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Supramicellar solutions of sodium dodecyl sulphate as dissolution media to study the in vitro release characteristics of sustained-release formulations containing an insoluble drug: nifedipine

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Abstract

In this study we consider some different approaches to analyze the in vitro dissolution behaviour of different dosage forms containing nifedipine. Because this drug is practically insoluble in water, the in vitro release characteristics of the formulations were verified using different dissolution methods. A new sustained-release dosage form, formulated in two different strengths: 30 and 60 mg, was tested and compared to an extended-release commercial product. Initially, the dissolution tests were carried out with the paddle method, in a large amount of water (5 l), to maintain the 'sink conditions'. Then the release tests were repeated using aqueous solutions of sodium dodecyl sulphate (SDS) as dissolution fluid (in 5 l, first, and then in 1 l of medium). Different supramicellar concentrations of the surfactant were used to verify how the different dissolution media could influence the release characteristics of the formulations proposed. The commercial product was tested in the same experimental conditions and was considered as reference dosage form. The results show that the surfactant concentrations above 0.50% are able to dissolve the drug content of all the dosage forms tested. Above this concentration, the dissolution profiles from the delivery systems considered are not affected by the presence of different percentages of SDS.

Keywords: Nifedipine; Sustained-release; Surface-active agent; Sodium dodecyl sulphate; Dissolution medium

1. Introduction

Nifedipine is a well-known anti-hypertensive agent, but, due to its very low water solubility, it often shows low and irregular bioavailability after oral administration (Syed Laik Ali, 1989). In this case the dissolution rate of the drug from the solid form could be the limiting step for the absorption process through the gastro-intestinal tract. At the same time, the half life of the drug after oral administration is rather short, from 2 to 4 h and repeated daily administrations are needed to maintain effective plasma levels (Murdoch and Brogden, 1991).

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For all these reasons, the formulation of sustained or extended-release dosage forms for once-daily administration is highly desirable, but, at the same time, the design and development of a sustained-release formulation, containing a drug of very low solubility, is particularly difficult. It should be a compromise between the enhancement of the dissolution rate of the drug and the modulation of the delivery rate from the dosage form. Moreover the study of the dissolution behaviour of such delivery systems may be highly problematic; in the case of nifedipine, water solubility: 11 μg/ml (Kohri et al., 1987), it is quite impossible to maintain the 'sink conditions' using the conventional dissolution methods and procedures described in the main Pharmacopoeias, even for the lower dosage strengths such as 10–20 mg. It is therefore quite impossible to perform a proper in vitro screening of different dosage forms and compositions, during the formulation design, and to test the release behaviour of a sustained-release delivery system that generally includes a high drug content. Consequently, it is extremely difficult to carry out a predictable and reliable in vitro-in vivo correlation to verify the efficacy and safety of the final dosage form (Gander et al., 1985; Abrahamsson et al., 1994).

Various methods have been proposed to test the dissolution performance of dosage forms containing drugs of low solubility, either for conventional products or for modified-release devices. Chaudhary et al. (1994) use a modified USP apparatus 2 (paddle), and carry out the tests in a biphasic system — octanol/water. During the dissolution test, the drug that shows more affinity with the lipophilic phase migrates to the octanol phase without affecting the release behaviour of the tablets. Several other approaches have been proposed, such as the use of large volumes of medium, or mixtures of water and water-miscible solvents, or the addition of organic phases or adsorbents to the dissolution medium (Walkling et al., 1979; Takahashi et al., 1994). Most of these approaches do not simulate the biologic environment, moreover, they are rather complex to carry out, and generally involve difficult analytical procedures.

Recently, Qureshi et al. (1994) have used a flow-through apparatus (USP Apparatus 4) to compare the dissolution performance of two different formulations: conventional capsules containing 10 mg of nifedipine, and extended-release tablets containing 20 or 30 mg of drug. Even if this apparatus maintains the 'sink conditions', being the dosage form always in contact with fresh dissolution medium, the authors still used an aqueous solution of Tween as wetting agent, in a concentration of 0.5%.

Surfactant solutions are often proposed as dissolution media for drugs characterized by low water-solubility (Shah et al., 1989; Veiga and Alvarez de Eulate, 1994; Abrahamsson et al., 1994). The ability of these molecules to enhance drug dissolution properties has been attributed to wetting and micellar solubilization that occurs when the surfactant is used at concentrations exceeding the Critical Micellar Concentration (CMC) (Gander et al., 1985); but even below the CMC, an enhancement of the dissolution process could be due to a reduction of the interfacial tension or a possible interaction between the drug and/or the excipients and the surfactant (Shah et al., 1989).

