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RESEARCH PAPER

Effect of Steareth-20 on the Release of Nitrofurantoin from Propylene Glycol Monostearate Microspheres

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ABSTRACT

In vitro release of nitrofurantoin (NFT) from microspheres of propylene glycol monostearate (PGM) was investigated at NFT:PGM ratios of 1:1, 1:1.5, 1:3, 1:4, 1:5, and 1:9 in distilled water at 37°C. The rate and extent of drug release declined with decreasing NFT:PGM ratio. A maximum drug release of 52.4% over 24 hr was recorded for the microspheres of formulation I (highest load). The effect of Steareth-20 (ESA) over the concentration range of 0.01% to 0.1% w/w of PGM on the size of the microspheres and on the release profile of nitrofurantoin from the microsphere formulations was examined at NFT:PGM ratios of 1:1 and 1:4. The cumulative % of NFT released over a 24-hr period was found to be maximum at ESA concentration of 0.03% and 0.05% w/w of PGM. The plots of T_{50} versus %w/w of ESA exhibited two minima, the first at 0.03% ESA and a second, weaker than the first, at 0.05% ESA, paralleling the earlier observations. Scanning electron micrographs of the exhausted microspheres revealed a very porous matrix of PGM at the ESA concentration of 0.03%. The formulations containing 0.03% and 0.05% ESA had the smallest mean particle diameter and the minimum contact angles (water over PGM–ESA films) corresponding to the two critical micelle concentrations (CMC), at 0.025% and 0.05% w/w.

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INTRODUCTION

In an earlier study of propylene glycol monostearate (PGM), Steareth-20, formerly identified as ethoxylated stearyl alcohol (ESA), and combinations thereof were shown to form thin films; and their potential application for the controlled release of cortisol was demonstrated by manipulating the ESA content of the films at concentration of 2–16% w/w (1). Later investigation of the PGM–ESA system has revealed that ESA exerts a strong and unique concentration-dependent effect on the release characteristics of entrapped agents from PGM matrices when incorporated in the range of 0.01–0.1% w/w. This report documents this observation. Specifically, in this study effect of ESA on the release of nitrofurantoin (NFT) from PGM microspheres has been investigated. Nitrofurantoin (1-[(5-nitrofurfurylidene)-amino]hydantoin), an effective antibacterial agent used widely for the treatment of urinary tract infections, was selected as a model drug since a controlled-release dosage form of NFT would potentially address a major concern of NFT therapy—the frequent occurrence of gastrointestinal side effects such as nausea and emesis. Several reports have documented the importance of incorporating NFT in a slow-release dosage form as an approach to minimize its gastrointestinal side effect (2,3). While these studies have not clearly delineated the mechanism of NFT-induced nausea or emesis, there is strong evidence that the rate of drug absorption could be a determining factor. In vitro release of nitrofurantoin from microcapsules prepared from a variety of coating materials including Eudragit S-100, shellac, ethyl cellulose, sodium carboxymethylcellulose (5), and others (6,7) have been reported, with mixed results. In the present study, a number of microsphere formulations containing NFT and PGM in proportions ranging from 1:1 to 1:9 have been prepared and in vitro release has been examined. ESA, a nonionic surfactant, was incorporated in selected formulations (NFT:PGM ratio of 1:1 and 1:4) over the concentration range of 0.01% to 0.1% w/w of PGM, and its effect on size and release characteristics of the resulting microspheres was investigated.

MATERIALS

Propylene glycol monostearate NF (PGM); Ruger Chemicals, Irvington, NY

Steareth-20 (ESA); Volpo S.20, Croda, New York, NY

Nitrofurantoin (NFT); Sigma Chemical Company, St. Louis, MO

METHODS

Preparation of the Microspheres

The microspheres were prepared by utilizing a melt dispersion and cooling process (8). A known amount of PGM was melted in 50-ml beaker on a water bath at 55°C and a predetermined amount of NFT was suspended into the melt with constant stirring. The melt was added gradually with a Pastuer pipette to 1000 ml of distilled water placed in an aluminum foil covered round-bottom flask while stirring by means of a Teflon-coated magnetic stirring bar and a magnetic stirrer at 43°C. The aqueous slurry was rapidly cooled to room temperature and the microspheres were isolated by filtration under vacuum, washed several times with cold distilled water, air dried, and kept in a desiccator for further studies. The filtrate was analyzed to determine the amount of NFT partitioned into the water phase during the preparation of microspheres. All formulations, I–VII (Table 1), were prepared similarly. Modifications of formulations I and IV (Ia–Ih and IVa–IVh) were also prepared by the same procedure by incorporating different proportions of ESA (0.01–0.1% w/w).

