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RESEARCH PAPER

PVP Solid Dispersions for the Controlled Release of Furosemide from a Floating Multiple-Unit System

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ABSTRACT

The poor bioavailability of orally dosed furosemide (FUR) is due to the presence of a biological window in the upper gastrointestinal tract. The purpose of the present study was to develop and optimize in vitro a multiple-unit floating system with increased gastric residence time for FUR. The incomplete release of FUR from the units, related to its low water solubility, led to the preparation and evaluation of different FUR samples to be incorporated into the units. The complete dose release over the actual intragastric residence time of the system (about 8 hr) was achieved by loading both the core and the membrane forming the units with a 1:5 FUR/polyvinylpyrrolidone (FUR/PVP) solid dispersion. Physicochemical analyses suggested the predominant role of the amorphous state of FUR in producing enhanced drug solubility and dissolution rate, which led to the desired release profile from the floating units.

Key Words. *Alginate; Floating system; Furosemide; Solid dispersion.*

INTRODUCTION

Oral devices, made to be retained in the stomach for a long time and to ensure slow delivery of the drug above its absorption site, could provide increased and more reproducible drug bioavailability. The prolongation of the gastric residence time of a drug delivery system could be achieved by administering the system after eating, by adhering the system to the mucous membrane, by preventing the system from passing through the pylorus, or by maintaining the system buoyantly on the gastric content (1–5). With regard to the floating devices, we previ-

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ously designed and evaluated both in vitro and in vivo the floating ability of an air compartment multiple-unit system. Such a system demonstrated the actual floatability of the units on the gastric content and their usefulness in achieving an extended gastric transit by dosing the system after a meal (6,7).

However, floating alone is not responsible for the effectiveness of an intragastric drug delivery system because suitable drug release profiles (i.e., related to the gastric residence time) also must be provided by the device.

Therefore, the present investigation was to evaluate the in vitro release behavior of a drug loaded into the designed floating system. For this purpose, furosemide (FUR) was chosen as the drug since it is indicated for the development of a dosage form with increased gastric residence time. In fact, FUR is characterized by poor (<60%) and variable (20–60%) oral bioavailability owing to the presence of an absorption window in the upper intestinal tract. Moreover, high peak diuresis can be generated by the administration of conventional formulations containing the drug (8–10). Therefore, a dosage form with enhanced gastric residence time could facilitate maximum drug absorption and, at the same time, decrease the side effects. In this paper, several FUR samples were prepared and analyzed to select the most suitable product to be incorporated into the floating units and then to achieve the complete dose release over the actual intragastric residence time.

MATERIALS

The following chemicals were obtained from commercial suppliers and were used without further purification. Sodium alginate (MW about 115,000, extracted from *Laminaria hyperborea*, containing 30% mannuronic acid and 70% guluronic acid), polyvinylalcohol 100,000 (PVA), polyvinylpyrrolidone K25 (PVP) (MW 24,000), and calcium chloride dihydrate were purchased from Fluka Chemie (Buchs, Switzerland); Tween 20 (polyoxyethylene sorbitan monolaurate) was purchased from Atlas Europol (Ternate, Italy); and FUR (MW 330.8) was purchased from Sigma Aldrich Chemie (Steinheim, Germany). All the solvents (analytical grade), sodium hydrate, and sodium citrate dihydrate were purchased from Carlo Erba (Milan, Italy).

METHODS

Preparation of Furosemide Samples

The following FUR samples were prepared:

FUR recrystallized from methanol (FUR from CH_3OH), prepared by evaporating a FUR methanol solution in a vacuum rotary evaporator (Rotavapor-H, Büchi HB-140, Büchi Laboratoriums, Technik AG, Flawil, Switzerland) at 70°C.

FUR milled for 15 min (milled FUR).

FUR/PVP physical mixtures in ratios of 1:3 and 1:5 (FUR/PVP mix) prepared by the intimate mixing of 90–180-μm sieve fractions of the individual components.

Comilled FUR/PVP physical mixtures in ratios of 1:3 and 1:5 (comilled FUR/PVP mix) prepared by milling FUR/PVP mixes for 15 min.

