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Dissolution testing of artemisinin solid oral dosage forms

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Abstract

Dissolution can best be described as a tool that can provide valuable information about the bioavailability of a drug product. But to obtain a good overall correlation with in vivo data, the presence of sink conditions is an essential requirement in the dissolution tests. The flow-through cell method has been recommended to be a dissolution method that most satisfactorily fulfils this requirement for poorly water soluble drugs. The present article demonstrates that in case of artemisinin, a hydrophobic compound used in high dose per tablet or capsule, even the flow-through cell method does not guarantee the presence of sink conditions during the total duration of the experiments.

Keywords: Dissolution testing; Artemisinin; Flow-through cell; Solid oral dosage form

1. Introduction

Artemisinin is an antimalarial drug, extracted from a Chinese traditional medicinal plant *Artemisia annua*, L. *Asteraceae*. It has been shown to be very effective against malaria parasites, including the case of multidrug-resistant falciparum strains (Thaithong and Beale, 1985). It is especially effective in the treatment of cerebral malaria (Li, 1982). Artemisinin has a very low toxicity in a normal therapeutical dose (Koch, 1981; WHO, 1981; Luo and Shen, 1987).

In 1972, the active compound, artemisinin (Fig. 1), was isolated and characterized by Chinese scientists. From then on, many patients have been treated with this product (Qinghaosu antimalarial Coordinating Research Group, 1979; China cooperative Research Group on Qinghaosu and its derivatives as antimalarials, 1982; Klayman, 1985; Bruce and Chwatt, 1982).

In the situation of multidrug-resistance of malaria parasites nowadays in many developing countries, priority is given to artemisinin as a possible candidate in the group of new antimalarial drugs (Dutta et al., 1989; Woerdenbag et al., 1990; Hien and White, 1993; Woerdenbag et al., 1994).

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Studies on the bioavailability of drugs from a given dosage form revealed that in many situations various dosage forms with the same content of the active compound did not give the same therapeutic effect. This is ascribed to differences in physical characteristics of the active compound in formulation factors or in technological processes used by different manufacturers, therefore, resulting in different bioavailability profiles (Banakar, 1992).

Pharmaceutical bioavailability or in vitro bioavailability is one of the aspects of drug bioavailability. Among all tests that can be performed on drug solids, dissolution testing is considered to be sensitive, reliable and rational for predicting in vivo drug bioavailability behaviour. Since it is one of the most important quality control tests performed on drugs and drug products, many apparatus for dissolution testing have been developed over the years. Mainly three types have been retained in the official compendia: the rotating basket, the paddle and the flow-through cell method. Each of these methods presents advantages and disadvantages. The choice of the method to be used is mainly governed by the characteristics of the drug product. In the beginning, the rotating basket method was very popular, but it was gradually replaced by the paddle method.

For any dissolution test, the demonstration of a good overall correlation with in vivo data is the ultimate proof of qualification. For this correlation, sink conditions prevailing for the total duration of the experiment are more than wanted (Gibaldi and Feldman, 1967).

However, in all beaker methods the drug concentration in the liquid increases from zero up to either the saturation limit or the concentration which corresponds to the completely dissolved drug amount. This concentration build up is different from the in vivo process in which the dissolved material is removed continuously from the liquid by absorption. Therefore, Langenbucher developed another approach which is easy to standardize and involves no arbitrary and material-dependent parameters. This method is based on the mass transfer in a fixed bed of drug material traversed by a continuous flow of solvent liquid in a vertical-exchange column. Later it was named the flow-through cell method and taken over by some pharmacopoeias (Langenbucher, 1969; Langenbucher and Rettig, 1977; Moller, 1983).

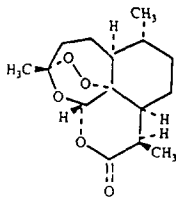

Fig. 1. Chemical structure of artemisinin.

Although artemisinin products such as tablets, capsules, etc. have widely been used against malaria in China, Vietnam, Thailand, etc. for a long time, up to now no results on dissolution profiles of those have yet been published.

This report presents the results of a first attempt to determine the dissolution profile of a series of artemisinin solid oral dosage forms and to compare their quality.

Among the official dissolution methods, the paddle and the flow-through cell method were chosen to test the dissolution of different formulations of Vietnamese tablets, capsules and of one example of a series of new tablet formulations, which were aimed to give fast dissolution.

