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Dissolution study of spiramycin: influence of agitation intensity and addition of several substances to the dissolution medium

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Abstract

The dissolution process of spiramycin, a low dissolution rate drug, was studied testing the drug alone and in physical mixtures, using different additives in the medium such as hydrophilic carriers (PEG 6000 and PVP) and surface-active agents (Tween 20 and sodium lauryl sulfate), at two stirring rates (100 and 30 rpm). In most cases, a significant improvement in the dissolution rate of spiramycin was observed, the largest enhancements corresponding to those assays of physical mixtures containing sodium lauryl sulfate, in this case the dissolution rate being practically independent of the experimental stirring rate. From these assays, it was seen that sodium lauryl sulfate has considerable wetting power, even greater than that of Tween 20 (whose wetting capacity depends strongly on medium concentration and stirring rate) for spiramycin. It was also demonstrated that hydrophilic carriers may improve dissolution rate only in physical mixtures, since they act as disaggregants, diminishing electrostatic forces that exist among drug particles.

Key words: Spiramycin; Dissolution profile; Surface-active agent; Polyethylene glycol 6000; Polyvinylpyrrolidone; Dissolution improvement; Dissolution medium composition

1. Introduction

The use of hydrosoluble excipients to improve the dissolution process of many poorly water-soluble drugs is a habitual practice, as demonstrated by several recently published works (Francés et al., 1991; Bettinetti et al., 1992; Tasic et al., 1992; Tripathi et al., 1992; Veiga et al., 1993). Prior to performing a dissolution assay, it is necessary to fix the apparatus and experimental conditions such as medium composition, volume, temperature and stirring speed.

Two different apparatuses are described in the Pharmacopoeias: the rotating basket and rotating paddle apparatuses, the former being suitable for the assay of solid dosage forms and the latter for testing powdered samples.

The temperature recommended by the Pharmacopoeias and official codes is 37°C, although some authors have occasionally used slightly different temperatures (Nikolic et al., 1992).

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The volume of the medium usually varies between 500 and 1000 ml according to official methods.

Agitation intensity is also an important parameter in dissolution assays whose influence on in vitro drug dissolution has been studied by several authors (Needham and Luzzi, 1974; Posti and Salomon, 1983; Newton and Muhammad, 1984; Ammar et al., 1993). Monographs recommend the use of rotation speeds between 50 and 150 rpm. In official methods, the most quoted dissolution medium is distilled water. In diverse monographs (USP, 1990), diverse dissolution media are described such as buffered solutions of different compositions and pH range between 2.5 and 10.0, aqueous solutions of different acids (hydrochloric, citric, tartaric and acetic acids); also, simulated gastric or intestinal fluid can be employed, commonly without enzymes. Occasionally, solutions of surface-active agents (polysorbate 80, sodium lauryl sulfate (SDS)) are used to test poorly water-soluble drugs such as estradiol, griseofulvin, megestrol acetate, norethindrone acetate, praziquantel, levonorgestrel or ethinyl estradiol in order to permit more correct quantification of the drug dissolved.

The aim of this work was to study the influence of the addition of several substances to the attack fluid on the dissolution process of a drug and to evaluate dissolution rate differences with the same additive either dissolved in the medium or present in a physical mixture. The drug selected was spiramycin, a macrolide antibiotic with a low dissolution rate.

2. Materials and methods

2.1. Materials

Spiramycin was a gift from Rhône-Poulenc (Madrid, Spain); sodium lauryl sulfate (SDS) and polyethylene glycol 6000 (PEG 6000) were supplied by Panreac (Barcelona, Spain); polyoxyethylene sorbitan monolaurate (Tween 20) was purchased from Sigma (St. Louis, MO, U.S.A.) and polyvinylpyrrolidone K 30 (PVP) was a gift from BASF (Ludwigshafen, Germany). All the materials were used as supplied, without any further purification.