FUR/PVP solid dispersions in ratios of 1:3 and 1:5 (FUR/PVP solid dispersion) prepared by dissolving both components in methanol and subsequently removing the solvent in a rotary evaporator under reduced pressure at 70°C. Recovered solids were vacuum dried for 48 hr and milled for 15 min.

All samples were screened through standard mesh screens to collect the 90–180-μm sieve fraction.

Characterization of Furosemide Samples

The FUR physical state in the samples prepared was examined by differential scanning calorimetry (DSC), X-ray diffractometry, solubility, and equilibrium dissolution rate determinations.

Differential Scanning Calorimetry

Thermograms of all the samples prepared were recorded on a differential scanning calorimeter (DSC-4, Perkin-Elmer, Norwalk, CT) coupled with a computerized data station (Perkin-Elmer). Samples (8–9 mg) were heated in crimped aluminum pans (Perkin-Elmer) at a scanning rate of 10°C/min using dry nitrogen flow (30 ml/min).

X-Ray Diffractometry

X-ray powder diffraction data were collected using a PW 1050 goniometer (Philips, Eindhoven, The Netherlands). Samples were scanned between 3° and 40° 2θ at a speed of 2° 2θ/min.

Solubility Determination

Saturated solubility of FUR in all the samples was determined by shaking an excess amount of each sample with HCl water solution at pH 5.0 at 37°C ± 0.1°C. After 48 hr, aliquots of the solutions were filtered, and the drug concentration was analyzed spectrophotometrically at 274 nm (model Lambda 3B, Perkin-Elmer). Each sample was analyzed in triplicate.

Equilibrium Dissolution Studies

Dissolution studies were carried out, under sink conditions, by placing exactly weighed samples containing the same amount of FUR (3 mg) in a USP 23 apparatus at 37°C ± 0.1°C in 900 ml of HCl water solution at pH 5.0 under stirring by rotating paddle at 50 rpm. FUR dissolution was monitored spectrophotometrically (274 nm) for 60 min. Each sample was analyzed at least in triplicate.

Floating Units Production

The floating units, each composed of a calcium alginate core separated from a porous calcium alginate membrane by an air compartment, were prepared by using the technique and the composition that provided the optimum buoyancy in the previous investigation (6). The procedure involved the following steps.

For preparation of calcium alginate cores, sodium alginate water solution (3 ml, 5%, w/w) was dropped through a 2-mm nozzle into a medium of *n*-heptane (20 ml) and a water solution (10 ml) of calcium chloride (10%, w/v) and Tween 20 (1%, w/v). The medium was stirred (1000 rpm) for 5 min at room temperature. The formed particles were separated from the medium and washed quickly with water and then diethyl ether.

For the coating procedure, calcium alginate membrane formation was carried out by soaking for 10 min undried (i.e., just prepared) calcium alginate cores in a water solution of sodium alginate (5%, w/w) and PVA (5%, w/v) as the porogeneous substance necessary for the buoyancy property of the units (6). The coated cores were rinsed quickly with water and diethyl ether and vacuum dried. Then, the resulting floating units (called ''units'' throughout the text) consisted of cores separated from a membrane by an air compartment.

The FUR was incorporated into the units in the following forms: untreated FUR and 1:5 FUR/PVP solid dispersion. By adding these products in the alginate solutions forming the core and the membrane before the cross-linking reaction, the following unit formulations were obtained:

F: untreated FUR loaded into the core.
F1: 1:5 FUR/PVP solid dispersion loaded into the core.
F2: 1:5 FUR/PVP solid dispersion loaded into the core and untreated FUR into the membrane.
F3: 1:5 FUR/PVP solid dispersion loaded into both the core and the membrane. These units, which contained PVP in the membrane, did not request PVA as the porogeneous substance.

The formulation parameters are listed in Table 1.

Floating Units Characterization

Morphological and Dimensional Analysis

The morphological structure of the units was examined with a scanning electron microscope (SEM) (XL-40, Philips). The size of the units was measured using an optical microscope (Carl Zeiss, Jena, Germany). Apparent density values of the units were determined from the mass volume of samples having known weights. All the data are averages of 10 units from three different batches.

Drug Content

The drug content was determined by dissolving an exactly weighed amount of each unit formulation and of the separated components (membrane and core) of F3 units in sodium citrate water solution (3% w/v). Afterward, drug concentrations in the filtered solutions were assayed spectrophotometrically at a wavelength of 274 nm. Each sample was analyzed in triplicate.

