International Journal of Pharmaceutics, 79 (1992) 67–69

IJP 02617

Notes

Effect of helix characteristics on the dissolution rate of hard gelatin capsules

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(Received 25 February 1991)
(Modified version received 23 July 1991)
(Accepted 22 August 1991)

Key words: Paddle dissolution method; Hard gelatin capsule; Helix characteristics

Summary

In a factorial experiment, the effect of the characteristics of the wire helix on the dissolution rate of theophylline capsules and on the reproducibility of the dissolution data has been investigated. The results support the 'helix-envelope' concept developed in this study. Thus, any change that favoured the 'enveloping' action of the helix, such as an increase in the number of turns and a decrease in the distance between the turns, decreased the dissolution rate of the capsules.

The paddle method possesses better hydrodynamic characteristics than the basket method (Hanson, 1982), being also more adaptable to automation (Compton and Hinsvark, 1986). Nevertheless, the paddle method suffers from the inability to maintain a dosage form in a unique and reproducible position with respect to the fluid flow. This causes unacceptable variability in the dissolution rate values when dosage forms of low specific gravity are tested.

Various devices have been used to sink hard gelatin capsules which otherwise would float (Lin et al., 1970; Carstensen et al., 1978; Brossard et al., 1981; Langenbucher and Moeller, 1981). The British Pharmacopeia (1988) and the United States Pharmacopeia XXII (1990) suggest that a wire helix should be used to sink the capsule. Since the helix is not fully specified in the Monographs, the effect of its characteristics on the dissolution rate of theophylline capsules has been investigated.

A $2 \times 2^3 \times 6$ factorial experimental design was used, the factors being:

(i) Formulation. Two formulations were tested. Capsules A_1 were filled with theophylline powder (60–125 μm) whilst capsules A_2 were filled with a mixture consisting of theophylline, lactose and magnesium stearate at a 49:49:2 weight proportion;

(ii) Helix characteristics. The following characteristics each on a low and a high level were

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TABLE 1

Fr30 values (mean of six replicates) given from helices with different characteristics

Helix	Capsules A_1	Capsules A_2
2-1.5-0.5 [a]		65.70 (10.86) [b]
2-1.5-2		65.37 (11.53)
4-1-0.5	55.02 (25.96)	56.50 (13.43)
4-1-2	59.12 (4.77)	54.25 (11.32)
4-1.5-0.5	60.32 (7.00)	45.81 (8.83)
4-1.5-2	64.51 (11.42)	58.55 (12.28)
6-1-0.5	58.84 (9.29)	58.86 (7.35)
6-1-2	65.45 (8.93)	59.80 (15.72)
6-1.5-0.5	59.44 (22.95)	38.82 (23.74)
6-1.5-2	57.70 (5.48)	60.06 (14.12)

[a] The first number is the number of turns, the second is the thickness of the wire (mm) and the third is the distance between two adjacent turns (mm).
[b] Coefficient of variance.

examined: number of turns (4 and 6 turns), diameter of the wire (1 and 1.5 mm) and distance between two adjacent (0.5 and 2 mm);

(iii) Replicates. Six runs were conducted with each treatment combination. The dissolution rates (expressed as fr30 = % of drug dissolved in 30 min) were measured with the paddle method (USP XXII). The stirring rate was 50 rpm and the dissolution medium 2 l of simulated gastric fluid (USP XXII) at 37 ° C.

The helix may be considered as an 'envelope' protecting the capsule from the dissolution medium. It hinders the contact between the liquid and the solid and the migration of the detached particles from the solid surface. The latter could result in high local drug concentration and consequently in a decrease in the dissolution rate. According to the 'helix-envelope' concept, any change in the helix that favours its enveloping action, such as an increase in the number of turns and a decrease in the distance between them, should decrease the dissolution rate of capsules. The capsule formulation itself may be expected to interfere with the action of the helix. The enveloping action will be more effective when the powder bed contained in the capsule cannot be dispersed (e.g., in case of poor wettability of the powder bed) and remains as a 'slug' of wet powder during dissolution. The results obtained (Table 1) indicate the validity of the preceding considerations. The decrease in the distance between the turns decreased the dissolution rate. Statistical analysis of the fr30 values showed that the distance between the turns was the most influential factor on the dissolution rate (Table 2). An increase in the wire thickness tended to increase the dissolution rate probably because the bulkier helices, manufactured from thicker wire, cause increased local turbulence of the dissolution medium. However, when the conditions favoured

TABLE 2

ANOVA of fr30 values shown in Table 1

Source of variation	D.F.	Sum of squares	Mean square	*F* ratio	Probability (> *F*)
Formulation	1	418.42	418.42	6.313	0.014
Number of turns	1	98.82	98.82	1.491	0.225
Thickness of the wire	1	728.42	728.42	10.990	0.001
Distance among turns	1	1385.78	1385.78	20.908	0.000
Formulation × number	1	94.61	94.61	1.427	0.236
Formulation × thickness	1	619.86	619.86	9.352	0.003
Formulation × distance	1	519.13	519.13	7.832	0.006
Number × thickness	1	1061.87	1061.87	16.021	0.000
Number × distance	1	185.76	185.76	2.803	0.798
Thickness × distance	1	28.45	28.45	0.429	0.521
Error	85	5633.83	66.28	0	
Total	95	10774.95	0	0	

the enveloping action of the helix, an increase in the wire thickness decreased the dissolution rate. It was characteristic that when the 6-1.5-0.5 helix, which formed a compact envelope completely covering the capsule body, combined with the less dispersible formulation A_2 the lowest fr30 value was obtained (Table 1).

The more slowly dissolved formulation A_2 was affected more strongly by changes in the characteristics of the helix, producing significant statistical interaction between the helix characteristics and the formulation (Table 2). This interaction may be regarded as a significant shortcoming of the helix, since this sinker would not affect to an equal extent the dissolution rate of all formulations tested, so that it would be impossible to distinguish the influence of the formulation factors from the influence of the helix. A change in the number of turns, from four to six, did not prove sufficient to cause a significant change in the dissolution rate of the capsules (Table 2). However, when helices with two turns were introduced in this study for comparison with those having four and six it could be shown, using formulation A_2, that this increase in the number of turns decreased significantly the dissolution rate, in accordance with the helix-envelope concept (Table 1).

In conclusion, the characteristics of the helix have been shown to affect the dissolution rate of hard gelatin capsules rendering necessary its standardization in future compendia.

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