Table 1
Composition (mg) of physical mixtures assayed

Physical mixtures	Spiramycin	PEG 6000	PVP	SDS
1	500	500	–	–
2	500	–	500	–
3	500	–	–	100
4	500	500	–	100
5	500	–	500	100

2.2. Methods

2.2.1. Preparation of physical mixtures

In order to prepare physical mixtures, the drug and the additives were previously sieved and the particle size range below 100 μm was selected, the materials then being mixed thoroughly. The compositions of the physical mixtures are listed in Table 1.

2.2.2. Dissolution assays

The process of dissolution of pure spiramycin and all the physical mixtures prepared was studied using different media. A Sotax AT-7 dissolution apparatus with paddles was employed. The experimental temperature was 37 ± 0.1°C, the volume of the dissolution medium was 1000 ml and two stirring rates were assayed (100 and 30 rpm). All samples, containing an amount equivalent to 500 mg (1.5×10^6 IU) of spiramycin, were added to the medium in a powdered form (size < 100 μm). At measured time intervals during a period of 3 h, samples of 10 ml were withdrawn and filtered through a porous filter of 0.45 μm pore diameter (HA Millex Millipore).

Analysis of dissolved spiramycin was carried out spectrophotometrically using a Beckman DU 6 spectrophotometer at the UV maximum absorption peak of the drug (234 nm). Three replicates were performed from each assay.

The dissolution media employed to assay pure spiramycin are all shown in Table 2. To assay all

Table 2
Composition of each medium (concentration in % w/v of additives in distilled water; no. 1 corresponds to distilled water with no additives)

Medium	PEG 6000	PVP	Tween 20	SDS
1	–	–	–	–
2	0.45	–	–	–
3	0.09	–	–	–
4	–	0.45	–	–
5	–	0.09	–	–
6	–	–	0.05	–
7	–	–	0.01	–
8	–	–	0.004	–
9	–	–	–	0.05
10	–	–	–	0.01
11	0.45	–	0.05	–
12	0.09	–	0.01	–
13	0.45	–	–	0.05
14	0.09	–	–	0.01
15	–	0.45	0.05	–
16	–	0.09	0.01	–
17	–	0.45	–	0.05
18	–	0.09	–	0.01

the physical mixtures described in Table 1, distilled water was used as the dissolution medium.

3. Results and discussion

Fig. 1 and 2 show the dissolution profiles of spiramycin in aqueous solutions of different hydrophilic agents.

The nature of the additive was demonstrated

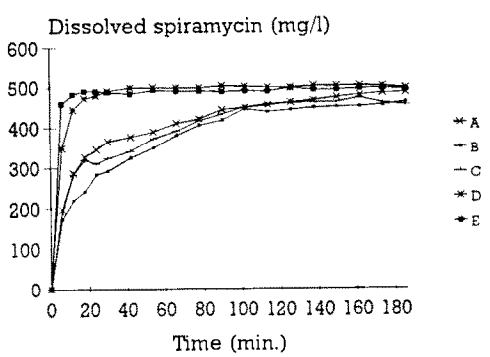

Fig. 1. Dissolution profiles of spiramycin in different aqueous media. (A) Distilled water; (B) 0.45% PEG 6000; (C) 0.45% PVP; (D) 0.05% Tween 20 and (E) 0.05% SDS.

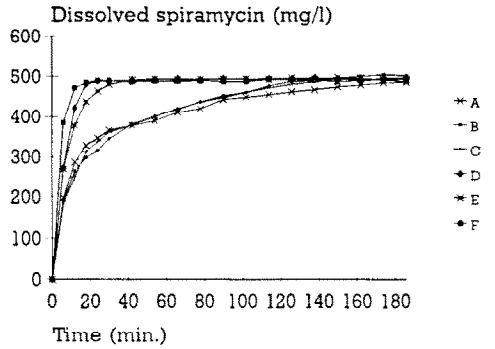

Fig. 2. Dissolution profiles of spiramycin in different aqueous media. (A) Distilled water; (B) 0.09% PEG 6000; (C) 0.09% PVP; (D) 0.01% Tween 20; (E) 0.004% Tween 20 and (F) 0.01% SDS.

to have a greater influence on the dissolution rate than its concentration. The polymeric agents used (PEG 6000 and PVP), being dissolved in the attack fluid, did not improve the dissolution process of the drug. Even a delay in dissolution was observed when PEG and PVP were added at high levels, as can be seen in Fig. 1.