In fact, the use of surfactant solutions as dissolution media for sparingly soluble drugs has had great success in the last few years, and is also recommended by the US Pharmacopeia. In many cases, this simple expedient enables the employment of the conventional equipment and techniques described in the official monographs, and available in all QC laboratories. Generally, aqueous solutions of such surfactants may simulate the physiologic environment more accurately rather than using adsorbents or hydroalcoholic and aliphatic media. Moreover, a study by Buri and Humbert-Droz (1983) showed that the presence of natural surfactants, such as bile salts, in the dissolution medium gives results comparable to those obtained using synthetic and less expensive molecules such as SDS.

In this work we propose and analyze different approaches to study the in vitro dissolution behaviour of a new formulation for the sustained-release of nifedipine, containing two different dosage strengths, either 30 or 60 mg, in comparison to a commercial product for the extended release of 20 mg of the same drug.

The tests were carried out in 5000 ml of water first, using a modified apparatus 2 (USP XXIII), equipped with vessels of enough capacity (Giunchedi et al., 1991), but, in this case, the 'sink condition' could be assured only for a very low drug content, such as 20 mg. If the dose is higher than 20 mg, saturation is reached just the same. For this reason, the tests were then repeated with the same experimental conditions, but using aqueous solutions of SDS at different concentrations, initially in 5000 ml and then in the more conventional volume of 1000 ml of dissolution medium. The critical micellar concentration of SDS is 0.045 w/v% (Gander et al., 1985). In our study, four supramicellar concentrations of the surfactant were considered: 0.25, 0.50, 0.75 and 1.00 w/v%, to verify how the presence or the different percentages of the wetting agent could interfere with the dissolution process.

2. Materials and methods

For the preparation of the tablets, the following products were used: nifedipine (Industrie Chimiche Italiane, Milan, Italy), average particle size: 18.9 μm (Coulter Counter); hydroxypropylmethylcellulose (Methocel® K15M, Colorcon, Orpington, UK), viscosity 15 000 cP (value stated by the supplier); polyvinylpyrrolidone (Plasdone® K29–32, ISP, Wayne, NY); cross-linked sodium carboxymethylcellulose (Acdisol®, FMC Corp., Philadelphia, PA); colloidal silicon dioxide (Syloid® 244, Grace GmbH, Worms, Germany). Magnesium stearate, talc and sodium dodecyl sulphate, all of USP grade, were supplied by C. Erba, Milan, Italy. The commercial product Adalat® retard (Bayer, Leverkusen, Germany), coded product A, is considered as a reference dosage form; it is described as an extended-release formulation, containing 20 mg of nifedipine, and was obtained on the German market.

The new formulation proposed for the sustained-release of the drug, is designed as a hydrophilic matrix, containing hydroxypropylmethylcellulose as retarding polymer and cross-linked sodium carboxymethylcellulose as hydration enhancer. The compositions of the tablets containing either 30 or 60 mg of drug are reported in Table 1. For the granulate preparation, the drug is mixed with cross-linked sodium carboxymethylcellulose and hydroxypropylmethylcellulose and then wetted with a 20% (w/v) ethanol solution of polyvinylpyrrolidone. The wetted mass was forced through a 710-μm screen (ATSM n. 25). The granules were dried in a circulating air oven, to reach a constant weight and then calibrated through the same screen. Talc, magnesium stearate and colloidal silicon dioxide were added to the granules and mixed in a Turbula Mixer (Bachofen, Basle, Switzerland) for 20 min.

The tablets were produced using a single-punch machine (Korsch EK0, Berlin, Germany) equipped with a set of concave punches of 8 mm in diameter for the lower dosage, 30 mg: N1 formulation, and 10 mm in diameter for the higher dosage, 60 mg: N2 formulation. The tablets were then coated with an opaque polymeric film to protect the sensitive drug from exposure to light. The coating applied is readily soluble in water.

The dissolution tests were carried out, initially in 5000 ml of deionized water using a modified apparatus 2, equipped with vessels of suitable capacity. Then, the release tests were carried out in the same conditions and volume, but using SDS solutions as dissolution media at four different concentrations: 0.25, 0.50, 0.75 and 1.00% (w/v). Finally the performance of the test in the conventional USP apparatus was verified using 1000 ml of SDS solutions at the same concentration described before. In all cases, the paddle

Table 1
Compositions of the two dosage forms, N1 and N2

Formulation	N1 (mg)	N2 (mg)
Nifedipine	30.0	60.0
Hydroxypropylmethycellulose	40.0	80.0
Sodiumcarboxymethylcellulose CL	40.0	80.0
Polyvinylpyrrolidone	10.0	20.0
Talc	5.0	10.0
Magnesium stearate	2.0	4.0
Colloidal silicon dioxide	1.0	2.0
Total weight	128.0	256.0