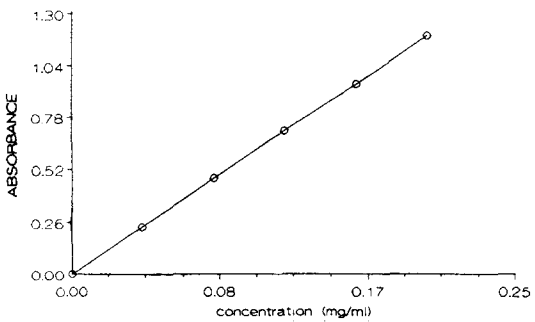

Fig. 2. Calibration curve of artemisinin.

Table 1
Dissolution data of tablet M2 obtained with the paddle method

Sample	Time (min)	Cumulative conc. of ART in dissolution medium (mg/l)	% ART released
1	15	23.64	9.50
2	30	29.23	14.53
3	60	36.00	20.74
4	120	44.66	28.53
5	180	47.28	34.94
6	240	44.93	39.67
7	300	43.76	44.59
8	360	38.98	47.90

2. Materials and methods

2.1. Materials

The following were used: artemisinin (ART) (Mediplantex, Hanoi, Vietnam), with a purity of 99.87%; from Institute of Materia Medica (Hanoi, Vietnam): tablet M1 (020292), tablet M2 (150993), capsule M3 (020993); from Central Factory N° 2 (Hanoi, Vietnam): tablet M4 (041092), capsule M5; from Mediplantex (Hanoi, Vietnam): capsule M6 (011193). Sodium lauryl sulphate (SLS) and sodium hydroxide were reagent grade.

2.2. Artemisinin assay

Concentrations of artemisinin were measured according to the method described by Zhao and Zeng (1985), in which artemisinin is transformed into a UV absorbing compound, with an absorbance maximum at 290 nm, by heating the solution with sodium hydroxide.

After appropriate dilution and heating for 30 min at 50°C with 0.2% sodium hydroxide, the concentration of artemisinin was determined at 290 nm with a UV spectrophotometer (Hewlett Packard 8452A).

The calibration curve of artemisinin is illustrated in Fig. 2.

2.3. Solubility determination

The solubility of artemisinin in different media has been determined by shaking 10 ml of the liquid with an excess of artemisinin powder during 48 h at 20°C. After saturation, the solution was filtered through a filter paper ($597_{1/2}$, Schleicher and Schuell) and the artemisinin concentration determined.

2.4. Dissolution experiments

Drug release was measured using two dissolution apparatus described in the USP-XXIII (1995): the paddle and the flow-through cell method. Artemisinin being a neutral compound, demi-water was used as dissolution medium instead of a recommended buffer.

The paddle method was performed at 100 rpm in 1000 ml dissolution medium at 37°C. At predetermined time intervals, samples of 300 ml were taken and replaced with the same volume of fresh solvent. Samples were assayed after carrying out the alkali reaction.

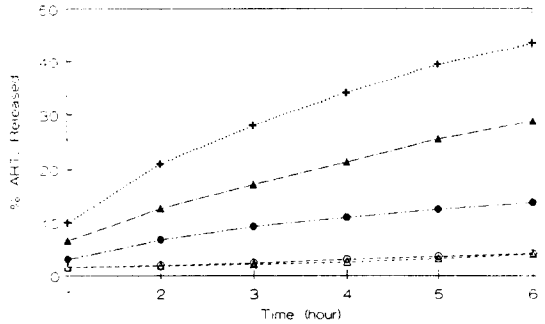

Fig. 3. Dissolution profiles of different Vietnamese tablets and capsules (mean ± 2.46 (n = 3)); ○ = M1; ▲ = M2; + = M3; △ = M5; ● = M6.

Table 2
Dissolution data of tablet M2 and M7 in water obtained with the flow-through cell method

Sample	Time (h)	Conc. of ART in dissolution medium (mg/l)		% ART released	
		M2	M7	M2	M7
1	1	16.58	38.65	6.63	19.33
2	2	15.23	29.49	12.72	34.07
3	3	10.99	24.67	17.12	46.41
4	4	10.80	22.17	21.31	57.49
5	5	10.60	20.05	25.55	67.52
6	6	8.10	16.00	28.79	75.52

The flow-through cell (Dissotest CE1, Sotax, Basle, Switzerland) was used in the open-flow system (unlimited supply of fresh solvent) at a flow rate of 1 l/h. Samples at different time intervals were assayed following the same procedure.

