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Research paper

Dose uniformity and redispersibility of pharmaceutical suspensions 2: assessment of three commercial erythromycin ethyl succinate oral liquids

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Abstract

The content of active ingredient of single doses of a suspension depends to a large extent upon the redispersibility of the product. Mathematical and technical aspects of a procedure to test this property have been discussed in a preceding article. Here, the method is applied to three commercial erythromycin ethylsuccinate suspensions obtained from community pharmacies in Germany. Three specimens of each product were tested in parallel. For approximately two weeks, samples were taken t.i.d. at 9 am, 1 pm and 5 pm after shaking the bottles on a prototype testing apparatus with an intensity of 134 m^2/s^3 per cycle corresponding to the 25th percentile of a group of 79 subjects, whose shaking habits had been assessed previously. In order to minimize volumetric errors, 2.5 ml samples were drawn using a syringe. They were assayed by HPLC with electrochemical detection using oleandomycin as an internal standard. While one of the products performed satisfactorily and one showed moderate shortcomings, the dose uniformity of two specimens of the third product was clearly deficient. The problem seems to be associated with poor wetting behaviour of the solids.

Keywords: Suspensions; Dose uniformity; Shaking intensity; Redispersibility; Erythromycin ethyl succinate; Wettability

1. Introduction

Dose uniformity and precision of pharmaceutical suspensions depend critically upon their homogeneity at the time of administration. Since dilute suspensions tend to settle, redispersibility is an important aspect of their pharmaceutical quality. Obviously, many dosing errors occur because patients do not observe handling instructions. With poorly formulated products, the physical limits of humans do not allow them to shake sufficiently vigorously for adequate redispersion of caked or coarsely flocculated suspensions [1]. It is well known that the aggregation of particles, the settling rate and the density of the sediment depend upon the choice of excipients, their concentration, and upon the concentration and particle size distribution of the active ingredient. A well-developed theory exists particularly for the interaction of charged particles in aqueous media [2].

Leading pharmacopoeias require that suspensions should be redispersible [3–5], but none specifies how this property can be verified experimentally. An apparatus and suitable operating conditions for testing the redispersibility of pharmaceutical suspensions under standardised yet practically relevant conditions have been described in the preceding article [1]. Linear motion and harmonic acceleration profiles have been observed in humans. Frequency, amplitude, and duration of the shaking process have been chosen accordingly. In this paper, we report on results obtained with three commercial erythromycin ethyl succinate preparations, which are distributed as powders or granulates and reconstituted with water before administration to form oral liquid suspensions.

Erythromycin is a basic compound, which is degraded to inactive anhydroerythromycin in acidic fluids. Therefore, ester-type prodrugs like the ethyl succinate and the stearate are preferred for oral administration. They are absorbed intact and hydrolysed in the circulating fluids to yield the active form. For juvenile patients, the poorly water soluble

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active ingredient is preferably formulated as a suspension because in this form the dose can easily be adjusted to body weight. Besides, children have less problems swallowing liquids than solid dosage forms and the bitter taste can be masked by suitable flavouring agents. Erythromycin ethyl succinate is hydrolysed in aqueous solutions [6]. Therefore, commercial products are formulated as powders or granulates for reconstitution. Before use, the pharmacist, parent or caretaker prepares a homogenous suspension by adding the required volume of water and shaking vigorously.

2. Materials and method for redispersibility assessment

2.1. Suspensions

Three preparations available in Germany with nominal potencies of about 235 mg erythromycin ethyl succinate per 5 ml suspension were tested. Product characteristics are given in Table 1. Three bottles of each product were studied.

2.2. Shaking intensity

In order to test the redispersibility of the suspensions, the shaking intensity of the apparatus was adjusted to match the 25th percentile of the population of subjects, in whom acceleration profiles had been measured [1]. Before sampling, containers were shaken for 3 s at 4.2 Hz with an amplitude of 5 cm. This corresponds to a shaking intensity of 134 m^2/s^3 per cycle and with a container of 259 g gross weight to a power of 34.7 W.

