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Search for technological reasons to develop a capsule or a tablet formulation with respect to wettability and dissolution

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Abstract

Proquazone, a poorly wettable compound, was used as a model drug in the search for reasons to develop a capsule or tablet formulation. The capsules were filled with proquazone as active ingredient, with lactose monohydrate (200 mesh) as filler and with magnesium stearate as lubricant. The tablet was made out of a granulate as internal phase which consisted of proquazone as active ingredient, lactose as filler, corn starch as disintegrant and PVP as a binding agent. The external phase consisted of magnesium stearate and corn starch. The concentration of proquazone in the capsule and in the tablet formulation was varied. The capsule formulations showed a significantly slower dissolution of the drug substance than the tablet formulations especially for a high-drug load. Independently of the drug load, only the tablet formulation showed a high-dissolution rate. Thus, concerning drug load, only the tablet formulations showed to be robust. It became clear that proquazone needs to be formulated as a granulate or a tablet to achieve a fast dissolution rate. Thus, a poorly wettable drug, especially when it is found in high concentrations, can have direct impact on the decision to develop a tablet or a capsule formulation.

Keywords: In vitro dissolution; Wettability; Tablet; Wet granulation; Hard gelatine capsule

1. Introduction

In the course of the 19th century, the discovery of substances in powder form like the alkaloids opened suddenly new therapeutic possibilities. With the new substances, new dosage forms were created (like in 1834 the hard gelatine capsule invented by Mothes and in 1843 the tablet invented by Brockedown). The chance to process powders on a large scale with a prolonged stability as compared to liquid or semi solid dosage forms opened all possibilities of industrial production.

Nowadays, solid dosage forms are still very popular because they have a high-metering accuracy, the application of them is very easy and comfortable and their stability is very good.

On the one hand, a capsule has a number of advantages as compared to a tablet: the work to develop a

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Table 1
The biopharmaceutical classification system (BCS)

Class I	High solubility–high permeability
Class II	Low solubility–high permeability
Class III	High solubility–low permeability
Class IV	Low solubility–low permeability

capsule formulation is in most cases not as complex as for a tablet formulation. A powder mixture can be filled directly into a capsule shell without a granulation and a compression process. For this reason, a capsule formulation often is in the industry the first dosage form for early clinical studies and the filling of capsules by hand is a common practice in pharmacies for an individual medication. For blinding purposes, an active ingredient can be easily encapsulated (Desai et al., 1996). After soaking and dissolving of the shell in the stomach the active may in some cases be available in a loose, dispersed and, for this reason, in an early dissolvable and well absorbable state if the permeability through a biomembrane is given (see Table 1). Different colours of the capsule shells allow the patients to distinguish their medications (Mallory and Schaefer, 1977). A bad taste of a substance can be covered by a capsule shell (e.g. Chloramphenicole). When a small sized capsule has to be administered the swallowing may in certain cases be more comfortable because after contact with the saliva it gets more slippery than a tablet. On the other hand, if a big amount of a compound has to be administered, the size of the capsule can easily get too big as compared to the same amount compressed to an oblong tablet. A disadvantage of the capsule, however, is the fact that producing a capsule formulation is more expensive as compared to a tablet formulation because the capsule shell has to be bought additionally. Thus, there is a number of reasons from the economic and marketing point of view to prefer a capsule or tablet formulation. In this paper, technological formulation properties of a poorly wettable drug are studied as a rational basis for the development of a capsule or a tablet formulation. A key property of a capsule or a tablet formulation is the in vitro dissolution rate of the drug substance. Before a drug is absorbed from the gastrointestinal (GI) tract, it has to be released and dissolved first. The in vitro dissolution test is a first important step to assess the quality of a certain compound and to guide development of new formulations. Such tests are extensively employed because of their simplicity, their low costs and because they are easy to validate and standardise.

On the one hand, in vitro dissolution may be relevant under certain conditions to the prediction of in vivo performance of a drug (Munday and Fassihi, 1995), on the other hand, there are a number of examples of unsuccessful correlation of dissolution characteristics to bioavailability (Meyer et al., 1998). These results can be explained on the basis of the biopharmaceutical classification system (BCS) (see Table 1).

According to BCS, easily soluble drugs with a sufficient permeability (Class I) do not require an intensive bioavailability testing in case of manufacturing a generic, i.e. a copy of the original formulation. Proquazone shows poor solubility in water (Roos and Hinderling, 1981). According to the Lipinski rules of five (Lipinski et al., 2001) which predicts absorption or permeation of a drug, proquazone containing four H-bond acceptors and no H-bond donors, having a molecular weight of 278.35 and a calculated $\log P$ of 3.13, would likely to be absorbed and thus belongs to Class II. The low bioavailability (about 7% of intact drug in the plasma compartment) after oral application is not an effect of a low permeability but of an important first pass effect (Hinderling and Roos, 1984).