Table 2
Nifedipine solubility in the different dissolution media considered at 37°C

Medium	Nifedipine solubility (mg/ml)
Water	0.011
SDS 0.25%	0.025
0.5%	0.105
0.75	0.174
1.00	0.250

speed was set at 100 rev./min and the fluid was maintained at 37 ± 0.5°C. The drug concentration was spectrophotometrically determined (Spectracomp 602, Advanced Products srl, Milan, Italy) at 237 nm. A personal computer, connected on-line to the spectrophotometer, was used for data processing. As the results are reproducible (S.D. < 3%), only the average values are reported in the graphs.

To verify the influence of the SDS concentration on the solubility characteristics of the drug, the maximum amount of nifedipine that could be dissolved in the four SDS solutions was determined. An excess of drug was placed in a known volume of the different dissolution media; the fluids were magnetically stirred in a thermostated bath at 37°C in a dark room, for 12 and 24 h. After these times, the drug concentrations were measured.

3. Results

The drug solubility, measured in the different dissolution media considered, shows that by increasing the SDS concentrations, the maximum amount of nifedipine that can be dissolved in a constant volume of fluid also increases (Table 2). It is generally accepted that, to maintain the 'sink conditions', the quantity of dissolution medium used should be not less than three times that required to form a saturated solution of the drug dose considered (USP XXIII); from our results it appears that for the dose of 30 mg of drug in 5 l of medium, the 'sink conditions' could be maintained even at the lower SDS concentration of 0.25%, while at least 0.50% of SDS is needed in the case of the higher dose of 60 mg. On the other hand, in 1 l of dissolution fluid, surfactant concentrations above 0.50% should be used for the N1 formulation and above 0.75% for the N2 tablets. However, the dissolution tests gave different results.

The dissolution profiles of the three different dosage forms, in 5 l of water, are compared in Fig. 1. Only in the case of the commercial product containing 20 mg of nifedipine, the drug dissolves completely in this volume of water and this process takes a very long time, more than 8–10 h. N1 and N2 tablets, instead, show a constant release behaviour as long as the 'sink conditions' can be maintained; then, in both cases, a typical plateau can be evidenced when the drug concentration reaches a saturation level.

The dissolution tests carried out in 5000 ml of SDS solution show that Product A releases the drug very quickly in these conditions, in 1–2 h with a burst of about 50% of the dose delivered in 15 min (Fig. 2). The dissolution curves recorded in the higher concentrations of surfactant, from 0.50 to 0.75 and 1.00% appear almost identical, but in the lowest concentration of SDS: 0.25%, a slower dissolution rate is achieved, which is only slightly faster than that obtained in water.

The results obtained from the solubility tests indicate that the lower dose of 20 mg of nifedipine (contained in the commercial form A) should dissolve even in the lowest (0.25%) concentration

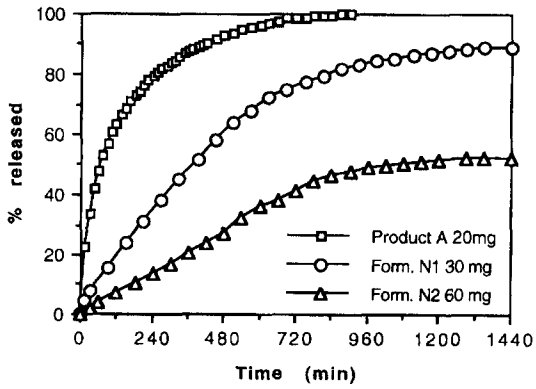

Fig. 1. Dissolution profiles in 5 l of water of the two extended-release dosage forms proposed: formulation N1 (30 mg) and N2 (60 mg) and the reference Product A (20 mg).

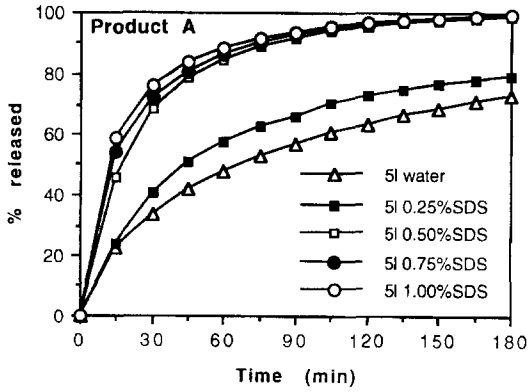

Fig. 2. Dissolution profiles of the reference Product A (20 mg) in 5 l of water or SDS solutions at four different concentrations: 0.25, 0.50, 0.75 and 1.00 w/v %.

