PROBLEMS WITH A PHARMACOPOEIAL DISSOLUTION TEST USING A BINARY MEDIUM

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ABSTRACT

Tablets of a low dose chlorthalidone formulation failed to meet the USP specification for dissolution in aqueous methanol though the rate of dissolution in water or dilute acid indicated that their dissolution characteristics were satisfactory. It has been shown that this is due to methanol retarding disintegration, and that this can occur with a wide range of different placebo formulations. Predisintegration of the tablet in the aqueous portion of the mixture is recommended.

INTRODUCTION

Dissolution testing is of particular importance in the development and control of solid dosage forms of drugs with low aqueous solubility and slow absorption such as chlorthalidone (Table 1).

For a normal commercial tablet of 100 mg, sink conditions are not maintained during dissolution tests in 900 ml of aqueous medium. In such cases, the following methods of maintaining sink conditions

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are available :

1. Increased volume
2. Continuous flow or replacement of medium
3. Mixed solvents
4. Biphasic systems
5. Surfactants (above CMC)

Option 3 is selected in the USP XX which specifies 900 ml of a 40 % aqueous methanol medium stirred by a paddle at 100 rpm, with 60 % of the labelled content of chlorthalidone to dissolve in 30 minutes.

We wished to study a prototype formulation containing only 25 mg of chlorthalidone which allowed us to conduct dissolution tests in water or 0.1 M HCl, and maintain sink conditions. The results were compared with those obtained using the USP medium.

METHODS & MATERIELS

Dissolution - Dissolution was conducted on at least 6 tablets in a USP XX apparatus (Hanson Research) with paddles rotating at 100 rpm using 900 ml of various media and sampling at 0, 30, 60, 90 mn.

Analysis - Samples were filtered through a 0.45 µm cellulose acetate membrane and analysed by HPLC using a 15 cm column packed with Spherisorb ODS 5 µm. The mobile phase consisted of 30 % acetonitrile and 70 % 0.05 M sulphuric acid and the chlorthalidone peak was measured by UV absorbance at 215 nm.

Disintegration - The method of the Ph.Eur was used, but with the various media shown in Table 2.

Solubilities - Excess chlorthalidone was added to each of the media shown in Table 1 in screw-capped bottles and shaken in a water bath for 3 days at 37° C. This was filtered and chlorthalidone measured by UV spectrophotometry.

Materiels - Calcium phosphate dihydrate USP (Encompress, Mendell) Microcrystalline cellulose USNF (Avicel PH 101, FMC), sodium carboxymethyl cellulose (Ac-di-sol, FMC) sodium starch glycolate

TABLE 1

Solubility of Chlorthalidone at 37° C

Medium	Solubility (g/L)
Water	0.27
HCl 0.1 M	0.30
methanol/water (40 - 60 % v/v)	6.2

TABLE 2

Disintegration of Chlorthalidone Tablets

Medium	Time (mins)
HCl 0.1 M	4.4 (s = 0.41)
Water	3.7 (s = 0.33)
Aqueous methanol 10 %	4.3 (s = 0.53)
Aqueous methanol 20 %	5.6 (s = 0.67)
Aqueous methanol 30 %	6.3 (s = 0.54)
Aqueous methanol 40 %	8.6 (s = 1.27)

s = standard deviation

USNF (Primojel, Scholter), Chlorthalidone B.P. ; other materiels were Ph. Eur.

RESULTS

Chlorthalidone tablets - Dissolution rates in water, acid and the USP aqueous methanol medium are shown in Figure 1. Although dissolution in water and acid was slow, sink conditions were maintained. The dissolution rate in the USP medium was only a third that in water, despite the higher solubility in this medium (Table 1). The tablets in the USP medium failed to disintegrate completely in 1 1/2 hours in the dissolution flask.