Sieve Analysis

Each batch of microspheres was segregated by size into suitable fractions by agitating a preweighed sample of microspheres for 15 min over a nest of standard sieves (Nos. 20, 40, 60, 80, 120, 140, 200, and 400) on a mechanical shaker (Sepor Laboratory Supply, Wilmington, CA). The segregated fractions were weighed and stored in a desiccator. The mean diameter of particles was calculated from the size-frequency data plotted on an arithmetic-probability grid by means of a well-documented method (9,10). The mean diameter was obtained by reading, from the plot, the size corresponding to the 50% value on the probability scale. Means of duplicate determinations are reported.

Scanning Electron Microscopy

Samples of microspheres were mounted onto stubs and coated with gold by vacuum depositing technique using a coater (SPI sputter, Westchester, PA), and then

examined with scanning electron microscopy (SEM) equipped with a camera SEM ISI-SX-30, Santa Clara, CA).

Contact Angle Studies

Contact angle was measured at ambient temperature using a Reflective Goniometer (Kernco Instruments, El Paso, TX) fitted with a protractor scale and an objective lens (magnification ×3). Films of PGM or PGM–ESA for contact angle measurements were cast on 3 × 1 in. glass slides. A 5-μl drop of distilled water was then applied on the film using a microburette and allowed to stand for 60 sec before reading the contact angle. A minimum of five readings at different locations on each sample were taken and averaged.

Critical Micelle Concentration Determination

The CMC of ESA was determined from the surface tension measurements at 25°C by the capillary height method (11). Samples were prepared by dissolving 0.050 g of each ESA–PGM formulation (0.0054–0.1% w/w of ESA in PGM) in 20 ml of distilled water. The aqueous solutions were then placed in a petri dish in which a capillary tube (with radius of 0.4 mm) was immersed vertically. The height of the liquid in the capillary tube was measured and surface tension (γ) was calculated in accordance with the following formula:

$$\gamma = 1/2\ h\rho gr \qquad (1)$$

where h is the height (cm) of the liquid in the capillary tube; ρ is the density (g/ml) of the solvent (distilled water); the downward force is the acceleration due to gravity, g (m/sec^2); and r is the radium (mm) of the capillary tube.

In Vitro Release Studies

The USP dissolution apparatus I was employed to examine the drug release pattern from the microspheres. An amount of microspheres (average particle size, 152.5 μm) equivalent to 25 mg of NFT were filled in size 0 colorless transparent gelatin capsules. These capsules were then placed in dissolution baskets and the basket assembly was immersed in 900 ml distilled water at 37° ± 0.5°C and rotated at 50 rpm. Perfect sink conditions were maintained throughout the study. Five-milliliter samples were withdrawn at suitable time intervals and analyzed spectrophotometrically at 370 nm (12).

Statistical Analysis

All data were statistically analyzed for significant difference between control data and those of the test formulations by the use of Dunnett's t test, which utilizes analysis of variance (ANOVA) to establish a pooled variance for all data. The calculated t values were compared with critical t determined from a table of Dunnett's t values ($p \leq 0.05$).

RESULTS AND DISCUSSION

The results of a 24-hr in vitro release study from formulations I–VII, conducted in distilled water at 37° ± 0.5°C, are shown in Table 1. The rate and extent of drug release declined with decreasing NFT–PGM ratio. None of the formulations released their entire drug content during the 24-hr period. A maximum drug release of only 52.4% during the 24-hr release period was recorded for the microspheres of formulation I (highest load), suggesting the need for incorporating a drug release enhancer, such as ESA, in the formulation in order to improve the rate and extent of release of NFT from the PGM microspheres. Formulations I and IV were chosen for further study and discussion since they represented a more meaningful NFT concentration range of 20–50% w/w in the formulation and yet demonstrated only 20–50% NFT release in the absence of ESA. Therefore, eight additional variations (a–h) of formulations I and IV were prepared representing ESA content of 0.01, 0.02, 0.03, 0.035, 0.040, 0.045, 0.050, and 0.10 expressed as %w/w of PGM, respectively; and the release of NFT was monitored as before. The cumulative %w/w NFT released over 24 hr from the microspheres of both sets of formulations, Ia–Ih and IVa–IVh, versus ESA, %w/w, shown in Fig. 1(a), was found to increase with increasing ESA content of the formulation, reaching a maximum at 0.03% ESA and declining ESA content of the formulations was raised to 0.04%, whereupon the trend reversed itself, leading to a second maximum at 0.05% ESA. Increasing the ESA content to 0.1% did not alter the NFT release significantly. Drug release—expressed as time for the release of 50% of the initial drug content, T_{50}, for the formulations Ia–Ih and IVa–IVh, determined from the log-normal probability plots of individual release data—was plotted against %w/w ESA [Fig. 1(a)]. The T_{50} plots for both sets of formulations exhibited two minima, the first minimum at 0.03% ESA and a second minimum, weaker than the

