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THE POTENTIAL USE OF COMPRESSION COATING IN THE BLINDING OF CLINICAL TRIAL SUPPLIES.

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ABSTRACT

The use of compression coating to blind tablets for use in clinical trials has been found to be acceptable for a number of products when comparing the 'in vitro' dissolution rate of the manipulated and the parent tablet. The apparent dissolution rate for some products was found to be dependent upon the quantity of compression coat surrounding the parent tablet and the compaction pressure utilised. This was in some instances found to be an artifact of the paddle dissolution method resulting from coning of the compression coat excipients over the parent tablet during dissolution.

INTRODUCTION

A large number of clinical trials utilise single or multiple blinding to avoid bias in the response of the patient or physician during treatment. Blinding of tablets is generally achieved by one of the following techniques:-

(a) Encapsulation of the intact parent product in a hard gelatin capsule.

(b) Milling the parent product and subsequent encapsulation of the powder in a hard gelatin capsule.

(c) Milling the parent product, blending with other excipients and recompressing.

(d) Complete formulation of the required product.

Encapsulation of tablets in capsules is often time consuming and there are limitations on the shape and size of tablet that can be accommodated. In each of the other methods described, substantial manipulation of the parent tablet or active is required often destroying the product integrity and increasing the quantity of development work necessary. In addition for those processes where a significant change to the parent product is made, bioequivalence studies are required. These extend clinical trial supply lead times and greatly increase the cost of supplies.

In these laboratories compression coating has been investigated as an alternative method of blinding tablets for clinical supply as it has the advantages of:-

(a) The parent product is not intrinsically adulterated (particularly useful for controlled release preparations).

(b) The operation is easily automated (e.g. Kilian Prescoter).

(c) Larger tablet sizes can be blinded than with encapsulation.

Compression coating is not a new technique and was initially evaluated as a possible successor to sugar coating. It offered the advantages of speed, the ability to coat water sensitive products and as a means of combining chemically incompatible drugs (1-5). However, many of the advantages claimed for compression coating were superceded with the advent of film coating technology.

MATERIALS AND METHODS

Film coated Indoramin tablets (12.5, 25 and 37.5mg) and Meptazinol tablets (100 and 200mg) were used as parent tablets and these were compression coated with a placebo. Details of the placebo are given in Table 1.

Compression coating was performed by manually operating a single punch tablet press (Manesty F3, Manesty Machines Ltd., Liverpool, England). The machine was operated with the powder hopper, feed shoe and feed shoe actuator arm removed. In all cases double radius tooling was employed. The lower punch was lowered through approximately one third of its travel and the die filled with placebo granule and the excess scraped clear. The parent product was laid centrally on the granule bed and the

TABLE 1

Placebo Formulations used for Compression Coating.

Placebo A	%
Microcrystalline cellulose N.F.	57.5
Dextrates N.F.	40.0
Calcium carboxymethyl cellulose N.F.	2.0
Magnesium stearate B.P.	0.5
Placebo B	
Microcrystalline cellulose N.F.	55.5
Dextrates N.F.	40.0
Calcium carboxymethyl cellulose N.F.	2.0
Crospovidone N.F.	2.0
Magnesium stearate B.P.	0.5

lower punch then taken to its maximum depth. The die was filled with placebo granule, the excess scraped clear and the mass compressed. The lower punch was raised to eject the tablet and the procedure repeated until sufficient samples to allow physical testing and dissolution studies to be performed had been obtained. For selected products, different crushing strengths were prepared to evaluate the influence of compaction pressure on the final product characteristics.

Dissolution testing was undertaken using the USP 2 apparatus with 0.06M hydrochloric acid as the dissolution medium. For those products containing Indoramin tablets the agitation rate was 50 r.p.m. and dissolution media volume was 900ml. For products containing Meptazinol the agitation rate was 45 r.p.m. and the dissolution media volume 500ml. All dissolution determinations were made at 37°C.

RESULTS AND DISCUSSION

Details of the tablet dimensions before and after compression coating are given in Table 2.