The influence of methanol on the disintegration of the chlorthalidone tablets was confirmed (Table 2) using the European Pharmacopoeia method. There is a linear relationship between the reciprocal of the disintegration time and the fraction of methanol (r = 0.993) and the increase in disintegration time on adding 10 % methanol to water is significant at the 99 % level. Methanol evidently impeded the disintegration of these tablets. The dissolution experiment was repeated, but with 540 ml of water only for the first 10 minutes, after which 360 ml of methanol was added. Dissolution was than rapid and well within the USP XX specification (Figure 1).

Placebo Tablets - A placebo tablet of equal weight containing the same excipients in the same proportions was prepared (Table 3a, Formula I) for which disintegration times (Table 4) show a similar increase with level of methanol.

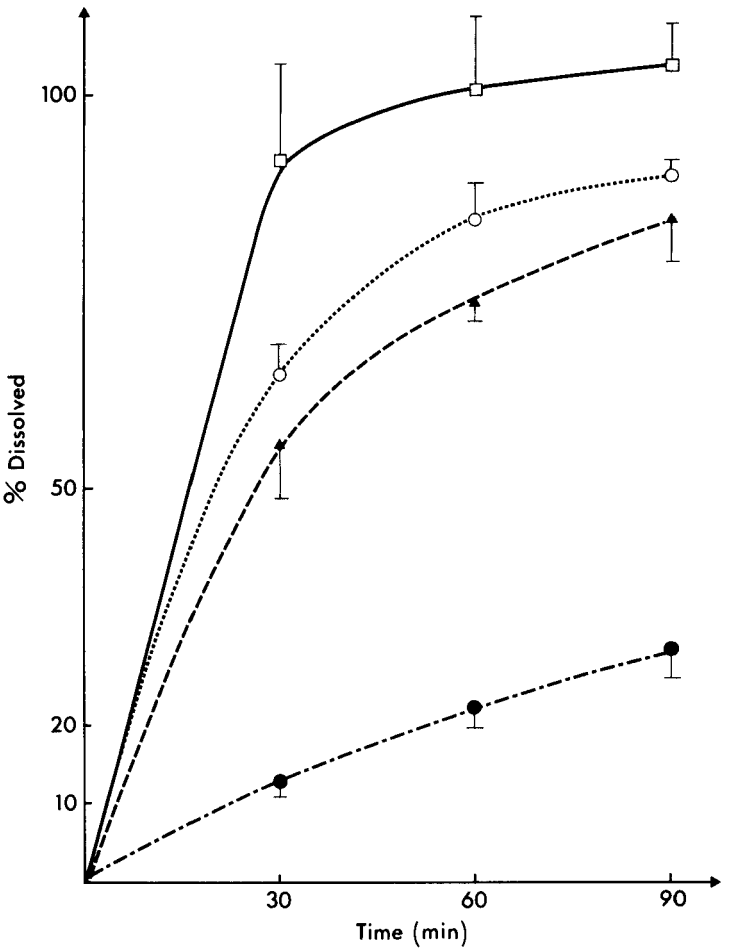

FIGURE 1

Dissolution of 25 mg Chlorthalidone Tablets in the USP Apparatus in various media (± Standard Deviation)

● Water : methanol 60 : 40

▲ 0.1 M Hydrochloric Acid

○ Water

□ Predisintegration in water followed by addition of sufficient methanol to give a 60 : 40 mixture

TABLE 3

Formulations of Placebo Tablets

Table 3a

Component	Placebo		
	I	II	III
Calcium phosphate dihydrate	242.7 mg	245.7 mg	244.2 mg
Microcrystalline cellulose	45.7 mg	46.3 mg	46.0 mg
Sodium carboxymethyl cellulose	0.55 mg	0.55 mg	0.55 mg
Talc	7.3 mg	7.4 mg	7.4 mg
Stearic acid	3.6 mg	-	-
Magnesium stearate	-	-	1.8 mg

Direct compression, 300 mg,* 8-9 kg (Schleuninger)