Drug Dissolution and Release

Drug dissolution and release from each unit formulation and from the separated components (membrane and

Table 1

Solution Components for the Floating Unit Production

Unit Code	Core			Membrane			
	Alginate (%, w/w)	Furosemide (%, w/v)	Furosemide Product	Alginate (%, w/w)	Furosemide (%, w/v)	Furosemide Product	PVA (%, w/v)
F	5	5	Untreated	5	—	—	5
F1	5	5	Solid dispersion	5	—	—	5
F2	5	5	Solid dispersion	5	1	Untreated	5
F3	5	5	Solid dispersion	5	1	Solid dispersion	—

core) of F3 units were examined using the USP paddle method in 900 ml of HCl water solutions at pH 5.0 at 50 rpm and 37°C ± 0.1°C. All experiments were carried out under sink conditions by determining the amount of drug released spectrophotometrically at fixed time intervals and at a wavelength of 274 nm. All the data are averages of three determinations.

During the drug release experiments, the floating ability of the units was checked by visual observation.

RESULTS AND DISCUSSION

A multiple-unit system shows several advantages over monolithic ones: more predictable drug release kinetics, less chance of localized mucosal damage, insignificant impairment of performance due to failure of a few units, coadministration of units with different release profiles or containing incompatible substances, larger margin of safety against dosage form failure (11).

In our work, to guarantee the above advantages and at the same time to allow ease of administration, 10 units were considered proper to constitute the system designed. Therefore, the drug loading was performed to incorporate into 10 units a dose of FUR corresponding to 25–30 mg.

The previous study regarding the in vivo behavior of the units demonstrated their ability to remain in the stomach for more than 8 hr over the control in fed conditions (7). Therefore, during this time period, the loaded dose of FUR should be released from the system to ensure complete absorption at the level of its biological window.

To establish the drug release characteristics from the floating units, a release medium at pH 5 was chosen since it could reproduce an averaged pH value occurring in fed conditions (12).

The release of FUR from F units, containing the untreated drug in the core, was sustained but incomplete (Fig. 1). In fact, only 20% of the loaded dose was released at the end of 8 hr. Such release behavior would not be expected from calcium alginate matrices, which generally deliver low molecular weight drugs quickly, as reported by several papers (13,14), so other factors should be considered.

The poor solubility of FUR in acidic solutions (15) could determine a marked decrease in dissolution rate of the drug incorporated into the units. A similar retardant effect was observed for FUR encapsulated in Eudragit microspheres (16). Therefore, to achieve a dissolution rate improvement leading to the complete release of the loaded dose, several FUR samples were prepared and analyzed: FUR from CH_3OH, milled FUR, 1:3 and 1:5 FUR/PVP mixes, comilled 1:3 and 1:5 FUR/PVP mixes, 1:3 and 1:5 FUR/PVP solid dispersions. PVP was selected for the hydrogen bond interaction with FUR, which produces stable amorphous solid dispersions (17). Since it is known that drug/PVP ratios in the range 1:3 to 1:7 can be regarded as the optimum (18), 1:3 and 1:5 FUR/PVP ratios were chosen in our study to produce both solid dispersions and physical mixtures. Higher amounts of PVP could not be used due failure of the unit formation.

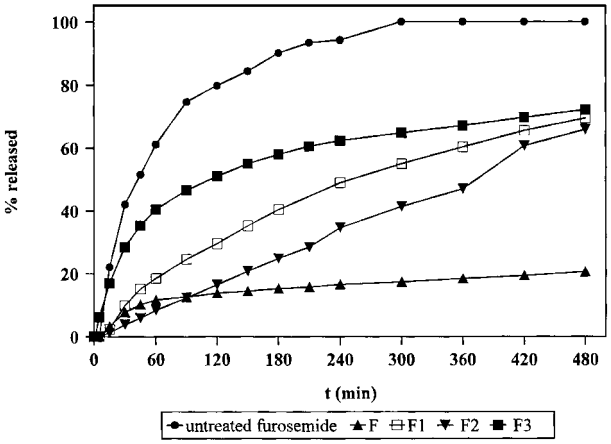

Figure 1. Furosemide release profiles from the floating units.