Table 1

Effect of Nitrofurantoin/Propylene Glycol Monostearate Ratio on In Vitro Release of Nitrofurantoin in Distilled Water at 37.0° ± 0.5°C and 50 rpm

	Cumulative Drug Release, %, from Each Formulation[a] (nitrofurantoin/propylene glycol monostearate ratio)						
Time (hr)	I (1:1)	II (1:1.5)	III (1:3)	IV (1:4)	V (1:5)	VI (1:7)	VII (1:9)
0.5	4.0	3.1	2.8	0.7	0.5	0.4	0.1
1.0	9.3	6.4	4.5	2.0	1.9	1.2	0.8
1.5	14.0	8.2	5.8	3.1	3.1	1.8	1.7
2.0	17.5	9.5	6.9	4.3	3.9	2.3	2.0
3.0	21.7	11.7	8.5	5.8	5.2	3.2	2.7
4.0	24.5	13.7	9.8	7.3	6.2	4.1	3.9
6.0	29.8	17.7	11.4	9.2	7.8	5.5	5.4
8.0	33.0	20.5	12.8	10.8	9.0	6.8	6.4
12.0	37.8	24.0	15.5	13.3	11.3	9.4	9.1
24.0	52.4	30.6	21.2	19.9	16.4	15.31	4.2

[a]Mean of duplicate measurements.

first, at 0.05% ESA, paralleling and confirming the earlier observations. The mean particle diameter of the microspheres was found to increase as the drug content was increased from 0% to 50%. This could be attributed to the increase in the viscosity of the NFT–PGM phase (observed) with increasing drug concentration. The incorporation of ESA significantly decreased the mean particle diameter of microspheres of formulations I and IV as shown in Fig. 1(b). The microspheres of the formulations Ic, IVc and Ig, IVg—corresponding to ESA levels of 0.03% and 0.05%, respectively—had the smallest mean particle diameter.

Scanning electron microscopy revealed that PGM microspheres had a rough and undulating surface. In contrast, the NFT–PGM microspheres appeared like spherical bundles of NFT needles impregnated in the PGM matrix. A comparison of microphotographs of the microspheres before and after the release of NFT revealed a very porous matrix at the ESA concentration level of 0.03% compared to other ESA concentrations. The contact angle measurements of ESA–PGM films of various compositions displayed a nonlinear dependence on ESA concentration with a stronger minimum in the range of 0.025–0.035% and a weaker minimum at 0.045–0.05% w/w of ESA [Fig. 1(c)].

Aforementioned studies have demonstrated that the concentration range of 0.025–0.035% of ESA and, to a lesser extent, 0.045–0.05% of ESA in the microspheres represented critical levels, and that effects of ESA were dependent to some extent on the proportion of other ingredients, PGM and NFT, present in the formulation. In order to gain further insight into the effects of ESA on the PGM microspheres, surface tension of several PGM–ESA solutions containing 0.0054% to 0.1% w/w of ESA were measured. A plot of surface tension (dyne/cm) against %w/w ESA exhibited a clearly defined minimum at 0.025% w/w ESA and a weaker minimum at 0.05% w/w ESA [Fig. 1(c)]. Since ESA is a surfactant, it affects the surface tension of the aqueous solutions in a profound manner over a narrow range of concentration that defines its critical micelle concentration (CMC). At levels equal to or greater than the CMC, the solute molecules self-associate to form soluble aggregates which exhibit markedly different properties from the monomers in solution. The observed effects of ESA on the rate and extent of NFT released parallel the contact angle measurements of water on PGM–ESA films and the ESA behavior in solution. With increase of surfactant concentration, the shape of the micelle changes from spherical to rod shaped (13,14). The second CMC is defined as the surfactant concentration at which the real rod-shaped micelle appears, and from this point the shape of the micelle is thought to be invariable even when the surfactant con-