The objective of this study was to assess if the compression coating technique was suitable for the manufacture of blinded clinical trial materials. The main criterion for judging acceptability of the technique was that the dissolution rate of the compression coated product matched that of the parent product.

For Indoramin 12.5mg tablets compression coated to a final tablet diameter of 11mm, poor dissolution rate profile matching with the parent product was obtained at all crushing strengths examined (Figure 1). This was attributed to the large quantity of placebo present in the compression coat. Although the coat quickly disintegrated, it did not readily disperse and formed a cone over the parent tablet at the bottom of the dissolution flask. This resulted in slower dissolution rates being obtained as the parent tablet was not totally exposed to the dissolution

TABLE 2

Tablet Dimensions and Placebo Coat used in Compression Coating Evaluation.

Product	Parent Product		Compression Coated Product		Placebo coat
	Diameter mm	Thickness mm	Diameter mm	Thickness mm	
Indoramin 12.5mg tablets	6.0	3.0	11.0	5.4	A
			8.0	4.2	B
Indoramin 25.0mg tablets	8.0	3.6	12.5	6.2	A
Indoramin 37.5mg tablets	9.0	4.0	12.5	6.5	A
Meptazinol 100mg tablets	8.0	4.4	12.5	6.1	A
Meptazinol 200mg tablets	10.0	5.5	12.5	7.0	A

medium. The problem was eliminated by reducing the quantity of placebo coat, increasing the quantity of disintegrant, and compressing the product on 8mm tooling (Figure 2). For Indoramin 25 and 37.5mg tablets and Meptazinol 100mg (Figures 3-5), good agreement between the compression coated and the parent tablet dissolution profiles was obtained at the range of crushing strengths evaluated. For Meptazinol 200mg tablets good profile matching was achieved at some compaction pressures but