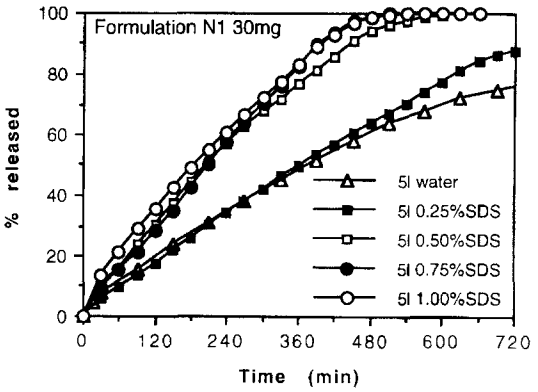

Fig. 4. Dissolution profiles of the formulation N1 (30 mg) in 5 l of water or SDS solutions at four different concentrations: 0.25, 0.50, 0.75 and 1.00 w/v %.

of surfactant, but the dissolution rate obtained in this medium is much slower compared to that measured in the other media and it is similar to the dissolution rate obtained in water. This result proves that the 'sink conditions' cannot be maintained in the medium containing the lowest SDS concentration.

Comparable results are obtained when the tests were carried out in 1 l of the same dissolution media (Fig. 3). In fact the drug dissolution profiles obtained in 0.50, 0.75 and 1.00% of SDS overlap while the delivery rate obtained in the presence of 0.25% of surfactant is remarkably slower.

The dissolution profiles of the N1 tablets, containing 30 mg of nifedipine, in 5 l of the four fluids considered, and in the same volume of water, are reported in Fig. 4, and the results obtained with 1 l of the different SDS solutions are shown in Fig. 5. In the two different volumes (5 or 1 l), the dissolution trends are similar: in water and in the lowest SDS concentration, the release rates are comparable, and the fluid is saturated before the complete delivery of the dose. In the range of surfactant concentrations from 0.50 to 1.00%, the dissolution rates are faster and the curves are completely overlapping.

In all cases, the new formulation is able to modulate the delivery of nifedipine from the

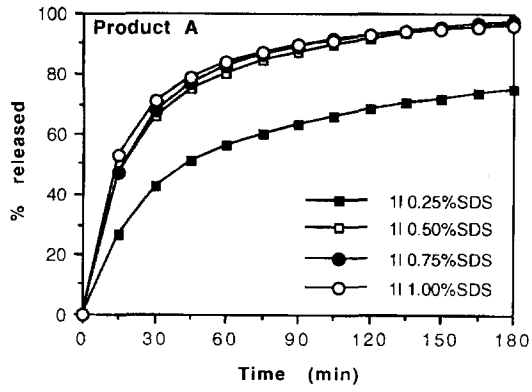

Fig. 3. Dissolution profiles of the reference Product A (20 mg) in 1 l of SDS solutions at four different concentrations: 0.25, 0.50, 0.75 and 1.00 w/v %.

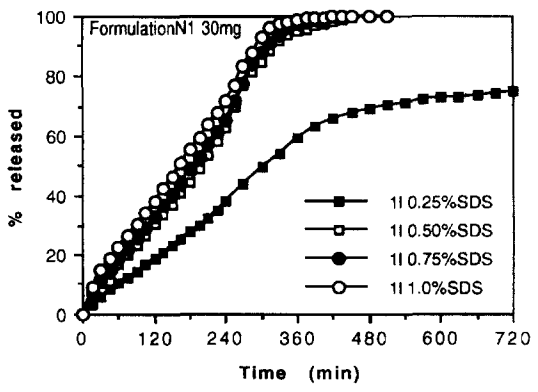

Fig. 5. Dissolution profiles of the formulation N1 (30 mg) in 1 l of SDS solutions at four different concentrations: 0.25, 0.50, 0.75 and 1.00 w/v %.

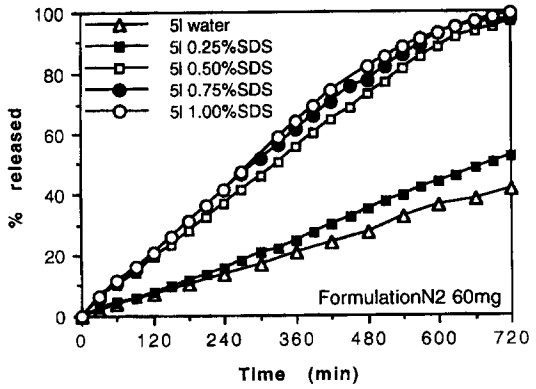

Fig. 6. Dissolution profiles of the formulation N2 (60 mg) in 5 l of water or SDS solutions at four different concentrations: 0.25, 0.50, 0.75 and 1.00 w/v %.

dosage form. An extended release of the drug, at a fairly constant rate, is achieved in all experimental conditions, without any burst effect: only about 5–7% of the dose is dissolved in the first 15 min.