The following work wants to point out the necessity of an in-depth preformulation work in order to develop rational criteria for the decision to develop a capsule or tablet formulation. Thus, it may be possible that a critical physical property such as the wettability of a drug substance may have a direct impact on the choice of a capsule or tablet formulation. Thus, the decision to develop a capsule or a tablet formulation should not only be based on marketing approaches.

2. Materials and methods

2.1. Materials

The following ingredients were used as received from the suppliers.

2.1.1. Drug substance

Proquazone (Sandoz AG, Lotnr: 87327, Basel, Switzerland) (see Fig. 1) with a $\log P = 3.129 \pm 0.265$ (partition coefficient P = [organic]/[water], where [ ]: concentration), a $\log D = 3.02$ (pH 1) (distribution co-

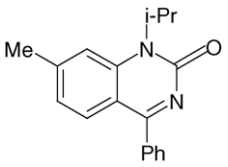

Fig. 1. Chemical formula of proquazone.

efficient $D = [\text{unionised}]_{(\text{organic})}/\{[\text{unionised}]_{(\text{aqueous})} + [\text{ionised}]_{(\text{aqueous})}\}$ calculated with Advanced Chemistry Development (ACD) Software Solaris V4.67 (© 1994–2003 ACD). Proquazone has a total surface free energy of 21.0 mN/m (polar contribution: 3.7 mN/m; non polar contribution: 17.3 mN/m) according to Owens and Wendt (Owens and Wendt, 1969) determined with a Krüss Processor Tensiometer K100 Mk2 (©Krüss GmbH, Hamburg, Germany). The experimental technique is described in detail in Michel et al., 2001. According to a reference list provided by Krüss, PTFE (Polytetrafluoroethylene, Teflon®) has an identical total surface free energy with a contact angle of 111° (water). Thus, it can be concluded that the contact angle of proquazone is >90° which is supported by the fact that the classical Washburn method is not working with water. Thus, the model drug has a poor wettability.

2.1.2. Excipients

α-Lactose monohydrate (200 mesh) (Borculo Domo Ingredients, Lotnr 3747, Zwolle, the Netherlands), corn starch (Maista® Agrana, Artnr: 21.000-50, Aschach, Germany), magnesium stearate (Siegfried, Artnr: 968786, Zofingen, Switzerland), polyvinylpyrrolidone (PVP) (Kollidon®, 29/30 BASF TXIII 08A, Minden, Germany). Furthermore, size no. 3 hard gelatine capsule shells (Elanco Lok-Caps® Dr. Wander, Lotnr: 3141625, Bern, Switzerland), size no. 2 hard gelatine capsule shells (Capsugel white 44.000/44.000, Bornem, Belgium,), potassium carbonate (Siegfried, Art Nr.: 162000–02, Zofingen, Switzerland) were used.

2.2. Preparation of the capsules

Three different powder mixtures which contained 10 (w/w) (capsule 1), 50 (w/w) (capsule 2) and 70 (w/w) (capsule 3) percent by weight (w/w) of proquazone were prepared with different contents of excipients (w/w).

Each powder component used for the blends was separately sieved through a screen of 250 μm. The three powder mixtures were prepared mixing them 3 min in a Loedige M5 high-shear mixer with a volume of 5 l (Loedige, Paderborn, Germany) at constant impeller speed of 278 rpm. The three powder mixtures were then encapsulated in size no. 3 capsules with a capsule filler Bosch GKF 602 (Robert Bosch Gmbh, Waiblingen, Germany) containing five tamp stations. The powder mixture used for capsule 2 was additionally filled by hand in size no. 2 capsules (capsule 2′). Furthermore, granulate 1 (see Section 2.3) containing 74% (w/w) of proquazone was also filled by hand in size no. 2 capsules (capsule 1′) (see Table 2a).

2.3. Preparation of granulates 1 and 2

Two different granulates were prepared containing 74% (w/w) (granulate 1) and 53% (w/w) (granulate 2) of proquazone (w/w) and diverse contents of excipients as shown in Table 3.

The previously screened (mesh size: 250 μm) proquazone, lactose and corn starch were put into a

Table 2a
Different capsule formulations were prepared

Ingredient	Composition (w/w)				
	Capsule 1	Capsule 2	Capsule 3	Capsule 2′	Capsule 1′
Proquazone	70	50%	10%	50%	–
Lactose	29.5	49.5%	89.5%	49.5%	–
Magnesium stearate	0.5	0.5%	0.5%	0.5%	–
Granulate 1	–	–	–	–	100%

Capsules 1, 2 and 3 (size no. 3) are made with the capsule-filling machine and capsules 2′ and 1′ (size no. 2) are filled by hand. The amount of ingredient used is shown in percent by weight.