When the attack fluid was an aqueous solution of a surface-active agent (Tween 20 or SDS), almost instantaneous dissolution occurred (Fig. 1), even when the additive was incorporated at concentrations below its CMC (Wan et al., 1974; Handbook of Pharmaceutical Excipients, 1986), as shown in Fig. 2. Hence, it was inferred that Tween 20 and SDS act via improving the wettability of the drug, which constitutes a preceding phase in the dissolution of any solute.

Fig. 3 and 4 display the dissolution profiles of spiramycin in aqueous solutions containing binary mixtures of a surface-active agent (Tween 20 or SDS) and a hydrophilic polymer (PEG 6000 or PVP).

In all cases, an enhancement of the dissolution rate compared with pure spiramycin was observed. The quantity and nature of additives in the dissolution medium also exerted an influence on the dissolution process. When the additives were present at high levels (Fig. 3), the dissolution profiles almost coincided with those obtained when only a surface-active agent was incorporated (Fig. 1). Otherwise, since the additives were

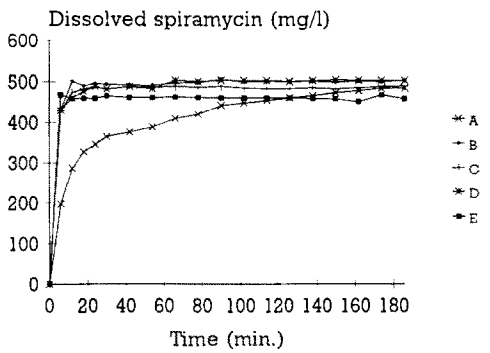

Fig. 3. Dissolution profiles of spiramycin in different aqueous media. (A) Distilled water; (B) 0.45% PEG 6000 and 0.05% Tween 20; (C) 0.45% PEG 6000 and 0.05% SDS; (D) 0.45% PVP and 0.05% Tween 20 and (E) 0.45% PVP and 0.05% SDS.

present at low levels (Fig. 4), a significant difference due to the nature of the surface-active agent was observed. Thus, when SDS exists in the attack fluid below its CMC, it is able to improve the dissolution profile of spiramycin in the presence of polymeric substances such as PVP and PEG 6000. When the surface-active agent employed was Tween 20 in low proportions beside PEG 6000, the enhancement in dissolution rate was not as clear as that produced when only Tween 20 was present in the medium (Fig. 2), which suggests a possible interaction between Tween 20 and PEG 6000. Since, in both cases, Tween 20

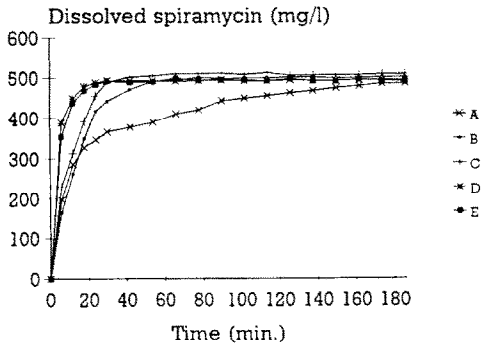

Fig. 4. Dissolution profiles of spiramycin in different aqueous media. (A) Distilled water; (B) 0.09% PEG 6000 and 0.01% Tween 20; (C) 0.09% PEG 6000 and 0.01% SDS; (D) 0.09% PVP and 0.01% Tween 20 and (E) 0.09% PVP and 0.01% SDS.