The efficacy of this formulation is confirmed by the results obtained from the N2 tablets containing the higher dosage of 60 mg nifedipine (Figs. 6 and 7). In this case, a good control of the drug delivery rate is also achieved. The dose is released at a constant rate over a period of about 12 h. In water and in the lowest concentration (0.25%) of SDS, the drug content cannot be completely solubilized and the dissolution rate of the drug is very slow. On the other hand, all the SDS concentrations above 0.50% allow dissolution of even the higher dosage strength of 60 mg, and no effect on the dissolution rate can be seen.

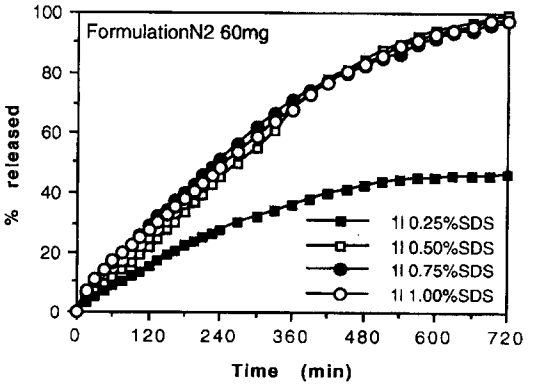

Fig. 7. Dissolution profiles of the formulation N2 (60 mg) in 1 l of SDS solutions at four different concentrations: 0.25, 0.50, 0.75 and 1.00 w/v %.

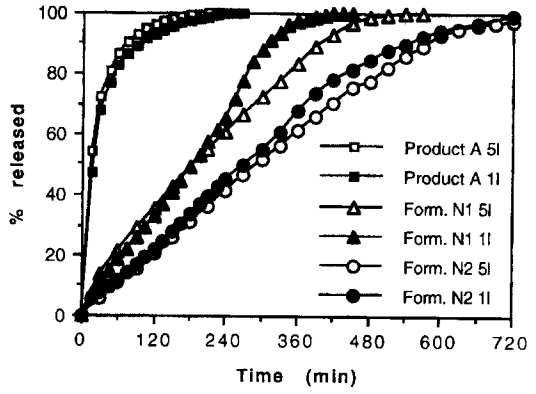

Fig. 8. Comparison of the dissolution profiles obtained in 5 or 1 l of SDS solutions at 0.75 w/v %, of the three dosage forms considered: Product A (20 mg), formulation N1 (30 mg) and N2 (60 mg).

From the solubility data it seems that the enhancement of the dissolution rate of the drug could be proportional to the amount of the solubilizing agent used. In the lowest surfactant concentration of 0.25%, slower release rates are always obtained for all the formulations tested, but above the concentration of 0.50%, the dissolution curves are comparable either in 1 or 5 l, and any further increase of the surfactant concentration does not lead to any appreciable variation in the drug dissolution profile.

By using a suitable surfactant concentration, it appears feasible to test the in vitro dissolution behaviour of the dosage form, not only in 5 l, but also in 1 l of dissolution fluid. In fact by comparing the dissolution profiles of the three dosage forms tested, in the same SDS solution (for example 0.75%, which is an intermediate value among those giving comparable results), the dissolution trends obtained in the two different volumes, 1 or 5 l, are quite comparable (Fig. 8).

4. Conclusions

The use of aqueous solutions of SDS appears a reliable approach to test the in vitro release be-

haviour of modified-release formulations containing an insoluble drug such as nifedipine. Due to the presence of a suitable concentration of the surfactant it is feasible to maintain the 'sink conditions' even in 1 l of dissolution fluid. As a consequence, the dissolution tests can be performed using the conventional equipment described in the Pharmacopeia, so avoiding other difficult and expensive procedures.

From this study it appears that SDS concentrations above 0.50% allow 'sink conditions' to be maintained during the whole dissolution test. Moreover, the presence of different amounts of surfactant, in the range from 0.50 to 1.00%, does not significantly affect the dissolution profile of the dosage forms considered.

The results obtained confirm that the formulations proposed are able to modulate the delivery of the insoluble drug — either 30 or 60 mg of nifedipine can be delivered at a constant rate over a period of 8–10 h.

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