Table 2b
Different tablet formulations were prepared

Ingredient	Composition (w/w)		
	Tablet 1	Tablet 2	Tablet 2′
Proquazone	–	–	50%
Lactose	–	–	49.5%
Corn starch	5%	5%	–
Magnesium stearate	0.5%	0.5%	0.5%
Granulate 1	94.5%	–	–
Granulate 2	–	94.5%	–

Tablets 1 and 2 are prepared with an excentric press whereas for tablet 2′ a Zwick® Universal Testing Instrument is used. The amount of ingredient used is shown in percent by weight.

Loedige M5 high-shear mixer with a volume of 5 l (Loedige, Paderborn, Germany) and mixed for 5 min (278 rpm). The amount of PVP used for each granulation was dissolved in distilled water. The granulation was carried out by adding the mixture PVP/distilled water as granulating liquid with a constant speed of 18 g/min while the powder components inside the mixer were merged further on with a constant impeller speed of 278 rpm. The total amount of granulation liquid was 255 g for granulate 1 and 200 g for granulate 2, respectively. The two granulates were screened (mesh-size: 2.2 mm) and dried in a dish dryer Hareus Typ UT 6200 (Sorvall® Heraus Instruments, Hanau, Germany) at a temperature of 40 °C until the water content was reduced to 10% (w/w), then they were sieved through a screen of 800 μm. The granulates were dried further until their moisture content was in equilibrium with 45% relative humidity at room temperature corresponding to the equilibrium moisture content of the original raw material.

Table 3
Two different granulates were prepared containing 74% (w/w) and 53% (w/w) of the model drug proquazone

Ingredient	% in formulation (w/w)	
	Granulate 1	Granulate 2
Proquazone	74.1	52.9
Lactose	5.8	27.0
Corn starch	15.9	15.9
PVP	4.2	4.2

The amount of excipients in the granulate is also shown in percent by weight.

2.4. Preparation of the tablets

Two blends giving two tablet formulations consisting of 70% (w/w) (tablet 1) and 50% (w/w) (tablet 2) of proquazone, respectively, 5.5% (w/w) (tablet 1) and 25.5% (w/w) (tablet 2) of lactose, respectively, 4% PVP and 20% (w/w) corn starch were prepared by mixing granulates 1 and 2 separately in a turbula mixer Type T2C (Willy A Bachofen AG (WAB), Basel, Switzerland) for 4 min with 5% (w/w) screened (mesh size: 250 μm) corn starch at a speed of 34 rpm. Then, 0.5% (w/w) of screened magnesium stearate (mesh size: 250 μm) was added and the blend was mixed for another minute in the turbula mixer. The two tablet mixtures were then compressed into tablets with a mass of 155–157 mg with an excentric press (Korsch EKO 1.0021.87, Berlin, Germany). The powder mixture that was used to prepare capsule 2 was also compressed into tablets (tablet 2′) using the a Zwick®1478 Universal Testing Instrument (Zwick GmbH, Ulm, Germany) in order to evaluate the effect of pressure on the release of proquazone (punch with a flat face and a diameter of 7 mm). Therefore, a compaction force of 6.9 kN was applied and the compression speed was set to the maximum of 25 mm/min (see Table 2b).

For the preparation of all tablets, a pair of punches (flat face) and a die with a diameter of 7 mm were used and tablets that showed a crushing strength of 50 N ± 5 N right after the compression were produced ($n = 10$).

In addition, the thickness, the diameter and the crushing strength determined with a tablet tester Dr. Schleuniger model 8M (Dr. Schleuniger Pharmatron, Solothurn, Switzerland) of the tablets were measured (see Table 4).

Table 4
Thickness, diameter, crushing strength. The absolute values as well as the relative standard deviation % R.S.D. are shown

	Thickness ($n = 10$)		Diameter ($n = 10$)		Crushing strength ($n = 10$)	
	mm	R.S.D. (%)	mm	R.S.D. (%)	*N*	R.S.D. (%)
Tablet 1	3.72	0.3	6.94	0.1	53	7.1
Tablet 2	3.49	0.3	6.92	0.1	51	5.4
Tablet 2′	3.19	0.5	6.96	0.2	51	5.2

2.5. Content uniformity

The content uniformity of proquazone in each formulation was determined according to USP XXIV ($n = 10$).