2.3. Reconstitution, sampling

Suspensions were prepared according to instructions given in package inserts. Tap water was added in two portions. First, bottles were filled up to 1.5 cm below the mark and shaken for 6 s as described above. Three min later, after the foam had largely vanished, the rest of the water was added. Proceeding as instructed, the amounts required for Ery-Diolan® 200 and Paediathrocin® Trockensaft were 70.0 g, while 80.0 g of water were added to Erythromycin ratiopharm® TS. Finally, the suspensions were shaken for another 12 s and after 20 s, a sample was removed from the container by means of a syringe. Subsequent samples were drawn in the same way after only 3 s of shaking.

Samples were taken t.i.d. for 2 weeks at 9 am, 1 pm and 5 pm until the containers were empty. During the intervals the containers were stored in a refrigerator at 8°C in an upright position. Measuring spoons for dosing lack the precision required for this kind of study, therefore, 2.5 ml samples were drawn via a three-way stopcock inserted in the cap of the container using a 5 ml syringe. The stopcock remained in place throughout the experiment.

2.4. Assay

Samples were weighed to the fourth decimal, transferred to a volumetric flask and reconstituted to 50.0 ml after addition of 5.0 ml of water. Acetonitrile was added in three approximately equal portions and the flask was agitated after each addition on a vortex mixer for 1 min. Most excipients are insoluble in the acetonitrile–water mixture, while the active ingredient is completely dissolved. To an aliquot of 0.5 ml, 2.0 ml of a solution of 0.2 mg Oleandomycin per ml acetonitril was added as an internal standard, and the mixture was filled up to 10.0 ml. The erythromycin ethyl succinate concentration was determined by HPLC with electrochemical detection and quantified by the ratio of peak areas of drug and internal standard. For details of the HPLC system and operating conditions see Table 2. Erythromycin ethyl succinate and base were purchased from Synopharm (D-Barmbek), Oleandomycin phosphate from ICN Biomedicals (D-Eschwege).

3. Methods for characterising granulates and suspensions

The wetting behaviour of granulates was assessed by measuring water uptake using a K12-MK5 digital tenisometer (Krüss, D-Hamburg) and by observing the disappearance of particles from a water surface according to Bullock [7].

3.1. Tensiometric method

A sample tube was filled with 4 ml granulate, which was condensed by tapping it 30 times. The lower end was brought into contact with a liquid surface and the weight increase was recorded as a function of time. For each granulate, three tests were performed with distilled water, and one reference experiment with *n*-hexane as a completely wetting fluid.

Table 1
Products tested

Brand name	Supplier	Lot	Excipients
Erythromycin-atiopharm® TS	Ratiopharm, D-Ulm	382106	Sodium cyclamate, colloidal silica, flavouring agents, macrogol, sodium carmellose, talc, saccharose
Ery-Diolan® 200	Engelhard, D-Frankfurt/M	97DO19A	Sodium cyclamate, sodium carmellose, flavouring agents
Paediathrocin® Trockensaft	Abbott, D-Wiesbaden	32408 VA	Saccharose, sodium carmellose, sodium saccharin, almasilat (Veegum F), flavouring agent, coloring agent E127

Table 2
HPLC system and operating conditions

HPLC-System		Operating conditions	
Pump	Bischoff, model 2200 (Bischoff)	Flow rate	0.85 ml/min
Column	12.5 cm reverse phase, sphere image-ODS2 5 μm, with pre-column (Schambeck, D-Bad Honnef)	Mobile phase	Acetonitrile (sds, F-Peypin), methanol (Fisher Scientific, UK-Loughborough), sodium dihydrogenphosphate monohydrate 0.04 M buffer (4:1:5 volumetric), pH 7.2
Detector	Esa Coulochem II with guard cell (USA-Chelmsford MA)	Detector voltages	Guard Cell: 1000; mV, Analytical Cell 1; 600 mV, Analytical Cell 2; 850 mV
Autoinjector	Shimadzu SIL 6A (Shimadzu, J-Kyoto)	Software	Peakwin V. 1.50 (Schambeck, D-Bad Honnef)

From these data, the dynamic contact angle of the granulates was computed according to Washburn [8].

