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Formulation of artemisinin tablets

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Abstract

Since artemisinin is known to be absorbed very fast from gastrointestinal fluid, while its solubility is very low, the formulation of the dosage form may be an important factor that might limit absorption after oral administration. The purpose of this investigation was to study the influences of some formulation variables on the time required to achieve a fast and complete dissolution of artemisinin. An experimental design that generated a maximum of information for a minimum of experimental work was used. The response selected for the factorial design was the time required for dissolution of 50% of the content (T_{50}), determined with a previous described two phase partition-dissolution method.

Keywords: Formulation; Factorial design; Artemisinin; Tablets

Artemisinin (ART) and its derivatives have gained increasing attention as new promising antimalarial drugs since their low toxicity and high efficacy against malaria parasites, including the cases caused by multidrug resistant and cerebral strains, were known (Klayman, 1985; Li Guo Qiao, 1982; Thai Thong and Beale, 1985; WHO, 1981; Woerdenbag et al., 1994). The major drawback of this compound is the occurrence of a recrudescence after treatment. The reason for this is not known, but the observation that the recrudescence rate is higher with tablets than after parenteral administration (Hien and White, 1993; Luo and Shen, 1987), suggests that a limited oral bioavailability may be one of the contributing factors. Because first pass metabolism has been suggested to be an important factor accounting for low oral bioavailability, a sufficient high concentration over a sufficiently long period of time is required to obtain a parasiticidal action (Tiulaer et al., 1991), and may reduce the prevalence of recrudescence. Fast and complete dissolution of the active compound from oral dosage forms is one of the most important factors to reach that goal.

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Table 1
Five-factor, two-level fraction factorial design

Formula	X1	X2	X3	X4	X5	Treatment combination	Response
FD1	−	−	−	+	+	X4.X5	Y1
FD2	+	−	−	−	+	X1.X5	Y2
FD3	−	+	−	+	−	X2.X4	Y3
FD4	+	+	−	−	−	X1.X2	Y4
FD5	−	−	+	−	−	X3	Y5
FD6	+	−	+	+	−	X1.X3.X4	Y6
FD7	−	+	+	−	+	X2.X3.X5	Y7
FD8	+	+	+	+	+	X1.X2.X3.X4.X5	Y8

The techniques of experimental design combined with optimization are well documented in the pharmaceutical literature (Doornbos and De Haan, 1995; Wehrle et al., 1989) and textbooks (Armstrong and James, 1990). In the factorial design, each variable is evaluated at several levels of all other variables. The levels of the factors involved can be set at will. Under such conditions, a complete factorial study is possible, but would involve a large number of experiments. A fractional factorial design can give a solution to this problem. This work is an application of fractional factorial method for the formulation optimization of ART tablets.

The method used for response measurement is at least as important as the proposed experimental methodology. In this study, dissolution rates of the ART tablets in the factorial design are the responses to analyse. Because of the low solubility of ART (Trigg, 1989) and the high content in a unit dosage of the commercially available products, all official dissolution methods described in pharmacopoeias were demonstrated to be unsuitable for ART solid oral dosage forms (Ngo et al., 1996). To ensure sink conditions during the total dissolution experiment, a two phase partition-dissolution method (Ngo and Kinget, 1996) was used. The results reported are mean values of three experimental runs.

For a very high hydrophobic compound as ART, wet granulation was chosen for the preparation of tablets. During compression of the different formulations with an instrumented KORSCH MP1 tabletting machine, compression forces were adjusted in order to produce tablets with similar crushing strength (Table 2). Dissolution rates of the tablets will mainly depend on the ingredients used.

On the ground of the data obtained by a series of preliminary test in order to select the excipients to be used and the parameters to be studied, a basic formulation was developed to set up the fractional factorial design.

Five parameters of the basic formula were selected to study, each at two levels:

X1: amount of lactose

X2: amount of sodium dioctyl sulfosuccinate 33%

X3: amount of sodium starch glycolate

X4: amount of gelatin

X5: amount of magnesium stearate

A complete factorial plan studying all interactions would include $2^5 = 32$ formulas. However, since the aim of the study was an evaluation of the variation of experimental response depending on the formulation and the dissolution method used, only eight formulas were envisaged, affording a fractional factorial design 2^{5-2} with a generator $I \equiv 134 \equiv 235 \equiv 1245$. The purpose is a study of the main effects and the two-factor interactions.

The factorial design with code variables is presented in Table 1. As usual in a factorial design, low levels of a factor are presented by a '−' and high levels by a '+'. The real data are reported in Table 2.

All dissolution experiments occurred under sink conditions in the water phase. Concentration of ART released in the water layer was always below 12.5% of the solubility (Fig. 1).