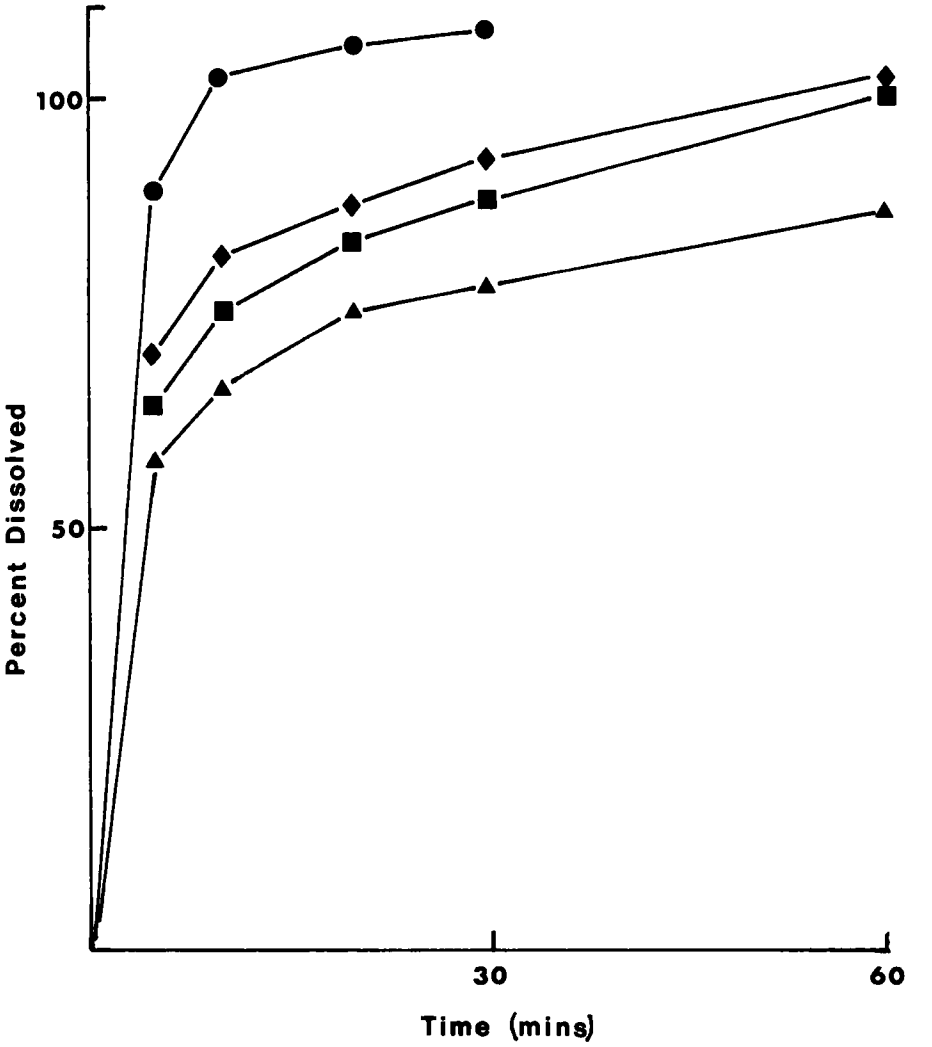

FIGURE 1

Dissolution profiles of Indoramin 12.5mg tablets (compression coated using 11mm tooling).

●—● parent tablet

■—■ compression coated tablet (13-14 S.C.U.)

◆—◆ compression coated tablet (15-17 S.C.U.)

▲—▲ compression coated tablet (19-22 S.C.U.)

(S.C.U. - Strong Cobb Units)