3.2. Immersion method

This method was adapted from a test used in the food industry. A quantity of 5 g of granulate was weighed into a glass cylinder (height 7 cm, diameter 4.7 cm), which was closed at the bottom with a metal sheet. The granulate was spread evenly and the cylinder was fixed above a 250 ml glass beaker (height 12 cm, diameter 6.5 cm) filled with 50 ml water. The distance between the bottom of the cylinder and the water surface was 10.5 cm. After removal of the metal sheet, the time interval to immersion of the last particle was measured. One series of determinations was carried out in stagnant water, in another, the water was stirred using a PTFE-coated magnetic bar (length 3 cm, diameter 0.6 cm, rate 120 rpm).

3.3. Specific surface

The specific surface of the granulates were measured with the Gas Sorption Analyzer Nova 2200 (Quantachrome, D-Odelzhausen), on the basis of a 3-point-BET isotherm [9,10].

3.4. Particle size distribution

Suspensions were diluted (about 1:2000) with demineralised water and a volume of 500 ml was pumped in circulation through a flow cell. The particle size distributions were measured by laser light diffraction on a Malvern Mastersizer Micro Plus (Malvern Instruments, D-Herrenberg). Equivalent diameters were calculated according to Fraunhofer.

3.5. Zeta potential

The Zeta potential of the dispersions was measured on a Malvern Zetasizer 3000 (Malvern Instruments, D-Herrenberg) after 1:1000 dilution with 0.001 M KCl solution.

3.6. Conductivity

The a.c. conductivity of undiluted suspensions was measured at a temperature of 21°C in a locally made apparatus with platinum electrodes and a Wheatstone bridge circuit. The cell constant was determined using 0.1 M KCl solution.

3.7. Surface tension

The surface tension was determined on a K12-MK5 digital tensiometer (Krüss, D-Hamburg) using a Wilhelmy plate [8] in combination with a Cryomat Cz thermostat (Lauda, D-Lauda-Königshofen). Suspensions were stirred for 5 min in a beaker using a PTFE-coated magnetic bar, 10 ml were transferred to a glass cylinder of 4.6 cm diameter and equilibrated at 25.0 ± 0.1°C for 5 min. The Wilhelmy plate (dimensions 10.0 × 19.9 × 0.25 mm) was immersed in the dispersions to a depth of 1.0 mm. The mean of three measurements for each of the suspensions is reported.

3.8. Viscosity

The viscosity of the suspensions was measured on a Rheometrics DSR dynamic stress rheometer (Rheometrics, D-Bensheim) using a 50 mm plate-plate system with 0.5 mm gap width under stress sweep conditions (50–200 s^{-1}) at 20°C.

3.9. pH

Instrument: WTW pH90 pH-meter (Wiss. Techn. Werkstätten, D-Weilheim), Ingold electrode, type 405-S7/165 (currently Mettler-Toledo, D-Gießen).

3.10. Volumetric precision of the sampling method

The volumetric precision of the sampling procedure was assessed by removing 50 2.5 ml samples from a suspension container (ratiopharm) filled with water and weighing them.

4. Results and discussion

Observed erythromycin ethyl succinate contents of

samples and their deviations from expected values based upon the manufacturers' nominal declaration are given in Fig. 1. Besides, the concentrations of free erythromycin as the main degradation product are shown. Both dose uniformity and conformity with the nominal potency were best for Ery-Diolan®200 (Fig. 2b), but drug content of single doses tended to increase as emptying proceeded (Fig. 1b). The concentration of free erythromycin remained low at 1–2 mg/g. Doses of Erythromycin-ratiopharm® TS were consistently too low (Fig. 2a) but almost constant (Fig. 1a). On the other hand, hydrolysis proceeded notably during the time interval observed and the concentration of erythromycin base increased to 3–3.5 mg/g after 2 weeks. There were remarkable differences in the dosing pattern between the three containers of Paediathrocin® Trockensaft tested. In one of them, the drug content of virtually all doses was consistent, if somewhat low, while the first samples taken from of the other two were significantly underdosed and the drug content rose steeply as the bottles were emptied (Fig. 1c). After removal of 36 samples, a viscous sediment adhered to the bottoms of these containers. The distribution