The DSC thermograms of the samples are depicted in Figs. 2 and 3. Untreated FUR showed the typical behavior of FUR form I with two endotherms (15). The first one was present in the range 135°C–137°C; the second one, corresponding to the melting endotherm, accompanied by degradation, was in the range 212°C–227°C. FUR recrystallized from methanol (FUR from CH_3OH) gave only a melting endotherm followed by degradation, in the range 195°C–196°C, corresponding to a form known as FUR form II (15). The grinding process of FUR did not produce any change in the thermal behavior (Fig. 2, milled FUR).

The thermal phenomena of FUR from 1:3 and 1:5 FUR/PVP mixes and from the corresponding comilled mixes showed the characteristic melting peaks of FUR form I, although less relevant. Differently, the peaks were slightly outlined from 1:3 solid dispersion and were absent from 1:5 solid dispersion (Fig. 3). The explanation is that PVP coprecipitated with FUR prevents the drug crystallization, providing a complete drug molecular dispersion at a ratio with the carrier of 1:5. Moreover, the presence of PVP avoids the change of the crystal form that would occur by recrystallizing the drug from methanol.

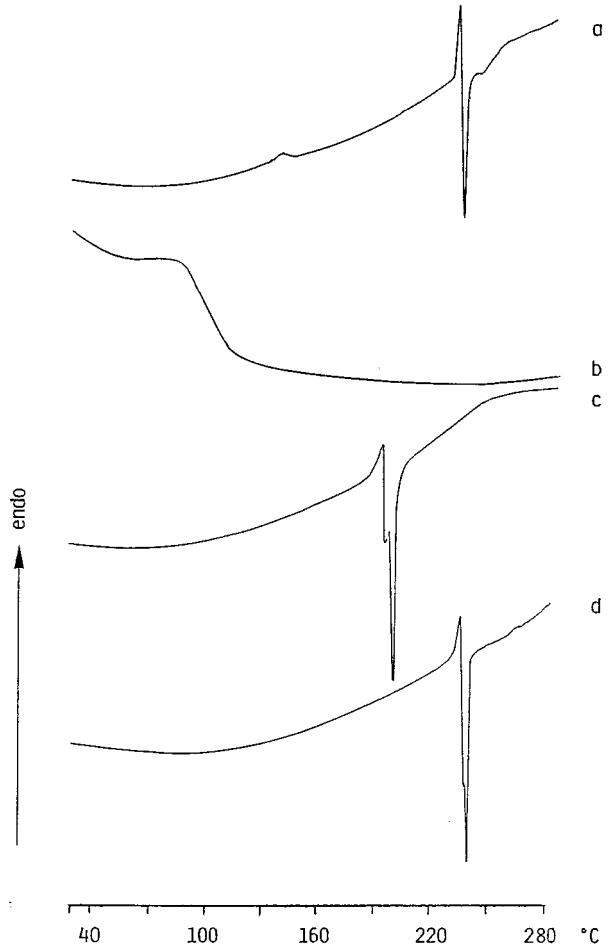

Figure 2. DSC thermograms: (a) untreated furosemide; (b) PVP; (c) FUR from CH_3OH; (d) milled FUR.