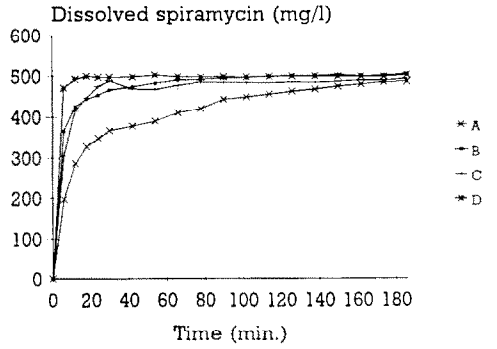

Fig. 5. Disolution profiles of spiramycin alone and from binary physical mixtures (p.m.) in distilled water. (A) Drug alone; (B) spiramycin/PEG 6000, 1:1 w/w; (C) spiramycin/PVP, 1:1 w/w and (D) spiramycin/SDS, 5:1 w/w.

was dissolved at concentrations above its CMC, it can be seen that this factor is not related with micelle formation.

Fig. 5 shows the dissolution profiles of spiramycin from binary physical mixtures prepared with the drug and either a hydrophilic or surface-active agent. Tween 20 was not included in the physical mixtures because it involved great difficulty due to its fluid nature. As could be seen in previous assays, SDS proved to be the optimum additive for enhancing the dissolution rate of spiramycin.

Comparing the dissolution profiles of spiramycin with hydrophilic agents in physical mixtures with those in which polymer was added to the medium (Fig. 1 and 2), a considerable enhancement in dissolution rate was evident, although the physical mixtures carried smaller amounts of polymer. The explanation for this observation is that electrostatic interactions among drug particles decrease when physical mixtures are prepared. Therefore, PEG 6000 and PVP act as disaggregants on drug particles when in physical mixtures. However, SDS acts as a disaggregant in physical mixtures, but mainly as a wetting agent once dissolved.

Fig. 6 demonstrates the dissolution profiles of spiramycin in ternary drug/hydrophilic agent/SDS systems. In both cases, the profiles practically coincide, dissolution being almost instantaneous, and the results are closely similar to

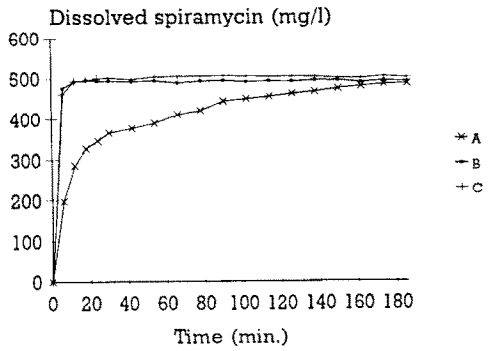

Fig. 6. Dissolution profiles of spiramycin alone and from ternary physical mixtures in distilled water. (A) Spiramycin alone; (B) spiramycin/PEG 6000/SDS, 5:5:1 w/w and (C) spiramycin/PVP/SDS, 5:5:1 w/w.

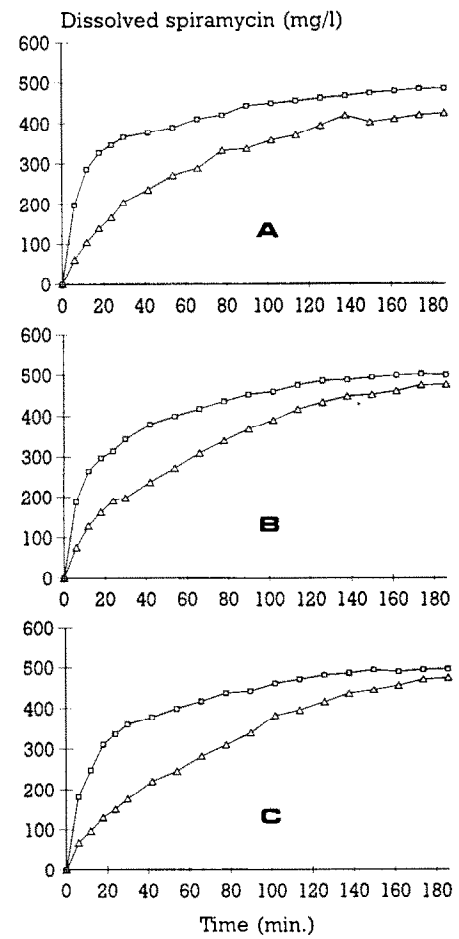

Fig. 7. Dissolution profiles of spiramycin in different aqueous media. (A) Water; (B) 0.09% PEG 6000; (C) 0.09% PVP. Stirring speed: (□) 100 rpm; (△) 30 rpm.