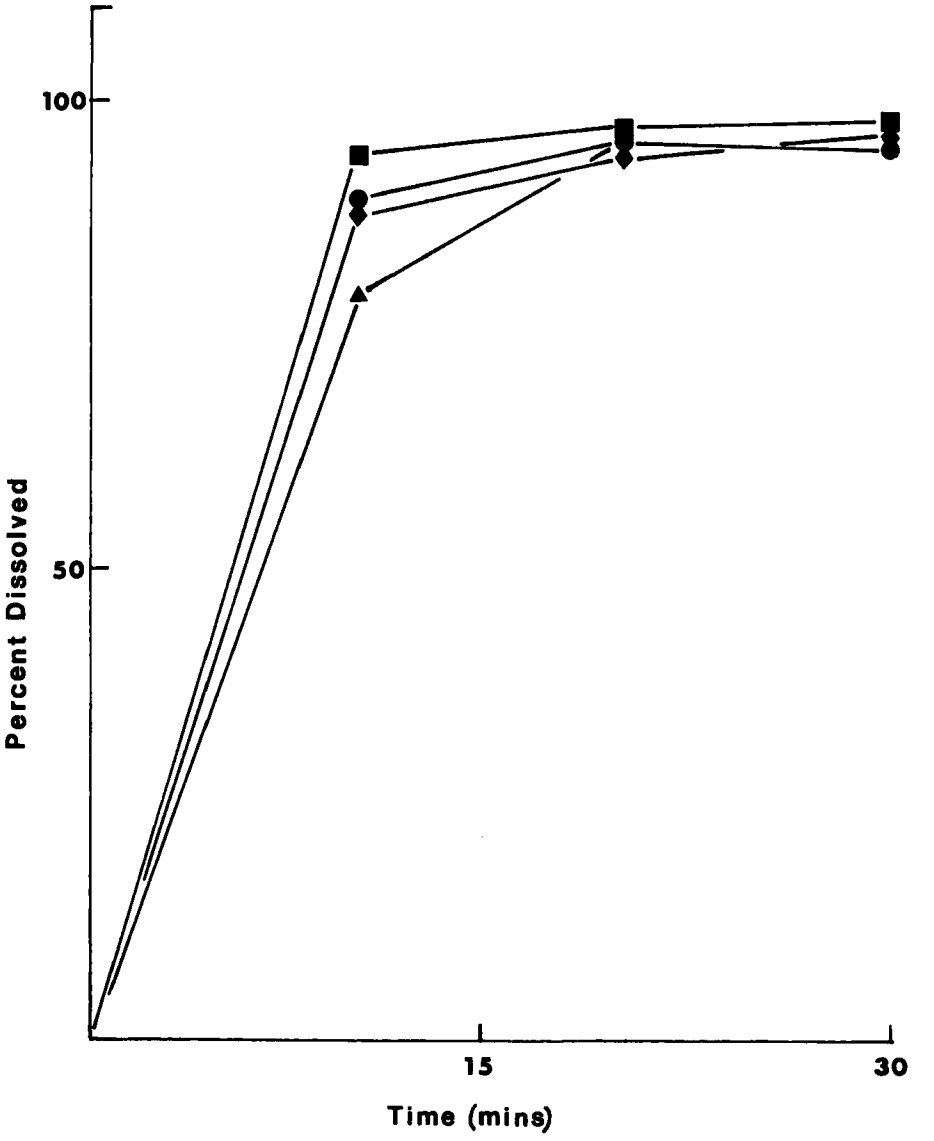

FIGURE 2

Dissolution profiles of Indoramin 12.5mg tablets (compression coated using 8mm tooling).

- parent tablet
- compression coated tablet (6-8 S.C.U.)
- compression coated tablet (15-17 S.C.U.)
- compression coated tablet (20-24 S.C.U.)

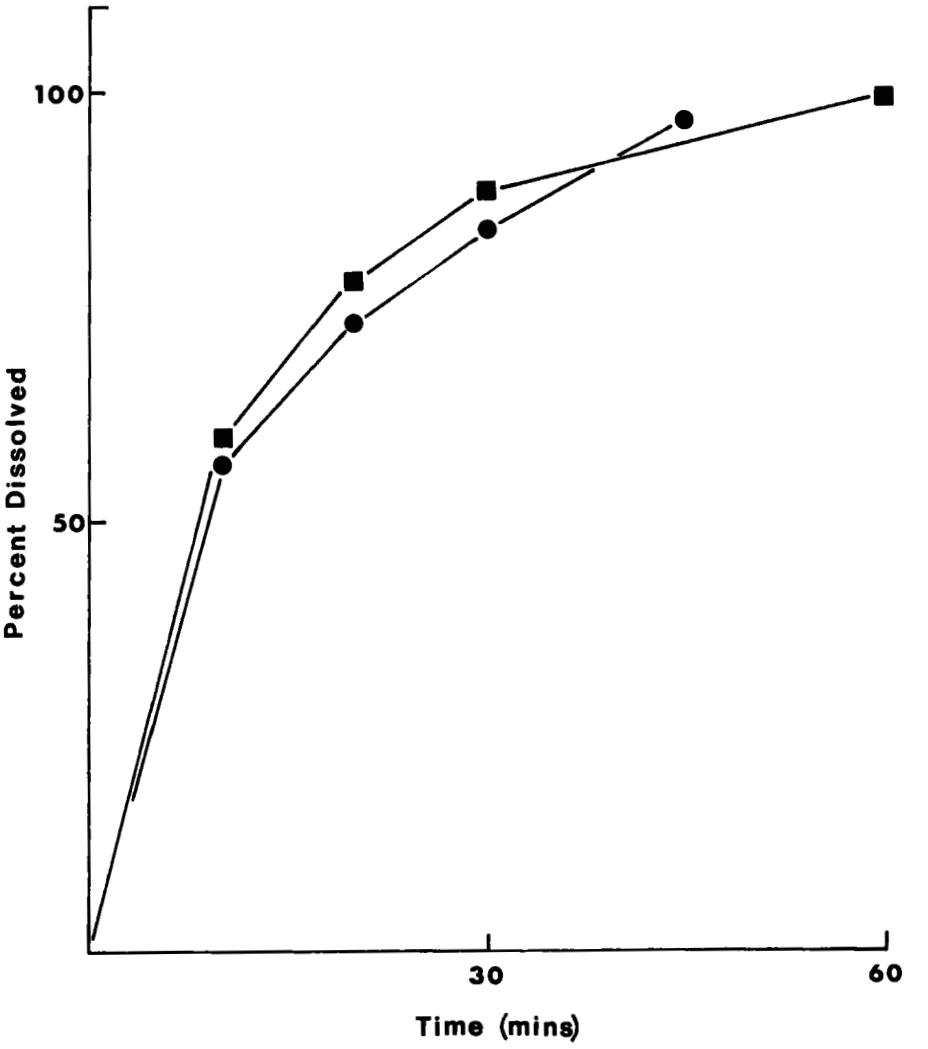

FIGURE 3

Dissolution profiles of Indoramin 25mg tablets.