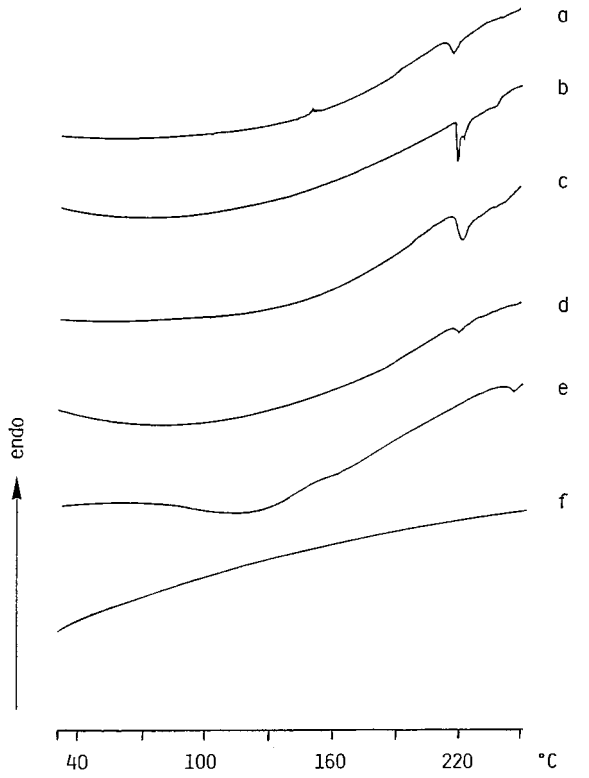

Figure 3. DSC thermograms: (a) 1:3 FUR/PVP mix; (b) comilled 1:3 FUR/PVP mix; (c) 1:5 FUR/PVP mix; (d) comilled 1:5 FUR/PVP mix; (e) 1:3 FUR/PVP solid dispersion; (f) 1:5 FUR/PVP solid dispersion.

X-ray diffraction patterns of the samples are shown in Figs. 4 and 5. The X-ray spectra of the untreated FUR exhibited the typical peaks of form I (15). FUR from CH_3OH resulted in X-ray spectra that significantly differed from that of the untreated FUR, with new diffraction lines and modifications of the relative peak heights of some other peaks. The differences in the X-ray patterns reflect a change in crystal packing and structure of the form II. On the contrary, milled FUR showed the same peak positions as the untreated one, although with diminished relative heights.

X-ray patterns of 1:3 and 1:5 FUR/PVP mixes exhibited the typical peaks of the untreated FUR, although less intense. Moreover, a decreased crystallinity was observed in the corresponding comilled mixes. In contrast, FUR was found in an amorphous state in both the solid dispersions, confirming the role of the coprecipitation with PVP in preventing the crystallization of the drug.

The change in drug crystal structure and crystallinity degree observed by both DSC and X-ray analysis provided modification of FUR solubility and/or dissolution rate values. In fact, FUR from CH_3OH (form II) showed increased solubility compared with that of the untreated sample (Table 2), indicating an increased crystal energy. However, this solubilizing effect did not increase the dissolution rate (Fig. 6). Differently, the presence of PVP in the mixtures and in the corresponding comilled mixtures increased both FUR solubility and dissolution rate, with the comilled samples dissolving faster than the unmilled ones. This phenomenon may suggest a dissolution-promoting effect of PVP physically mixed with the drug. Such an effect was emphasized by the milling process, leading to an intimate mixing of FUR with PVP and to a semicrystalline state of the drug.

Both solubility and dissolution rate values of FUR resulted increased significantly from the solid dispersions (Table 2, Fig. 6). In fact, the solubility values from 1:3 and 1:5 FUR/PVP solid dispersions were about 15-fold and 20-fold increased over that for untreated FUR, re-

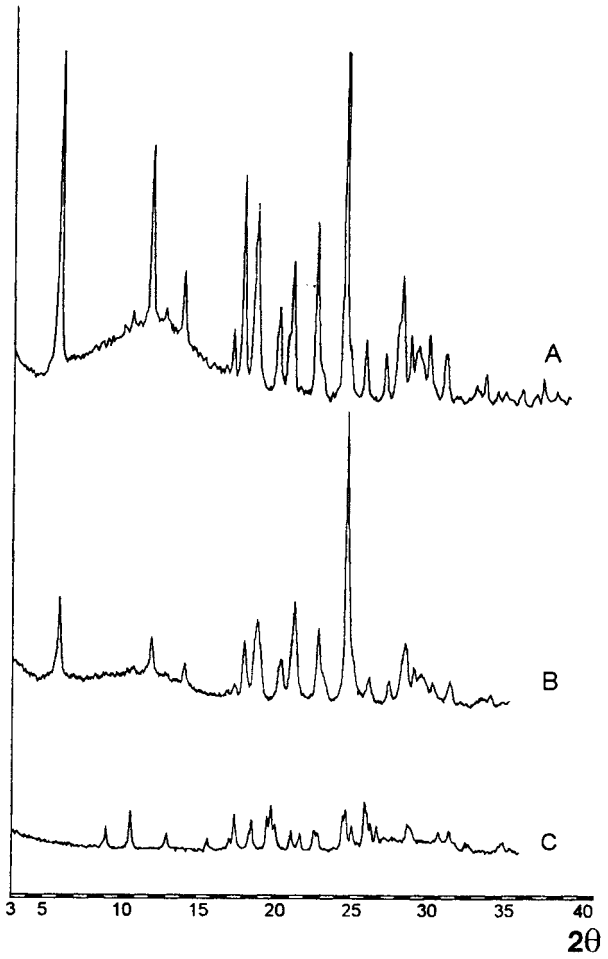

Figure 4. X-ray diffraction patterns: (A) untreated furosemide; (B) milled FUR; (C) FUR from CH_3OH.