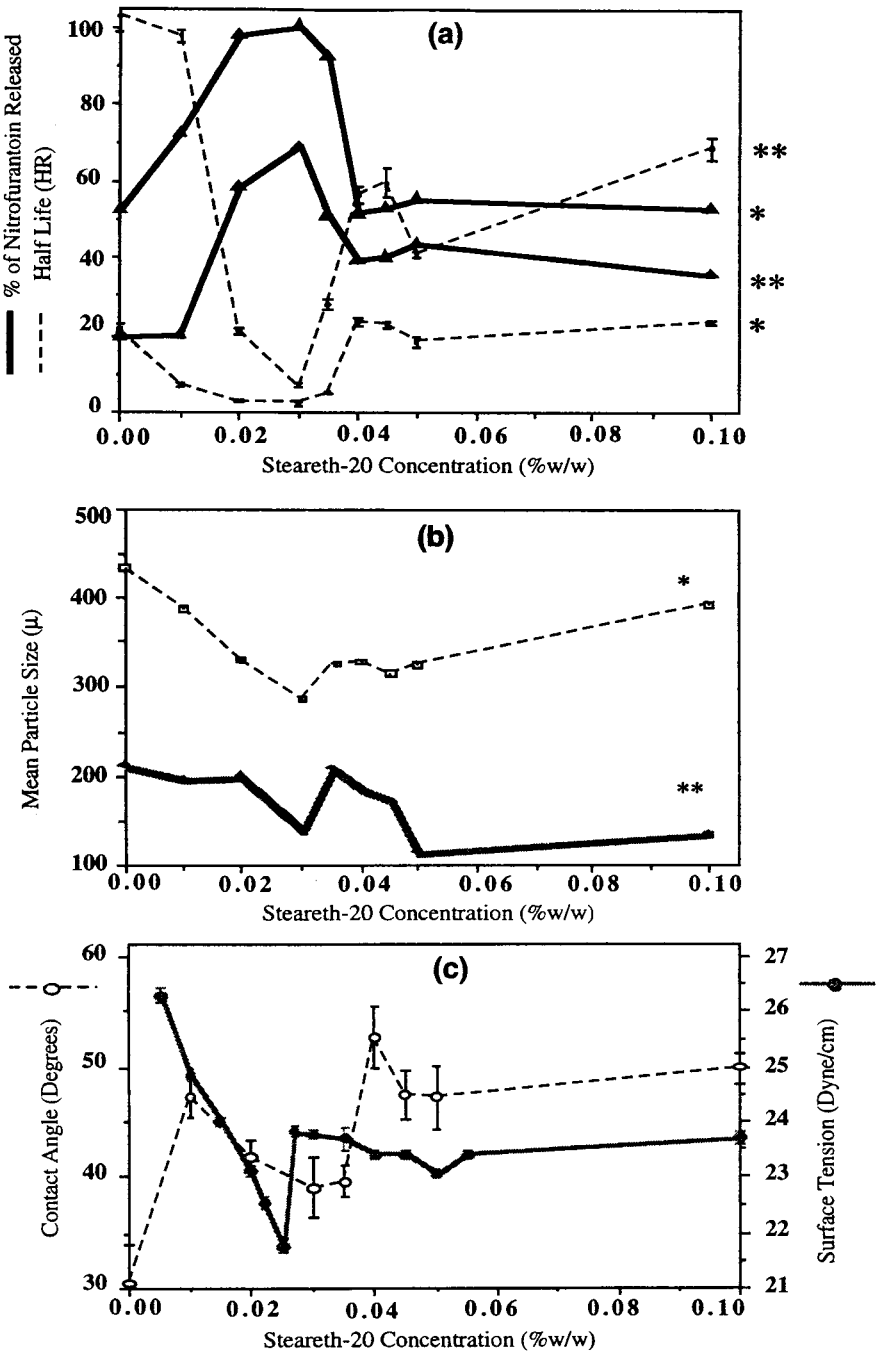

Figure 1. Effect of Steareth-20 concentration on: (a) the 24-hr release of nitrofurantoin in distilled water at 37°C, and T_{50} for the release of nitrofurantoin in distilled water at 37°C (each point represents mean of triplicate trials); (b) the mean particle diameter of microspheres; and (c) the contact angle of water over propylene glycol monostearate films and surface tension of propylene glycol monostearate aqueous solutions. Asterisk (*) represents formulations I–Ih; double asterisk (**) represents formulations IV–IVh.

centration increases. At higher concentrations of ESA, surface tension remained nearly constant. This would explain why higher concentrations of ESA did not yield higher NFT release rates, since the bulk of the surfactant molecules present at concentrations in excess of the CMC are aggregated into micelles. These micelles form for essentially the same reasons that cause molecules to be adsorbed: the lack of affinity of the hydrophobic chains for water molecules and the tendency for strong hydrophobic chain–chain interactions when the chains are oriented closely together in the micelle. This leads to a favorable free-energy change for micellization. Therefore, once the first CMC is reached, micellization has been completed and ESA monomers can no longer enhance the solubility of the matrix and the drug (and hence porosity of the matrix), and they literally "escape" from the water to form micelles. The observed effects are less pronounced at the second CMC because they are predominantly due to shape transformation of the micelles. The rod-shaped micelles are thought to be larger and more densely packed than the spherical micelles.

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