●—● parent tablet

■—■ compression coated tablet (13-15 S.C.U.)

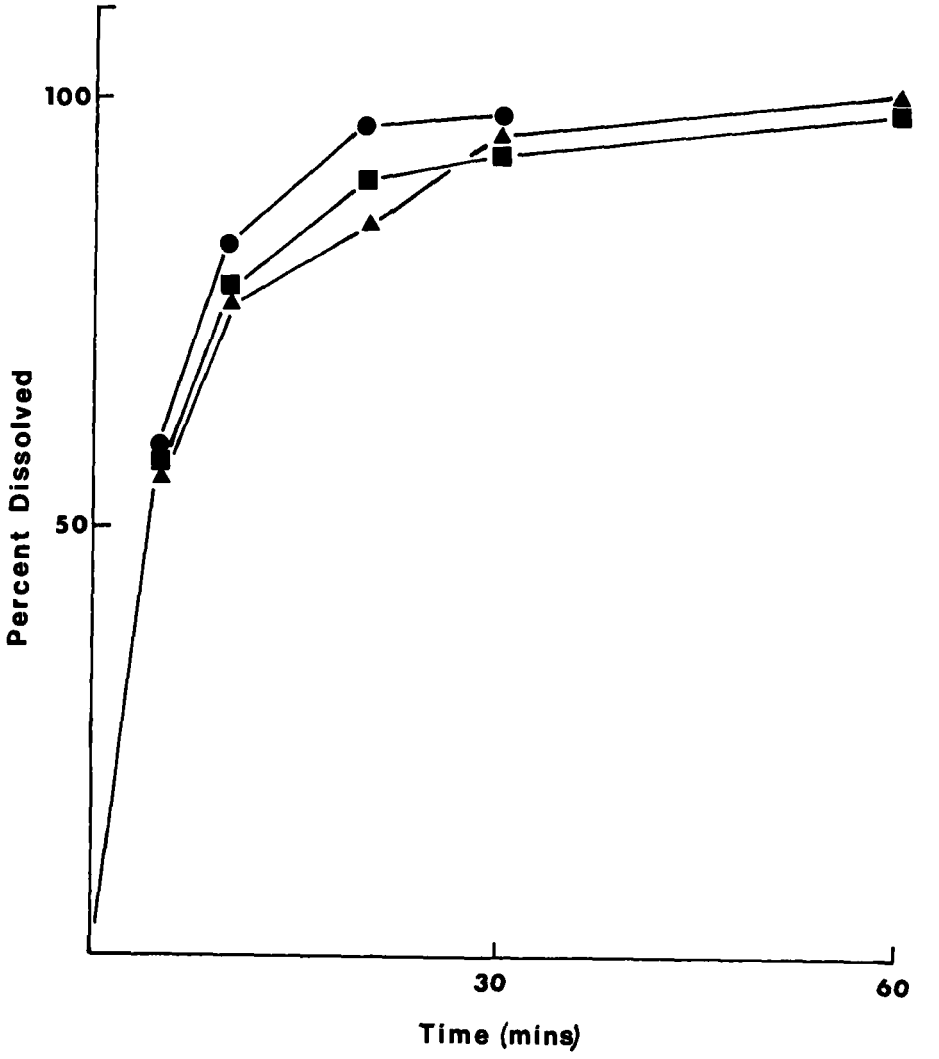

FIGURE 4

Dissolution profiles of Indoramin 37.5mg tablets.

●—● parent tablet

■—■ compression coated tablet (16-18 S.C.U.)