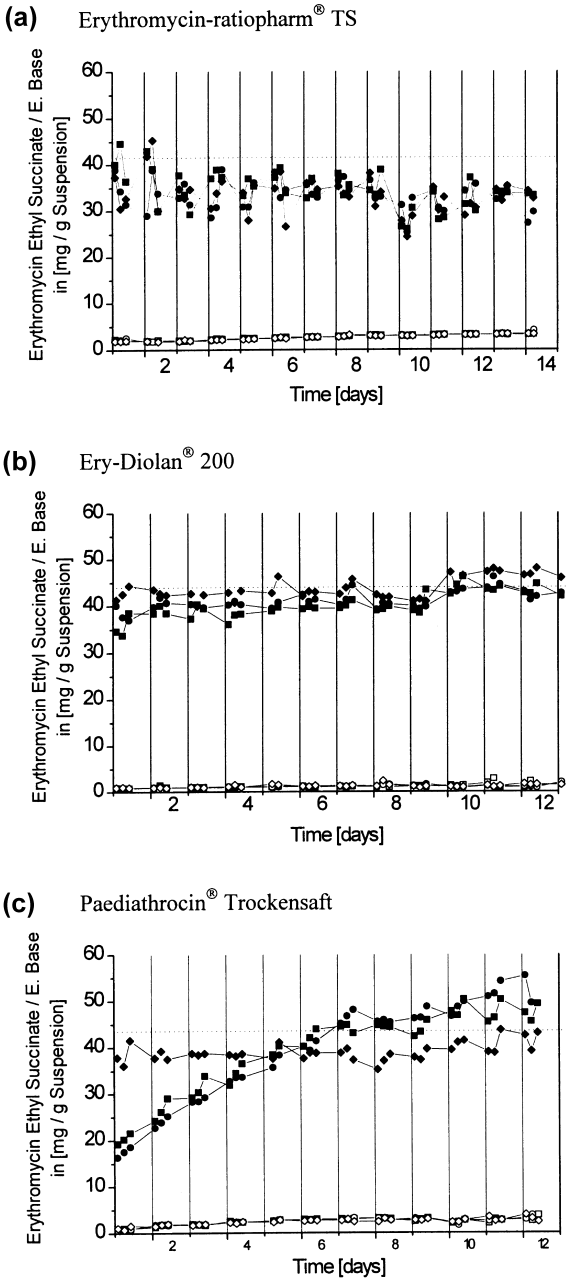

Fig. 1. Dose uniformity of three oral suspensions. (a) Erythromycin-ratiopharm® TS, (b) Ery-Diolan® 200, (c) Paediathrocin® Trockensaft. ■, ● and ◆ drug content in specimens 1, 2 and 3; - - - nominal drug content; □, ○ and ◇ Erythromycin base in specimens 1, 2 and 3.