Table 2
Composition and the data concerned of tablets in the factorial design

Formula	X1 (mg)	X2 (mg)	X3 (mg)	X4 (%)	X5 (mg)	Compression force (N)	Hardness (kP)	T_{50} (h)
FD1	40	5	5	1.8	3	5300	4.6	4.69
FD2	60	5	5	0.7	3	5300	4.7	7.29
FD3	40	20	5	1.8	1	4200	4.5	2.14
FD4	60	20	5	0.7	1	4550	5.0	1.56
FD5	40	5	25	0.7	1	6900	4.7	3.01
FD6	60	5	25	1.8	1	5900	4.7	3.24
FD7	40	20	25	0.7	3	8100	4.2	2.3
FD8	60	20	25	1.8	3	7000	4.1	1.79

The time required for dissolution of 50% of the content (T_{50}) was calculated (Table 2), and analyzed by the ANOVA (analysis of variance) technique using the SOLO statistical software (BMDP statistical software, Los Angeles, CA). The ANOVA treatment resulted in the following conclusion: (1) changing the level of any ingredient used within the amount limited by the factorial design did not exhibit any significant influence at the 95% confidence level; (2) sodium dioctyl sulfosuccinate gives the largest positive effect; (3) an amount of magnesium stearate exceeding 1% gives a negative effect; (4) the effects of the other compounds were noticed to follow the order: sodium starch glycolate > gelatin > lactose. In a study on influence of formulation on dissolution rate, Finholt (1974) also found starch to be more effective than gelatin and lactose.

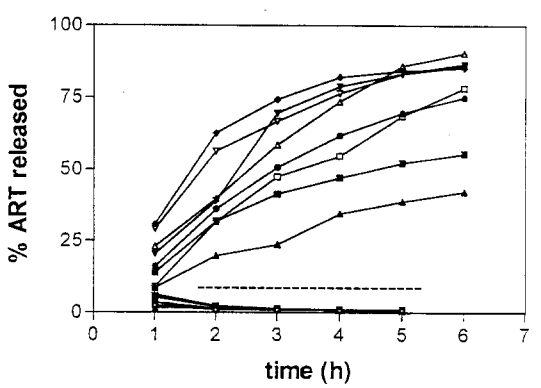

Fig. 1. Dissolution profiles of ART tablets studied in the factorial design (■ = FD1; ▲ = FD2; ▼ = FD3; ◆ = FD4; ● = FD5; □ = FD6; ▽ = FD7; + = FD8 (mean ± 8.44 (n = 3)). Above part: cumulative concentration of ART in the chloroform layer. Under part: cumulative concentration of ART in the water phase.

From the results, depicted by the graph in Fig. 1, it is clear that formulae containing a higher amount of sodium dioctyl sulfosuccinate (e.g. FD3, FD4, FD7, FD8) show a higher dissolution rate than those with a lower amount of this compound, even if they contain a higher amount of other ingredients such as lactose, sodium starch glycolate or gelatin.

To control the reliability of the results obtained, some additional tests were carried out and these additional dissolution tests confirmed the conclusions resulting from the ANOVA treatment.

With allowance for factors such as the appearance of tablets, tablet weight, dissolution rate (T_{50}) and occlusion of the dissolution processes, formula F_{opt} (Table 3), comprising the conclusion of ANOVA, was investigated in a final test. With a T_{50} of 1.64 h, F_{opt} belongs to the group of formulations with the fastest dissolution rate (Fig.

Table 3
Composition of ART tablet F_{opt}

Artemisinin powder (<0.25 mm)	200 mg
Lactose 200 mesh	30 mg
Sodium dioctyl sulfosuccinate 33%	20 mg
Gelatin	1.8%
Glycerin	0.72%
Sodium starch glycolate	20 mg
Magnesium stearate	1.25 mg
Compression force	6700 N
Hardness	4.4 kP
Disintegration time	≃ 1 min

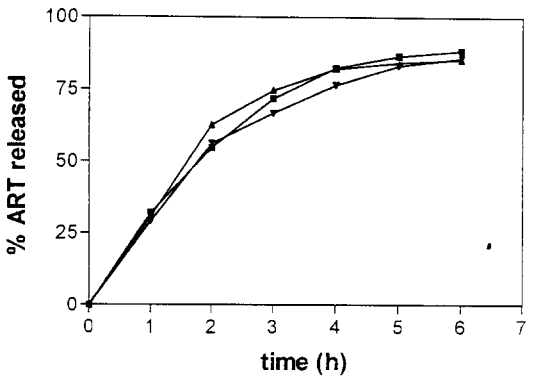

Fig. 2. Dissolution of artemisinin from tablet F_{opt} compared with the formulae with the fastest release tested in the factorial design (■ = F_{opt}; ▲ = FD4; ▼ = FD8) (mean ± 6.52 (n = 3)).

2). For industrial production, a tablet weight of 272 mg and a diameter of 9 mm are acceptable. Moreover, the tablets show a good appearance, a hardness of 4.7 kP and a disintegration time of approximately 1 min.

In conclusion, the formulation of the tablets gave a very fast dissolution of ART when compared to commercially available conventional tablets (Ngo et al., 1996).

During all experiments, sink conditions prevailed in the water phase, so that these results can be added to those previous reported (Ngo and Kinget, 1996), as a further validation of the two phase partition–dissolution method.

Acknowledgements

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