▲—▲ compression coated tablet (30-32 S.C.U.)

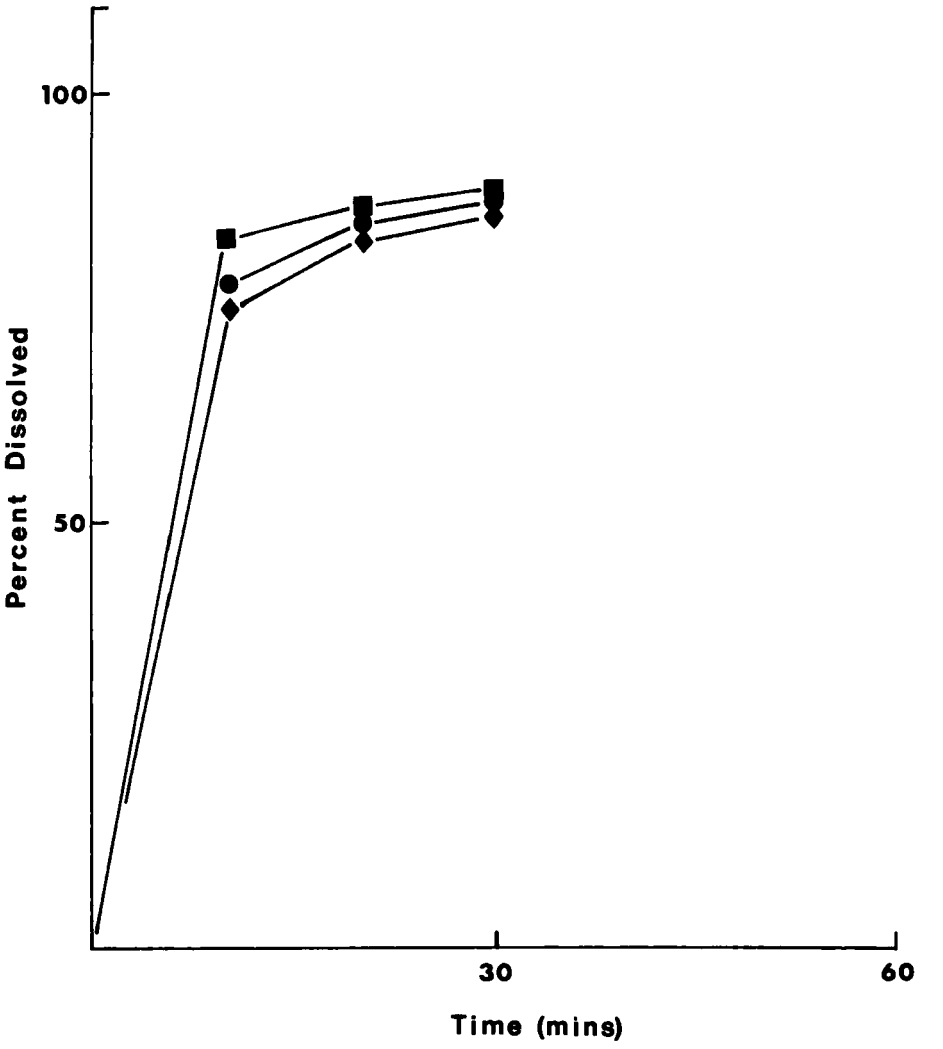

FIGURE 5

Dissolution profiles of Meptazinol 100mg tablets.

- parent tablet
- compression coated tablet (11-14 S.C.U.)
- compression coated tablet (17-21 S.C.U.)