The cumulative release of drug was calculated from the sample assays using equation:

$$\text{mg dissolved } t_i = \frac{A_{sti}}{A_{ref}} \times fV_b + \int_{x=2}^{x=i-1} \frac{A_{sti}}{A_{ref}} \times fV_s$$

where, A_{sti} is the absorbance of the sample at time t, A_{ref} denotes the absorbance of the reference, f is the dilution factor, V_b is the volume of medium in the beaker (paddle method) or volume fraction (flow-through cell method) at time t and V_s denotes the sample volume taken.

The results are mean values of 3 experimental runs.

3. Results and discussion

3.1. Paddle method

The saturation concentration of artemisinin is 0.113 mg/ml in water at 37°C (Trigg, 1989), which means that for sink conditions, a concentration lower than 22.6 mg/l should be expected.

The results listed in Table 1 clearly show that sink conditions were not present.

To ensure the maintenance of sink conditions throughout the dissolution process, at least 11 l water as dissolution medium would be required for one tablet or capsule containing 250 mg artemisinin. Since such large volume is unrealistic, the paddle method was replaced by the flow-through cell method for further testing.

3.2. Flow-through cell method

Fig. 3 illustrates the dissolution behavior of a series of Vietnamese artemisinin tablets and capsules. Tablet M14 showed a poor disintegration and did release less artemisinin than tablets M1 and M5. These low values were not illustrated in this graph. For almost all formulations sink conditions exist, except for capsule M3, for which during the first 2 h, the concentration of artemisinin released in the dissolution medium was slightly higher than 20% of the solubility.

In order to control the general applicability of the flow-through cell method, tablets with faster dissolution were tested. Tablet M7 is one of the newer formulations (Ngo Thu Hoa, 1995). The data in Table 2 show that the situation of nonsink conditions can occur with more than one formula of artemisinin oral dosage forms when using the flow-through cell.

According to Posti and Speiser (1980), the effective surface area of the sample is one of the essential parameters needed to define the experimental conditions. If the sample has an effective surface area larger than a certain limiting value, sink conditions in the cell may not exist any more.

In case of tablets and capsules, the excipients added to the formulations and the technological manufacturing processes applied will be at the origin of variability in dissolving area. The reported findings clearly confirm that conclusion.

Table 3
Dissolution data of tablet M2 and M7 in 0.25% SLS obtained with the flow-through cell method

Sample	Time (h)	Conc. of ART in dissolution medium (mg/l)		% ART released	
		M2	M7	M2	M7
1	1	34.31	63.04	13.72	31.52
2	2	28.34	32.58	25.06	47.81
3	3	24.10	26.02	34.70	60.82
4	4	21.59	20.43	43.34	71.04
5	5	17.54	16.77	50.25	79.42
6	6	17.54	12.92	57.37	85.88

3.3. Effect of surfactant on dissolution

In case of difficulties for maintaining sink conditions, the addition of wetting agents to the dissolution medium in order to increase the solubility of water insoluble drugs has been described. The surfactants also improve the penetrability of the dissolution medium into the matrix by lowering the contact angle, thereby enhancing the dissolution process (Banakar, 1992). The influence of a lowered surface tension is also of some practical importance, since the surface tension of human gastric juice is known to be around 40 mNm^{-1}.

Of the many surfactants (Banakar, 1992), 0.25% sodium lauryl sulphate was selected for this study.

The saturation concentration of artemisinin in 0.25% SLS solution was found to be 237 mg/l at 20°C. So, for sink conditions, a concentration lower than 50 mg/l is required. Table 3 gives the dissolution data obtained from dissolution tests with tablets M2 and M7.

In case of tablet M2, sink conditions were present with both dissolution media (water and SLS solution) while with tablet M7, nonsink conditions were observed in water as well as in SLS solution during the first hour period (Tables 2 and 3).

4. Conclusion

The initial results mentioned in this report show that for artemisinin solid oral dosage forms the classical dissolution methods do not fulfil the sink condition requirement, even with the flow-through cell apparatus, which is still considered as a valid dissolution method for poorly water soluble drugs. Moreover, these findings confirm the warning by Posti and Speiser (1980) on sink conditions in the flow-through cell during dissolution.

The results obtained also show that, if no strict requirements on dissolution control of final product are issued, drugs with a large difference in dissolution characteristics can reach the market. Eventually, there is a product as tablet M4, no artemisinin released could be measured during the first 6 h of experimental process. The need of dissolution control in drug production is indispensable to ensure drug quality. Therefore, studies in these laboratories are concerned with the development of methodology for the determination of dissolution rates of artemisinin from disintegrating tablets and capsules dosage forms.

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