The samples were centrifugated (14,000 rpm) and the amount of proquazone was quantified by HPLC. The equipment consisted of a Hewlett Packard series 1050 pump (Hewlett Packard, Walbronn, Germany) connected to Hewlett Packard Series 1050 UV-detector model 79853A (Hewlett Packard, Walbronn, Germany), a Hewlett Packard series 1050 auto injector (Hewlett Packard, Walbronn, Germany) and a Macherey-Nagel (MN) Nucleosil reversed phase C8 ec 5 μm column (2 mm × 125 mm) (Macherey-Nagel AG, Oensingen, Switzerland). As mobile phase, a mixture of bidistilled water and methanol 40:60 (v/v) was used. The injected sample volume was 20 μl, the flow rate was set to 0.25 ml/min and the quantification was done at a wavelength of 275 nm. The content uniformity of each formulation (named M_0 (mg) ± R.S.D. (%)) is shown in Table 5.

2.6. Solubility of the model drug proquazone in 0.1 M HCl

To assure to work under sink conditions, a saturated solution of proquazone in 0.1 M HCl at a temperature of 37 °C was prepared and analysed (sink conditions were defined in this study as follows: the total concentration of proquazone dissolved should not be significantly higher than 10% of its saturated concentration (Gibaldi and Feldman, 1967)). Excess drug to saturate the solvent was added to 500 ml of the medium. It was stirred with a paddle at a speed of 100 rpm. Samples were taken after 16 h and 30 h and quantified by HPLC with the same method described above (see Section 2.5). The solubility of proquazone at 37 °C is equal to 1.25 g/l ± 0.03 g/l (after 16 h, $n = 3$) and 1.28 g/l ± 0.02 g/l (after 30 h, $n = 3$).

2.7. Dissolution rate measurements and evaluation

The release of proquazone from the different formulations was accomplished using the basket method with a constant speed of 100 rpm ($n = 6$) according to the guidelines of USP XXIV (Dissolution apparatus: Sotax AT 7, Allschwil/Basel; Switzerland). The volume of the dissolution medium was 900 ml 0.1 M HCl at a temperature of 37 °C ± 0.5 °C. Samples (10 ml) of dissolution medium were removed at regular time intervals. An equal volume of dissolution medium at 37 °C was added to maintain a constant volume.

The samples were prepared and the drug concentration quantified by HPLC (see Section 2.5). The data points were fitted with SYSTAT Version 7.0 for Windows® (SYSTAT Inc., Evanston, IL, USA) using the Weibull equation (see Eq. (1)); (Thawatchai et al., 2000; Kachrimanis and Malamataris, 2000).

$$M = M_0 \left[1 - e^{(-(t-T)^b/a)}\right] \quad (1)$$

where M is the amount of drug released as a function of the time t; M_0 is the amount of drug in the formulation at the time zero. T is a parameter equivalent with the lag-time of the drug release; a denotes a scale parameter that describes the time dependence; whereas b is

Table 5
The dissolution profiles of all formulations ($n = 6$ for each formulation) can be described with Eq. (1)

($n = 6$)	r	$t_{50\%}$ (min)	$t_{90\%}$ (min)	M_0 (mg) ± R.S.D. (%)	M_0 (%)	T (min)	a	b
Capsule 1	0.997	308	849	108.8 ± 5.3	101.5	1	1069	1.15
Capsule 2	0.995	44.9	207	78.2 ± 1.7	99.3	1	28.00	0.79
Capsule 3	0.991	3.33	6.17	15.5 ± 1.6	99.9	1	5.18	1.51
Capsule 2′	0.999	43.1	130	78.2 ± 1.7	98.7	1	57.34	1
Tablet 1	0.997	2.22	4.76	108.6 ± 0.7	100	0	5.01	1.56
Tablet 2	0.997	2.35	5.27	77.0 ± 0.5	99.9	0	5.15	1.49
Capsule 1′	0.997	4.71	9.04	115.9 ± 0.6	99.4	1	11.18	1.57
Tablet 2′	0.998	439	1220	77.5 ± 1.7	100	0	1787	1.17

M_0 (mg) denotes the result of the content uniformity test with its relative standard deviation, R.S.D. (%) and corresponds with the total amount of drug released M_0 (%). T describes the lag-time of the drug release, a describes the time dependence and b expresses the shape of the dissolution curve. The time when 50% and 90%, respectively, was released, was calculated according to Eq. (2). r stands for the correlation coefficient.

a shape parameter (Koch, 1984). The time, when 50% (w/w) and 90% (w/w) of drug being in each formulation was released, was calculated using the inverse function of the Weibull equation (see Eq. (2)).

$$t = \left(-a \ln \frac{M_0 - M}{M_0}\right)^{1/b} + T \quad (2)$$

2.8. Disintegration time

The disintegration of the different capsule and tablet formulations was determined with the apparatus according to Ph. Eur. 2002 (disintegration apparatus: Sotax DT 3, Allschwil, Basel, Switzerland). The disintegration media was distilled water at a temperature of 37 °C.

