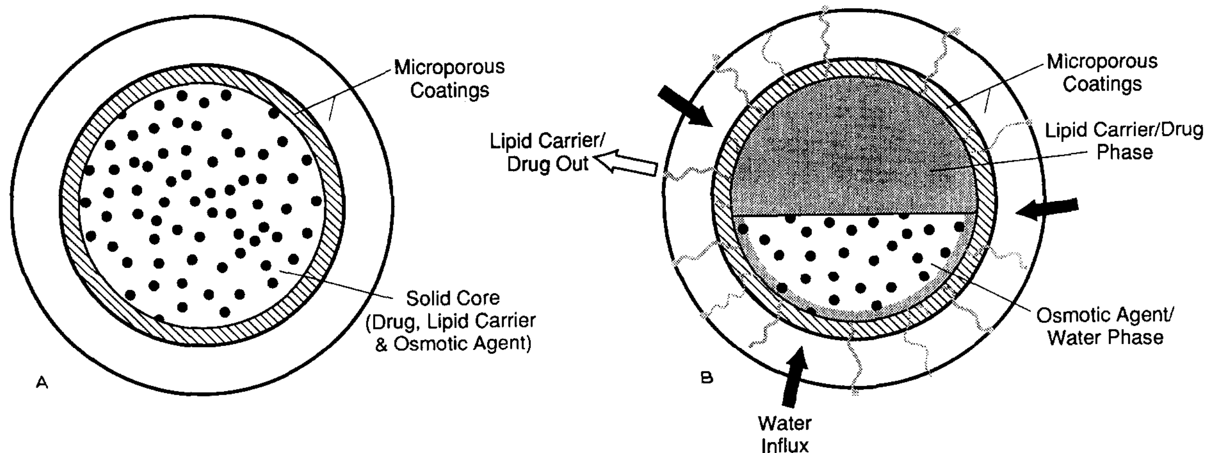

Fig. 2. Schematic drawing of coated beads at room temperature (A) and at 37°C (B).

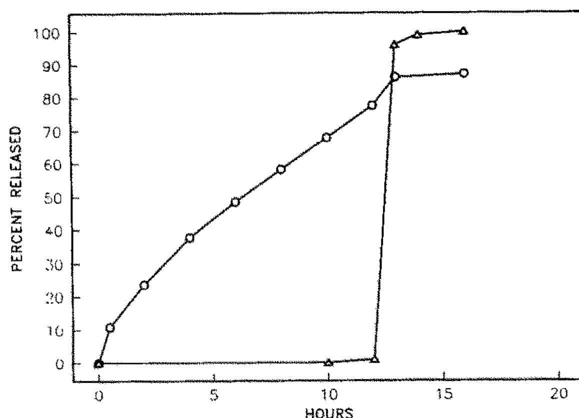

Fig. 3. Scarlet red (○) and sodium chloride (△) release from coated beads in water at 37°C.

paration of an osmotically mediated, controlled release system. Earlier methods described in the literature for measuring the release rate of lipid soluble compounds were not practical or feasible for testing the performance of the current multiparticulate system. Instead, both the released lipid carrier and scarlet red were taken up by a microporous polypropylene film added to the aqueous medium. The lipoidal components were then extracted from the film with ethanol which allowed the films to be reused after drying. It is also possible to adopt this general procedure to determine the release rate profile by weighing the films after sorption. In the present system, the dry film (50 mg) would be expected to pick up between 30–60 mg of released material in any sampling interval. This technique might also prove useful for monitoring the release of drugs from suppositories or other systems requiring release rate testing of a lipoidal agent in an aqueous medium. Studies are in progress with other lipid soluble compounds to determine the broader utility of the method.

References

Amidon, G.L., Higuchi, T. and Dressman, J.B., Lipid osmotic pump. US Patent 4,685,918 (1987).

Bates, T.R., Gibaldi, M. and Kanig, J.L., Solubilizing properties of bile salt solutions. I. Effect of temperature and bile salt concentration on solubilization of glutethimide, griseofulvin and hexestrol. *J. Pharm. Sci.*, 55 (1966) 191–199.

Batt, B.C., An experimental study of osmotic pumping by highly microporous polymer membranes. M.Sc. Thesis, University of Kansas, Lawrence, 1985.

Donbrow, M. and Friedman, M., Enhancement of permeability of ethylcellulose films for drug penetration. *J. Pharm. Pharmacol.*, 27 (1975) 633–646.

Gander, B., Ventouras, K., Gurny, R. and Doelker, E., In vitro dissolution medium with supramicellar surfactant concentration and its relevance for in vivo absorption. *Int. J. Pharm.*, 27 (1985) 117–124.

Gibaldi, M. and Feldman, S., Establishment of sink conditions in dissolution rate determinations. Theoretical considerations and applications to nondisintegrating dosage forms. *J. Pharm. Sci.*, 56 (1967) 1238–1242.

Haslam, J.L., Merfeld, A.E. and Rork, G.S., Surface wetting effects in the lipid osmotic pump. *Int. J. Pharm.*, 56 (1989) 227–233.

Samuelov, Y., Donbrow M. and Friedman, M., Sustained release of drugs from ethylcellulose-polyethylene glycol films and kinetics of drug release. *J. Pharm. Sci.*, 68 (1979) 325–329.

Vaution, C., Treiner, C., Puisieux, F. and Carstensen, J.T., Solubility behavior of barbituric acids in aqueous solution of sodium alkyl sulfonate as a function of concentration and temperature. *J. Pharm. Sci.*, 70 (1981) 1238–1242.

Walkling, W.D., Nayak, R.K., Plostnieks, J. and Cressman, W.A., A partially organic dissolution medium for griseofulvin dosage forms. *Drug Dev. Ind. Pharm.*, 5 (1979) 17–27.