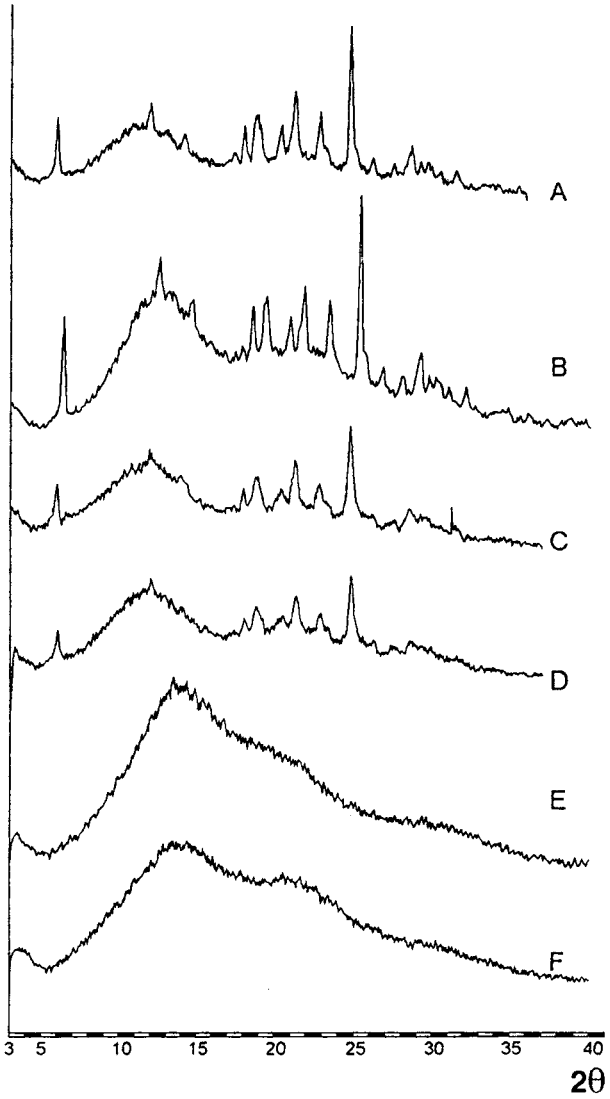

Figure 5. X-ray diffraction patterns: (A) 1:3 FUR/PVP mix; (B) 1:5 FUR/PVP mix; (C) comilled 1:3 FUR/PVP mix; (D) comilled 1:5 FUR/PVP mix; (E) 1:3 FUR/PVP solid dispersion; (F) 1:5 FUR/PVP solid dispersion.

spectively. In agreement with the results of DSC and X-ray assays, the solubilizing effect of PVP coprecipitated with the drug, greater than that offered by PVP in a simple physical mixture, is related to the amorphous state of FUR. According to this high-energy state, the FUR dissolution rate was found to increase, with that from 1:5 solid dispersion being the faster (Fig. 6).

Therefore, 1:5 FUR/PVP solid dispersion, providing the highest drug solubility and dissolution rate, was selected to achieve the suitable release profiles from the floating units. Such a solid dispersion was differently incorporated into the units to obtain the samples listed in Table 1. The physical characteristics and drug-loading values are shown in Table 3. The units showed a size of 4-7 mm and apparent density values less than unity (6). This result confirmed the possibility of incorporating effective doses of drugs without compromising the unit characteristics, as previously hypothesized (7). The units showed a nearly spherical shape and the same morphological characteristics and floating abilities observed previously for the unloaded sample (6).

The F1 units, obtained by incorporating the solid dispersion in the core, showed a drug-loading level lower than that of F units (Table 3). The release rate of FUR from F1 units was found to be significantly higher than that from F units (Fig. 1). In fact, about 65% of the dose was released at the end of 8 hr with a monophasic pattern and a t_{50} of about 4 hr.