2.9. Water absorption measurement

The sorption ability of granulate 1, tablet 1, capsule 1 and proquazone was determined in order to characterize the wetting behaviour of the different formulations ($n = 3$) with a Krüss Processor Tensiometer K100 Mk2 (©Krüss GmbH, Hamburg, Germany). The test was performed with distilled water.The increase of mass squared of the samples was plotted against time (g^2/min) and the slope was calculated according to the modified Washburn equation (Luginbühl and Leuenberger, 1994) (see Eq. (3)).

$$M^2(t) = Kt \quad (3)$$

where M is the absorbed mass of water at a certain time t, K stands for a velocity constant of the water uptake.

3. Results and discussion

In this chapter, dissolution characteristics, disintegration time and the water uptake of the formulations are discussed.

The weight of each tablet used in the dissolution test and the weight of the powder or the granulate in each capsule formulation was within the limits of 155.2–156.6 mg (mean value: 156.0 mg; S.D.: ±0.3 mg; R.S.D. (%): 0.2). To prevent the capsules from swimming at the surface, the basket method was used. In order to be able to compare all dissolution profiles, the basket method was also applied to all tablet formulations.

It became evident that the different dissolution behaviour can be related to the difference in the formulations. In order to describe the different dissolution processes in this study, a single equation the "RRSW" or "Weibull" equation was chosen (see Eq. (1)).

In this equation M is the amount of drug dissolved as a function of time t. M_0 is total amount of drug being released. Because the total amount of drug was released in each dissolution experiment, this value corresponds with the mean value determined in the content uniformity test according to USP XXIV. T accounts for the lag time measured as a result of the dissolution process. In case of the tablets, the dissolution process started immediately and there was no lag time ($T = 0$). For the capsules, however, the lag time, namely the dissolving of the capsule shells of both sizes (nos. 2 and 3), was 1 min ($T = 1$). Parameter a describes the dependence on time of the process. Parameter b describes the shape of the dissolution curve progression. For $b = 1$, the shape of the curve corresponds exactly to the shape of an exponential profile with the constant $k = 1/a$ (see Eq. (4)).

$$M = M_0(1 - e^{-k(t-T)}) \quad (4)$$

If b has a higher value than 1, the shape of the curve gets sigmoidal with a turning point, whereas the shape of the curve with b lower than 1 would show a steeper increase than the one with $b = 1$. In order to discuss the profiles more easily, the times $t_{50\%}$ and $t_{90\%}$ were calculated according to Eq. (2). The amount of the different variables of the Eq. (1) for the dissolution profile of every formulation based on the experimental data and the corresponding correlation coefficient r is shown in Table 5.

3.1. Dissolution profiles of the capsule formulations

It could be seen that all dissolution experiments were conducted under sink conditions as defined in 2.6. solubility of the model drug proquazone in 0.1 M HCl at 37 °C. The dissolution profiles of capsules 1, 2 and 3 are shown in Fig. 2.

Capsule 1 containing 70% (w/w) of proquazone showed a very slow dissolution rate. After approximately 308 min 50% (w/w) and after about 849 min

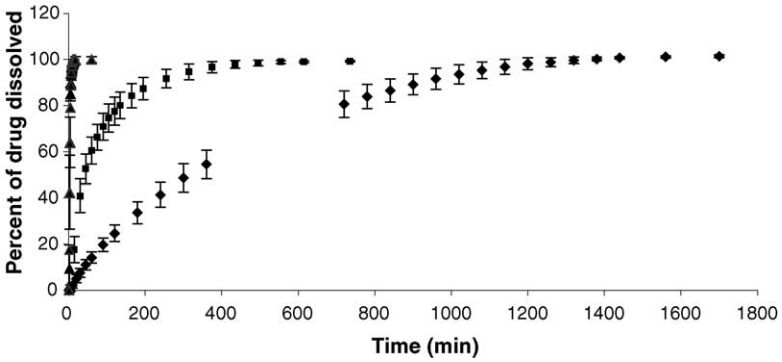

Fig. 2. The dissolution profiles of capsules 1 (♦), 2 (■) and 3 (▲) containing 70% (w/w), 50% (w/w) and 10% (w/w), respectively, of the model drug substance proquazone corresponding to a dose of 108.8 mg, 78.2 mg and 15.5 mg, respectively. The bars represent the standard deviation of the mean ($n = 6$).