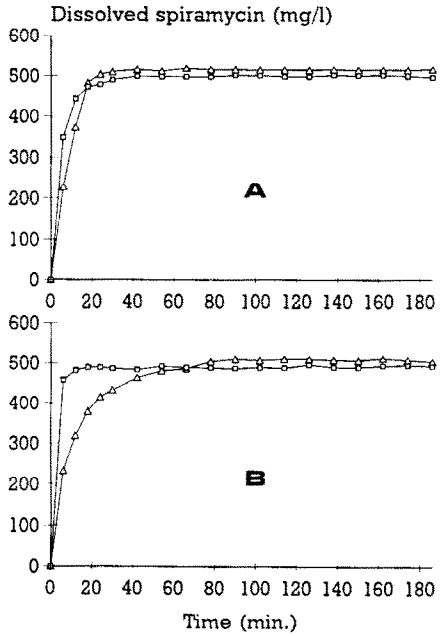

Fig. 8. Dissolution profiles of spiramycin in different aqueous media. Medium: (A) 0.05% Tween 20; (B) 0.05% SDS. Stirring speed: (□) 100 rpm; (△) 30 rpm.

those obtained when SDS was included in the physical mixture with spiramycin or when a low concentration of this additive existed in the attack fluid, which indicates that the mere presence of this surface-active agent is sufficient to optimize the dissolution process of spiramycin such that it occurs almost instantaneously.

Since the many dissolution processes assayed resulted in practically identical profiles, the same assays were carried out at a stirring rate of 30 rpm with the purpose of evaluating the disaggregant and wetting properties of the additives mentioned above without the influence of the agitation speed on the dissolution rate.

Fig. 7 shows a comparison of the dissolution profiles of spiramycin at 100 and 30 rpm, the influence of the stirring rate on the drug dissolution process being clearly manifested. This phenomenon was clearly demonstrated in the assays with distilled water as attack fluid and those in which a polymer (PEG 6000 or PVP) was dissolved in distilled water at low levels.

The presence in the medium of a surface-ac-

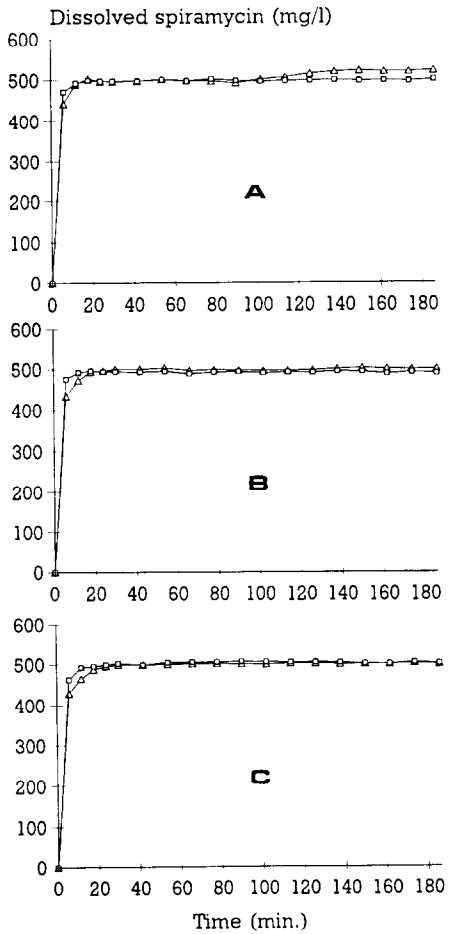

Fig. 9. Dissolution profiles of spiramycin from physical mixtures in water. (A) Spiramycin/SDS, 5:1 w/w; (B) spiramycin/PEG 6000/SDS, 5:5:1 w/w; (C) spiramycin/PVP/SDS, 5:5:1 w/w. Stirring rate: (□) 100 rpm; (△) 30 rpm.

tive agent (SDS or Tween 20) at concentrations above its CMC did not lead to any considerable differences between the assays carried out at different stirring rates, as illustrated in Fig. 8.