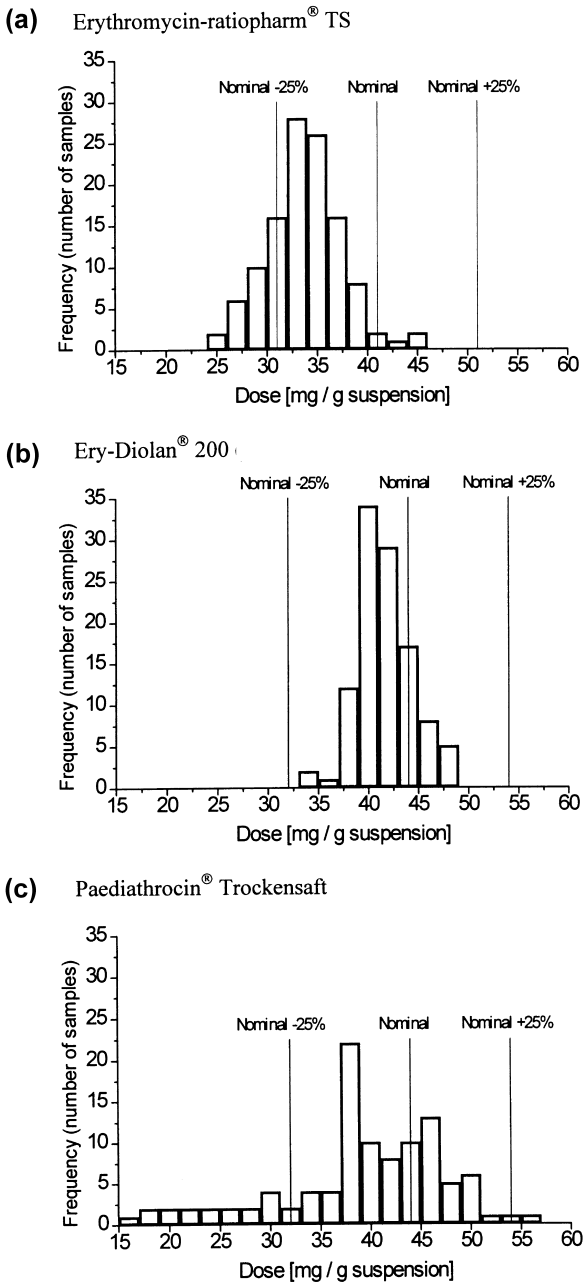

Fig. 2. Distribution of doses. (a) Erythromycin-ratiopharm® TS, (b) Ery-Diolan® 200, (c) Paediathrocin® Trockensaft.

Table 3
Wetting characteristics and specific surface of erythromycin ethyl succinate granulates

Product	Wetting characteristics				Specific surface 3-point BET (m^2/g)
	Tensiometric method (Krüss)		Immersion method, wetting time [7]		
	Capillary ascent (g^2/s)	Contact angle (°)	Unstirred (h:min:s)	Stirred (h:min:s)	
Erythromycin-ratiopharm® TS	1.2×10^{-3}	88.3	00:02:30	00:01:52	1.6556
Ery-Diolan® 200	1.1×10^{-4}	89.5	00:41:56	00:37:58	1.7016
Paediathrocin® Trockensaft	5.6×10^{-5}	89.9	18:00:00	03:37:00	0.4337

of doses shows a long left tail (Fig. 2c). The rate of hydrolysis was similar to the previous product with a final level of erythromycin base of 3–3.5 mg/g after 2 weeks.

For all products, the variability of active ingredients was significantly greater than the coefficient of variation of volumetric sampling by syringe, which amounted to 1.5%.

Consistent with therapeutic patterns of drug administration, sampling intervals were not equally long: two 4 h intervals during daytime were followed by a 16 h night interval. The hypothesis that morning doses might deviate consistently from noon and afternoon doses was tested and found not to hold for any of the brands tested.

There are two properties of the granulates which seem to be related to the pattern of single dose drug contents: the wettability of the granulates determined by the immersion method and their specific surface (Table 3). It is remarkable that the more sophisticated capillary ascent determination of wetting behaviour and the contact angle computed from these results did not discriminate as well between products. The wetting behaviour of all granulates was poor and computed contact angles were at the limits of the range to which the modified Washburn equation is applicable. Neither did zeta potential, conductivity, surface tension, viscosity or pH reveal any patterns that could be related to precision and uniformity of the drug content of single doses (Table 4). On the other hand, both the stirred and unstirred form of Bullock's simple immersion method were equally discriminating (Table 3).

Particle size distributions were remarkably different, but again, the best and the worst product tested were quite similar in this respect. Scanning electron micrographs of filtered and dried samples of the dispersed solids indicated clear differences but are difficult to interpret. The particles of Paediathrocin® appear to be imbedded in an unstructured matrix (Fig. 3).