90% (w/w) of the porquazone in the formulation was released. The capsule formulation (capsule 2) containing 50% (w/w) of proquazone showed still a slow release as compared to the formulation containing 10% (w/w) of proquazone: after 44.9 min 50% (w/w) and after 207 min 90% (w/w) of the drug in capsule 2 was released, whereas the time for a release of 50% (w/w) and 90% (w/w) of the model drug in capsule 3 constituted about 3.33 min and 6.17 min, respectively. The shapes of the dissolution profiles of capsule 1 ($b = 1.15$) and 3 ($b = 1.51$) tend to describe a sigmoidal progression, whereas the dissolution profile of capsule 2 showed a steeper progression as compared to Eq. (4) ($b = 0.79$).

The fast drug release of capsule 3 as compared to capsule 1 can be explained with the percolation theory (Leuenberger et al., 1987). In three dimensions, there are two percolation thresholds, which describe three regions of the drug/excipient system. Below the lower percolation threshold, the drug particles are embedded in a continuous phase of the excipients. Above the upper percolation threshold, the relatively low amount of excipients is embedded in a continuous phase of drug particles. Thus, in case of 10% (w/w) drug substance, it is expected that the excipients percolate the system and dominate its behaviour. In case of 70% (w/w) drug substance, it can be expected that the drug substance dominates the system. For the intermediate case of 50% (w/w) drug substance and 50% (w/w) excipients both components percolate the system and it is difficult to give a prediction which of the components will dominate. The drug substance proquazone shows a low solubility and a poor wettability. It seems to be evident, that if the drug substance is embedded in a well soluble powder matrix of the excipients used, that the dissolution rate of the drug substance can be increased. However, in case of a higher dose 78.2 mg (50% w/w) and 108.8 mg (70% w/w), respectively, the dissolution rate is not sufficient fast. It is evident that the basic capsule formulation is not a robust one as the dissolution rate depends significantly on the drug load.

3.2. Dissolution profiles of the tablet formulations

The dissolution profile of the drug of the tablet formulation is summarised in Fig. 3. The release of tablets produced from two granulates (granulates 1 and 2) after wet granulation is much faster than in case of the capsule formulations. It could be observed that all tablets swelled and were disintegrated rapidly at the beginning of their dissolution process, offering more surface area available for dissolution. Tablets 1 and 2 were released after 2.22 min and 2.35 min, respectively, for 50% (w/w) and after 4.76 min and 5.27 min, respectively, for 90% (w/w) of their content.

The difference in the dissolution behaviour is more than impressive as compared to the capsule formulations with an equivalent amount of drug substance: the factor of dissolution enhancement for $t_{50\%}$ (min) corresponds in this comparison between 70% (w/w) drug load tablets versus capsules and 50% (w/w) drug load tablets versus capsules to 308/2.22 = 139 and to 44.9/2.35 = 19.1, respectively.

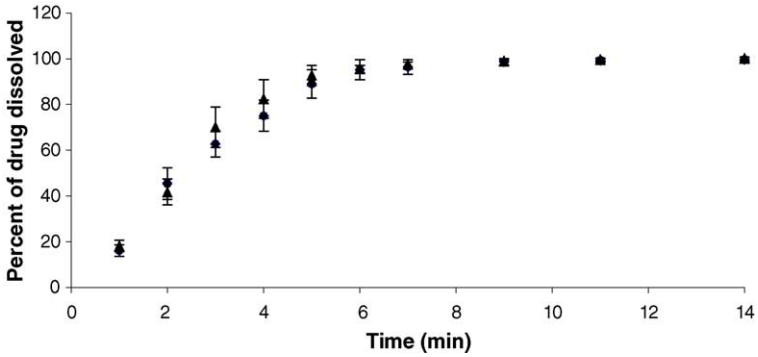

Fig. 3. The dissolution profiles of tablets 1 (■) and 2 (▲) containing 70% (w/w) and 50% (w/w), respectively, of proquazone corresponding to a dose of 108.6 mg and 77.0 mg, respectively. The bars represent the standard error of the mean ($n = 6$).

Surface properties of a system can be influenced by different excipients coating or embedding a drug or by various types of matrixes formed with different proportions of drug and excipients (Rowe, 1988; Planinsek et al., 2000). It is evident that the improvement of the dissolution rate is a result of the wet granulation process, which coats the poorly wettable drug substance with the well wettable excipients. In the contrast of percolation theory, the well wettable coating of the excipients forms a solvent matrix, i.e. a percolating phase. Thus, the explanation is not in contradiction to the explanation given for the dissolution behaviour of the capsule formulation. It is also impressive that the basic tablet formulation is a robust one and the dissolution rate does not depend on the drug load in the range of 50–70% (w/w).