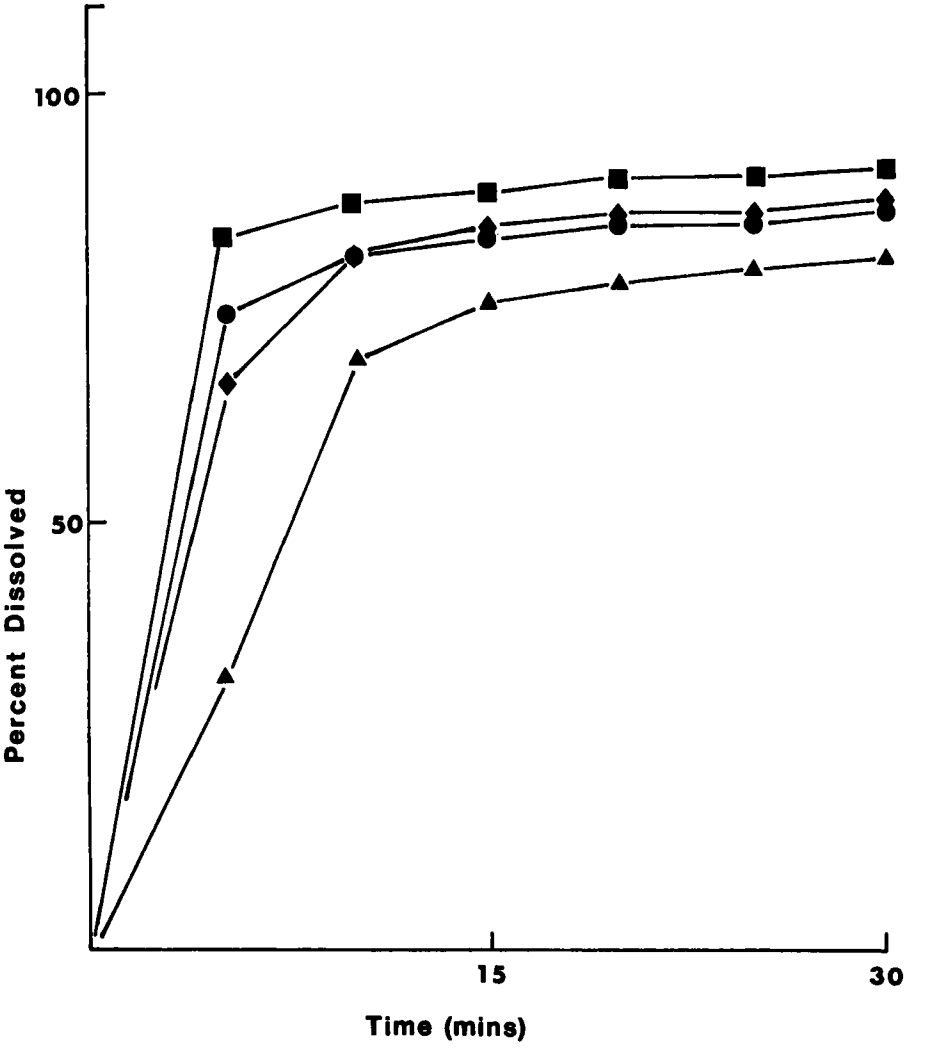

FIGURE 6

Dissolution profiles of Meptazinol 200mg tablets.

- parent tablet
- compression coated tablet (15-18 S.C.U.)
- compression coated tablet (20-23 S.C,U.)
- compression coated tablet (27-30 S.C.U.)

not at the highest compaction pressure studied (27-30 S.C.U.) where a reduction in dissolution rate was observed (Figure 6). At the higher compaction pressures it may be anticipated that dispersion time of the compression coat would be extended due to reduced porosity and that secondary compression effects may also influence the parent product. It is clear from these results that some evaluation of the influence of compaction pressure on dissolution rate is mandatory during compression coated product development.

From the data presented here it would appear that compression coating can be used as an alternative means of blinding tablets for use in clinical supplies. In each case a product has been manufactured which closely matches the dissolution profile of the parent tablet.

In this work using the paddle dissolution method, the problem of poor dissolution profile matching has been overcome by the judicious choice of compaction pressure, placebo coat formulation and final product size. However, it is apparent from other studies performed in this laboratory that use of a basket dissolution method, where the dispersed compression coat materials fall to the base of the dissolution flask and the tablet remains within the basket, also reduces the incidence of poor dissolution profile matching. This suggests that the paddle method may not be the most suitable dissolution method for compression coated products.

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