Table 2

Solubility Values at pH 5.0 of Furosemide from Different Samples (SD in Parentheses)

Sample	Solubility (mg/100 ml)
Untreated furosemide	2.43 (0.6)
FUR from CH_3OH	8.79 (0.6)
Milled FUR	4.52 (1.0)
1:3 FUR/PVP mix	4.28 (0.2)
Comilled 1:3 FUR/PVP mix	5.95 (0.3)
1:5 FUR/PVP mix	3.86 (0.4)
Comilled 1:5 FUR/PVP mix	4.78 (0.8)
1:3 FUR/PVP solid dispersion	37.26 (1.2)
1:5 FUR/PVP solid dispersion	51.49 (4.1)

Table 3

Physicochemical Characteristics of the Floating Units (SD in Parentheses)

Unit Code	Weight (mg)	Diameter (mm)	Drug Content	
			%, w/w	mg/unit
F	13.3 (1.7)	3.9 (0.5)	21.0 (3.7)	2.8 (0.3)
F1	39.5 (4.3)	6.9 (1.3)	4.7 (0.2)	1.9 (0.2)
F2	27.4 (4.9)	5.3 (1.5)	9.6 (0.5)	2.2 (0.2)
F3	25.9 (2.3)	4.7 (1.0)	10.7 (0.2)	2.9 (0.1)

To increase the drug loading and at the same time to provide an attack dose considered necessary to provoke a sufficient diuretic effect (19), untreated FUR was also incorporated in the membrane (F2 units). F2 units showed a higher drug loading level than that of F1 (Table 3). However, the resulting drug release profile was monophasic without a burst phase and with a t_{50} of about 6 hr. The unexpected decrease in release rate could be attributed reasonably to the presence of the drug in the membrane, which provided diminished wettability and, consequently, a diminished water diffusion rate across the membrane. To overcome this drawback, 1:5 FUR/PVP solid dispersion was incorporated in the membrane (F3 units). F3 units, after immersion in the release medium,

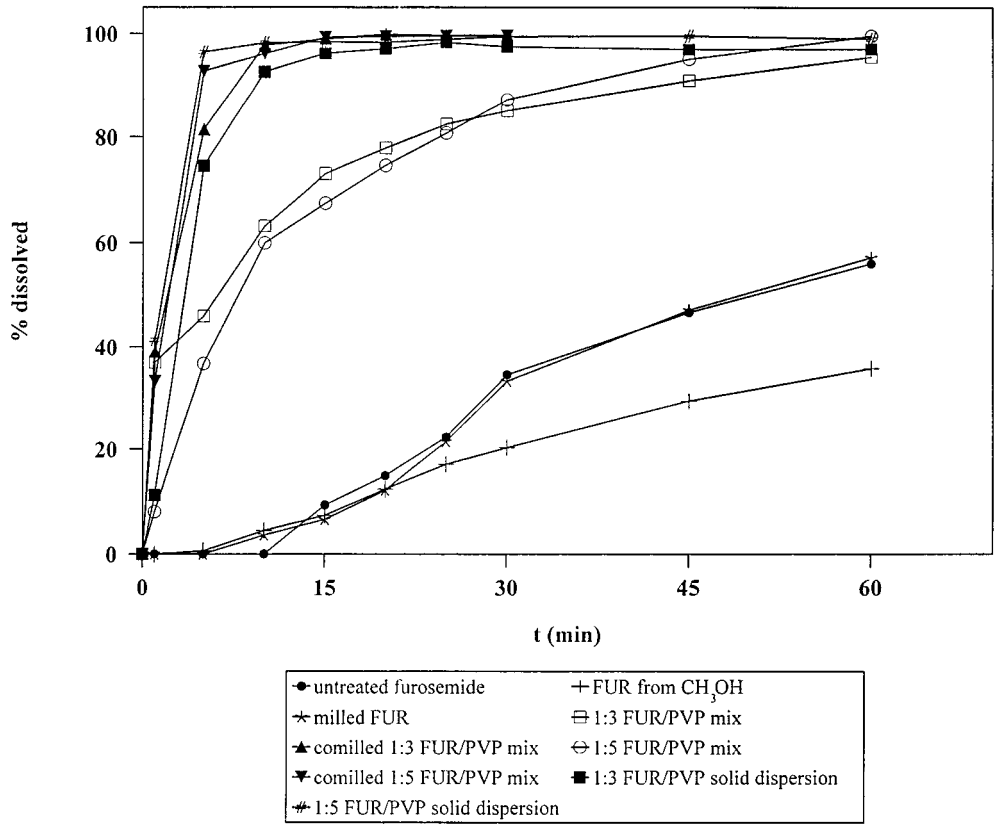

Figure 6. Furosemide dissolution profiles from different samples.