3.3. Dissolution profile of additional formulations

In order to get a better insight of the difference in the dissolution behaviour of the capsule and tablet formulations studied, the following additional formulations were prepared.

- Preparation of a capsule formulation (capsule 1′) with the inner phase of the granulate (granulate 1) used for the tablet formulations. This formulation was prepared by hand filling.
- Preparation of hand-filled capsules (capsule 2′) with the powder used for the preparation of capsule 2.
- Preparation of tablets with the powder used for the preparation of the capsule formulation. These tablets were made with the Zwick® Universal Testing Instrument individually yielding the batch of tablet 2′.

The results of the dissolution profiles are summarised in Fig. 4. It is evident, that the poor wettable drug exhibits a good dissolution rate if the drug is initially prepared as a granulate. The tablet prepared from the powder showed again an extremely slow dissolution. Thus, the granulation process is the unit operation of choice improving the dissolution rate dramatically.

3.4. Effect of compaction in case of the capsule formulation

To investigate the influence of pressure that may influence the release of proquazone, hand-filled capsules were made. The same powder mixture as for capsule 2 was used. It was not possible without applying a small pressure to fill the same amount of the powder mixture by hand into size no. 3 capsule shells, used with the capsule-filling machine. In order to fill the powder blend loosely into a capsule shell, size no. 2 was chosen for the hand-filled capsules (capsule 2′), resulting more surface area of the blend available for dissolution. The dissolution rate of those capsules was faster than the release of the corresponding machine-made capsules (capsule size 3). After 43.1 min, 50% (w/w) of the drug, and after about 130.5 min, 90% (w/w) of proquazone was released. If both capsule formulations, capsule 2 (size 3, machine made) and 2′ (size 2), were compared, both curves after a drug release of 50% (w/w) looked likewise. For amounts >50% (w/w) the two

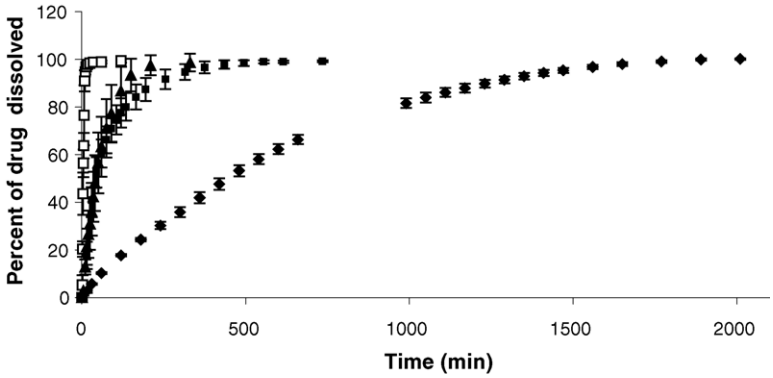

Fig. 4. The dissolution profiles of tablet 2′ (♦), capsule 2 (■) and capsule 2′ (▲) containing 50% (w/w) corresponding to a dose of 77.5 mg, 78.2 mg and 78.2 mg, respectively, and granulate 1 (□) containing 74% (w/w) corresponding to a dose of 115.9 mg of the model substance proquazone. The bars represent the standard error of the mean ($n = 6$).

profiles differ. A possible explanation could be found when the capsules were opened. Some weak clusters of condensed powder sections could be found in the machine-made capsules in contrast to the hand-filled capsules. The forming of variably condensed powder sections in a compressed core is described elsewhere (Adams, 1994). Although in a capsule-filling process only little compression forces occur, as compared to the production of tablets where compression forces achieve easily several kN, those condensed sections, after the majority of the looser sections of powder had already been dissolved similarly to the powder mixture in the hand-filled capsules, could have been responsible for a further delayed release. To confirm this assumption, tablets were made from the same powder mixture (tablet 2′). The dissolution rate of these tablets was much slower than the one of both capsules. After 439 min only 50% (w/w) and after 1220 min only 90% (w/w) of proquazone was released. Thus, the wetting effect of 49.5% (w/w) of the well water-soluble lactose in this formulation did not help to improve the dissolution rate, (i.e. the effect of pressure is negative resulting in a low porosity of the tablet and in a lower specific surface of the poorly wettable drug substance). It has to be mentioned that this formulation as in the capsule formulation does not include a disintegrant. Thus, it is not surprising that the disintegration time is 125 min. Further studies of the thesis of J. von Orelli will include a "direct tabletting" formulation. However, it is important to notice that, as far as the tablets on the basis of the (tablet) granulate formulation are concerned, no negative effect of the compression force was observed. In fact, the fastest dissolution rate was observed with the tablets prepared on the basis of the granulate formulation. Thus, it is not surprising that one of the standard procedures in the pharmaceutical industry is first the wet agglomeration process to prepare granules as an intermediate product to manufacture tablets.