5. Conclusions

The differences in drug content of samples drawn from the three suspensions indicate that the pharmaceutical quality of marketed preparations is not always satisfactory. Similar results were obtained earlier with suspension eyedrops [11]. Pharmacopoeial monographs on oral liquids and ophthalmic preparations should be amended to include a standardised procedure for testing the redispersibility of suspensions. In the conditions of this test, the shaking intensity measured in patients and subjects [1] should be taken into account, although more observations in humans are required for evidence-based specifications.

Table 4
Characteristic parameters of erythromycin ethyl succinate suspensions

Product	Particle size distribution[a] (μm)			Zeta potential[b] (mV)	Conductivity (μS/cm)	Surface tension (mN/m)	Viscosity (mPa s)	pH
	D_{10}	D_{50}	D_{90}					
Erythromycin-ratiopharm® TS	5.31	28.90	90.27	−58.6[c]	937	50.60	16.69	7.32
Ery-Diolan® 200	2.65	8.24	27.00	−75.2	9496	51.31	157.35[d]	7.37
Paediathrocin®	2.03	9.32	35.56	−75.1	5490	49.18	102.73[d]	8.61

[a] After 1:2000 dilution with distilled water.
[b] After 1:1000 dilution with 0.001 M KCl solution.
[c] Instable bimodal mobility distribution, sedimentation of coarse particles.
[d] Slight shear-thinning.

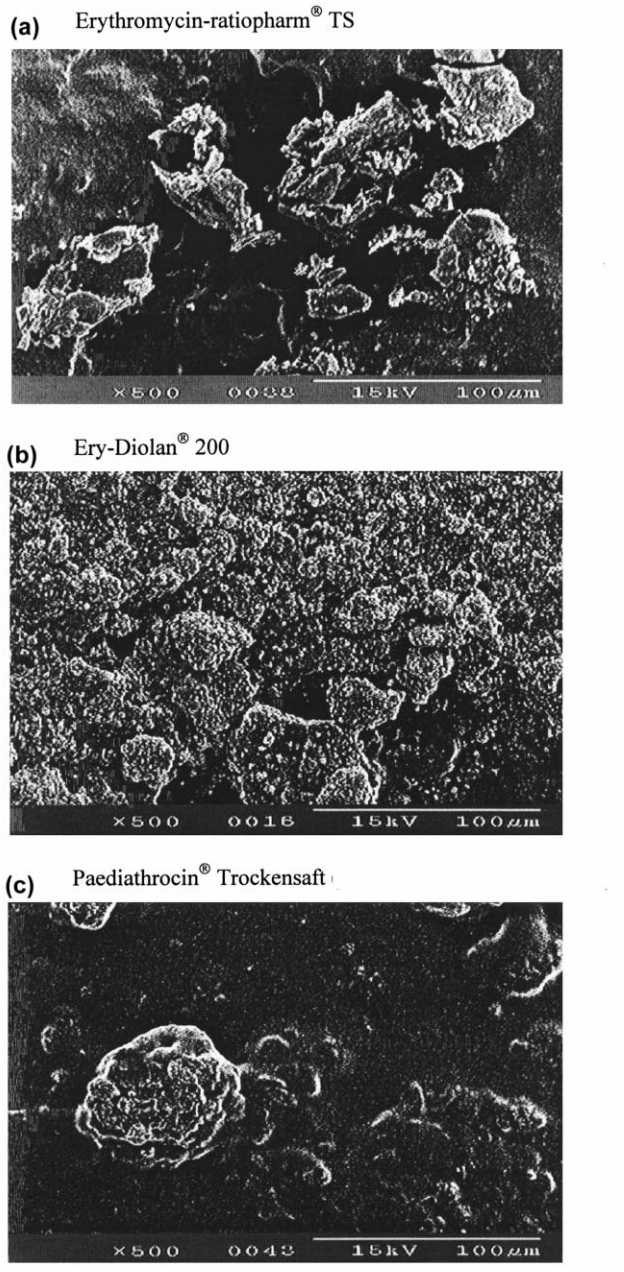

Fig. 3. Scanning electron micrographs of particle size. (a) Erythromycin-ratiopharm® TS, (b) Ery-Diolan® 200, (c) Paediathrocin® Trockensaft.

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