Table 3b

Component	Placebo	
	IV	V
Lactose	323.0	314.9
Sodium Starch glycolate	13.6	-
Alginic acid	-	16.8
Magnesium stearate	3.4	3.3

IV Direct compression, 7,5 - 8-5 kg
V Direct compression, 5,5 - 7-5 kg

Table 3c

Component	Placebo	
	VI	VII
Calcium phosphate dihydrate	180.0	180.0
Microcrystalline cellulose	90.0	90.0
Povidone	13.5	13.5
Sodium Starch glycolate	15.0	15.0
Magnesium stearate	1.5	1.5
Purified water	-	qs

VI Direct compression, 20 kg
VII Wet Granulation, 20 kg

* The ratio of the components other than the lubricants was constant in these formulations.

TABLE 4

Disintegration Times of Placebo Tablets

Table 4a

Medium	Placebo		
	I	II	III
Water	13 min	1.5 min	3.8 min
Water : methanol 90 : 10	22 min	3 min	4.5 min
Water : methanol 80 : 20	90 min	5 min	12 min
Water : methanol 60 : 40	90 min	14 min	35 min

Table 4b

Medium	Placebo	
	IV	V
Water	26 sec	28 sec
Water : methanol 90 : 10	33 sec	31 sec
Water : methanol 80 : 20	-	-
Water : methanol 60 : 40	45 sec	36 sec

Table 4c

Medium	Placebo	
	VI	VII
Water	7 min	4 min
Water : methanol 90 : 10	11 min	4 min
Water : methanol 80 : 20	14 min	5 min
Water : methanol 60 : 40	45 min	11 min

For placebos with the stearic acid omitted (II) or replaced with magnesium stearate (III) disintegration was more rapid but still retarded by methanol. The results in Table 4 also show that this was true of placebos containing the disintegrants sodium starch glycolate or alginic acid with lactose (Table 3b). For an alternative formulation prepared either by direct compression (Table 3c, VI) or by granulation with water (VII) similar increases in disintegration time were observed, the granulated formulation showing less change with the addition of methanol.

With other formulations, (for example, formulations similar to IV and V but containing cross-linked povidone, cross-linked sodium carboxymethylcellulose or microcrystalline cellulose) methanol had little effect (unpublished observations).

DISCUSSION

The chlorthalidone tablets did not meet the USP dissolution specification. Whilst dissolution in water or acid was slow, it was nonetheless faster than in the USP medium and was acceptable for a drug of such low solubility, remembering that the USP specification is written for dissolution in a medium in which chlorthalidone is twenty times more soluble.

The slow dissolution in the USP medium was due to the methanol retarding disintegration, possibly by competing with the cross-linked sodium carboxymethylcellulose for water.

Studies on the disintegration of placebo tablets showed that this was not due to the chlorthalidone itself or to the lubricant

(although the effect was more obvious in the case of tablets containing stearic acid). Furthermore, the effect is not peculiar to one formulation but can occur with a range of disintegrants and diluents. Retardation of disintegration in binary mixtures of water and various non-aqueous solvents has also been observed by Guyot-Herman and Ringard.[1]

There is thus a possibility that the use of a mixed solvent system for a pharmacopoeial dissolution test may make it necessary to develop formulations to conform to test specifications under physiologically unrealistic conditions, rather than to optimise release in the GI tract. Such test methods may lead to the rejection of formulations which perform adequately in-vivo, possibly in favour of inferior products.

The formulator should thus interpret results of dissolution tests in binary media with extreme caution. The predisintegration of tablets in water prior to the addition of the non-aqueous component is a potential means of overcoming the difficulties with this method. This is in agreement with the recommendations of the FIP working party on dissolution testing.[2] Predisintegration should be incorporated in pharmacopoeial methods employing binary solvent mixtures. It would be suitable to permit retesting using this technique if tablets failed to disintegrate in the normal dissolution test.

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