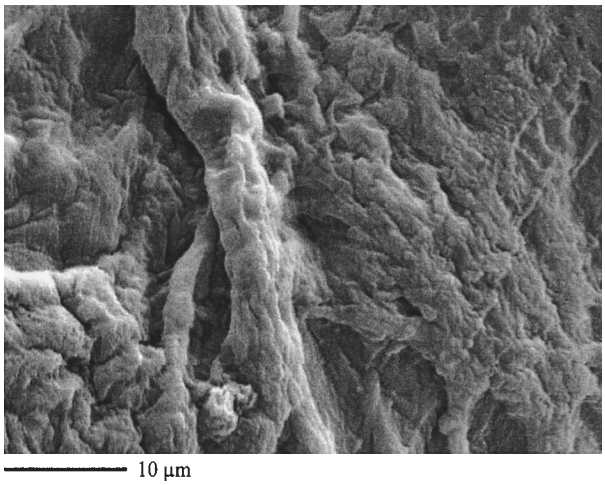

Figure 7. SEM micrograph of F3 units after immersion in the release medium.

showed a porous membrane structure (Fig. 7) comparable with that obtained using PVA and, then, allowing the buoyancy (6). Therefore, the inclusion of the solid dispersion with PVP avoided the addition in the membrane of PVA as the porogeneous substance (6). F3 units showed the same drug loading level as F2 units (Table 3). On the contrary, the units exhibited a biphasic behavior of drug release, with a first burst phase in which about 40% of the dose was delivered in about 2 hr and a second, sustained phase achieving the release of about 65% of the dose after 8 hr. The burst phase was due to the release of the drug loaded in the core, as the release diagram of the separated components of the units shows (Fig. 8). This finding was in agreement with the FUR content determined for each component: 1.3 ± 0.1 mg, corresponding to 45% ± 3.5% of the drug loading, in the membrane and 1.6 ± 0.2 mg, corresponding to 55% ± 5.0% of the drug loading, in the core.

Therefore, F3 units prepared by incorporating the solid dispersion both into the core and into the membrane could be considered as the optimum formulation.

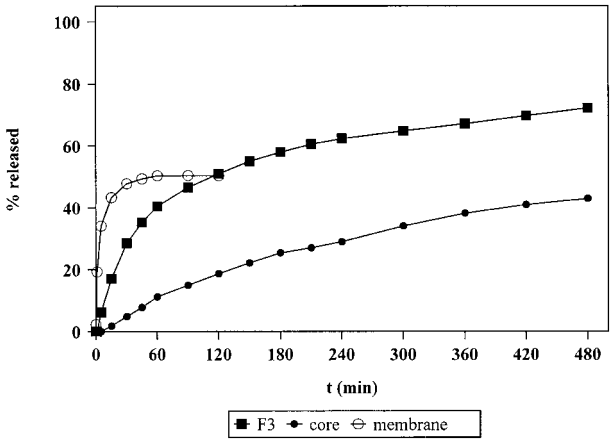

Figure 8. Furosemide release profiles from F3 units and separated components.

CONCLUSIONS

The present formulation study involving the optimization of FUR release profile from a floating multiple-unit system revealed the incorporation of the drug in solid dispersions with PVP as an effective method to achieve the desired release behavior. In this regard, the amorphous state of the drug obtained by the solvent coevaporation process resulted in a relevant factor. By including the drug in a solid dispersion with PVP both into the core and into the membrane of the units, the release of the dose over the actual intragastric residence time was obtained.

The designed system, combining excellent buoyant ability and suitable drug release pattern, could offer clear advantages in terms of increased bioavailability of FUR. Furthermore, by considering the drug loaded in each unit, about 10 units should be administered by capsules to provide the proper dose and, at the same time, the advantages offered by a multiple-unit formulation.

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