If spiramycin is formulated in physical mixtures containing SDS, the stirring rate does not influence the dissolution process (Fig. 9).

One parameter that provides an accurate indication of drug dissolution behaviour in the selected medium is the dissolution efficiency (DE). From observation of the variation undergone by this parameter on reducing the agitation speed from 100 to 30 rpm, it is possible to deduce whether any additive or additives are capable of providing agitation speed-independent drug dissolution.

The data on dissolution efficiencies for the different assays discussed above are listed in Tables 3 and 4. In general terms, a diminution of DE values with decreasing stirring speed was

Table 3
Dissolution efficiencies (%) employing only spiramycin as sample

Quantities of additives in dissolution medium	DE (100 rpm)	DE (30 rpm)
None	82.62	62.82
4.5 g PEG 6000	76.30	71.37
0.9 g PEG 6000	84.46	68.20
4.5 g PVP	80.01	62.81
0.9 g PVP	84.14	64.33
0.5 g Tween 20	96.65	98.41
0.1 g Tween 20	95.18	92.08
0.04 g Tween 20	94.37	77.96
0.5 g SDS	96.41	93.85
0.1 g SDS	95.55	91.68
4.5 g PEG 6000 + 0.5 g Tween 20	97.79	88.81
0.9 g PEG 6000 + 0.1 g Tween 20	87.75	80.55
4.5 g PEG 6000 + 0.5 g SDS	95.29	88.05
0.9 g PEG 6000 + 0.1 g SDS	95.55	86.53
4.5 g PVP + 0.5 g Tween 20	97.37	90.58
0.9 g PVP + 0.1 g Tween 20	96.02	83.55
4.5 g PVP + 0.5 g SDS	90.93	88.47
0.9 g PVP + 0.1 g SDS	95.95	89.48

Table 4
Dissolution efficiencies (%) employing physical mixtures as sample in distilled water

Sample	DE (100 rpm)	DE (30 rpm)
Spiramycin/PEG 6000 1:1 w/w	95.17	75.01
Spiramycin/PVP 1:1 w/w	93.13	81.05
Spiramycin/SDS 5:1 w/w	97.87	99.23
Spiramycin/PEG 6000/SDS 5:5:1 w/w	96.86	97.63
Spiramycin/PVP/SDS 5:5:1 w/w	98.52	97.54

observed, being practically imperceptible in the cases of assays at the highest values of dissolution efficiencies (media containing surface-active agents), as can be seen in Table 3.

If spiramycin is formulated in physical mixtures with PEG 6000 or PVP, a pronounced diminution of DE with decreasing stirring rate can be observed.

Otherwise, physical mixtures containing SDS provide maximal and agitation-speed independent DE values.

4. Conclusions

The nature of the additive incorporated into dissolution medium governs the rate of dissolution of spiramycin. Only surface-active agents are able to enhance the drug dissolution process due to improvement in the wettability of spiramycin.

In general, the simultaneous presence of a polymeric agent (PEG 6000 or PVP) and a surface-active agent (SDS or Tween 20) enhances the dissolution of spiramycin, the results being almost identical to those obtained with only one surface-active agent in the medium.

PEG 6000 and PVP may improve the drug dissolution profile only when present in physical mixtures with spiramycin, owing to a considerable diminution in the electrostatic charges among drug particles which are the main factor responsible for the slow rate of drug dissolution.

When SDS is employed, either dissolved in the medium or in the physical mixture, it leads to the optimum drug dissolution results which cannot be reduced, even on decreasing the agitation speed from 100 to 30 rpm. The use of SDS in dissolution studies of very poorly water-soluble drugs is a useful recommendation made by official codes (USP, 1990). However, in the case of spiramycin, whose slow dissolution is not due to low water solubility, the use of SDS in dissolution studies may mask the influence of other agents able to modify the dissolution of a drug.

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