3.5. Disintegration time of the formulations

With the exception of the capsule formulation, which was compressed to a tablet but did not contain a disintegrant, all formulations did comply with the pharmacopeal requirements (<15 min). The disintegration time of capsules 1, 2 and 3 accounted for 10.5 min, 5.5 min and 5.8 min, respectively, while tablets 1 and 2 showed a disintegration time of 6.5 min and 6 min, respectively. Thus, with the exception of the capsule formulation compressed to a tablet, no correlation between the dissolution behaviour and the disintegration time could be observed. These results confirm the superiority of the dissolution rate experiments as compared to the disintegration time determination for a better discrimination between different formulations.

3.6. Results of the water sorption experiments

However, when the different systems are evaluated from the point of view of sorption of water, which indicates the wettability behaviour of the different systems, a clear difference between the formulations

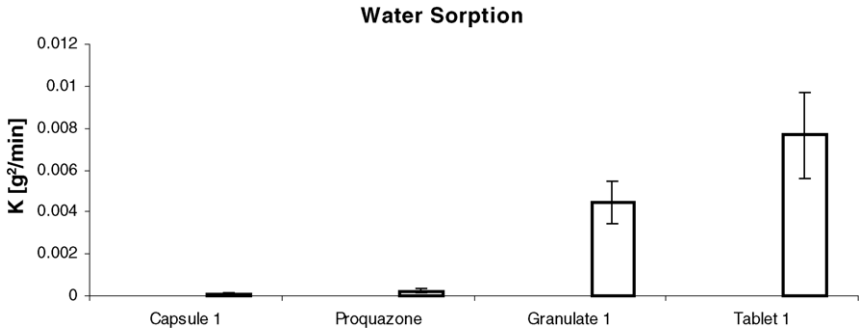

Fig. 5. The water sorption constant K (see Eq. (3)) for capsule formulation 1, proquazone powder, granulate 1 and tablet 1 ($n = 3$).

can be observed. In order to get a linear function, the gain of mass squared was plotted against time (g^2/min) and the slope was used as a degree of wettability of the different systems (see Fig. 5). The following K-values were obtained: for granulate 1 and tablet 1 $K = (4.47 \pm 0.99) \times 10^{-3}$ g^2/min and $(7.65 \pm 2.07) \times 10^{-3}$ g^2/min, respectively, while the sorption of water of the proquazone powder and capsule 1 came to $K = (2.31 \pm 1.03) \times 10^{-4}$ g^2/min and $(7.10 \pm 4.97) \times 10^{-5}$ g^2/min, respectively. According to these differences, it could be seen that proquazone was much better wetted in this particular granulate or the tablet formulation. The results are very consistent with the results from the in vitro dissolution experiments.

The K-values of tablet 1, granulate 1 (capsule 1′) and capsule 1 were plotted against the $t_{50\%}$- and the $t_{90\%}$-values of the dissolution experiments, and it was possible to detect a correlation between the dissolution behaviour and the water uptake of the formulation with ($r^2(t_{50\%}) = 0.8308$ and $r^2(t_{90\%}) = 0.8288$). Thus, it is suggested to include water sorption measurement in preformulation studies.

In this case, it is evident that the formulation consisting of a granulate has lead to an improved wettability. However, it has to be checked in each case whether such an approach is of advantage. In the case of proquazone, the granulate containing a high amount of active ingredient could also be filled in capsule shells, i.e. for marketing reasons.

4. Conclusions and recommendations

The present work shows that the choice of a capsule or tablet formulation needs to be related not only to marketing aspects but also to technological considerations. The choice to develop a drug as a capsule or as a tablet formulation can play an important role. With a capsule formulation containing the model drug proquazone, it is possible to have really prolonged releases, especially when it is found in high concentrations. When the same amount of proquazone is formulated as a granulate or a tablet, a fast dissolution can be achieved. Thus, it can be put forward a hypothesis that such a dissolution behaviour of proquazone could be characteristic for poorly wettable drugs. However, to confirm this assumption further examples are needed. In case of proquazone, the results of water sorption experiments of the formulations contain much more information than disintegration time values. The work confirms and shows the superiority of dissolution experiments to describe best the formulation studied. For preformulation studies of a new drug substance, it is strongly recommended to include water sorption experiments especially in the case of a high-drug content. Such an approval fits well into FDA's new concept of quality assurance in the 21st century, i.e. to understand the process and the formulation, to build in and not to test in the quality.

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