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DISSOLUTION BEHAVIOUR OF INDOMETHACIN CAPSULE FORMULATIONS:COMPARISON OF TWO TYPES OF USP APPARATUS

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ABSTRACT

The dissolution behaviour of indomethacin from six commercial brands of indomethacin capsules, using the USP rotating basket apparatus and the USP paddle apparatus have been studied. The products showed marked differences in their dissolution profiles. The dissolution rates have been different in different brands, and variation has also been observed depending on the method of testing used. The rotating basket apparatus showed superior discriminating capacity than the paddle method.

INTRODUCTION

Indomethacin has a poor wettability characteristics and is very slightly soluble in gastric fluid, which indicates that variation in the dissolution behaviour will lead to variation in its bioavailability. This makes indomethacin a drug with potential bioavailability problems and thus the dissolution test for its capsules is specified in USP XXI using rotating basket assembly (1). Turakka et al. (2) observed the variation in the bioavailability for four brands of indomethacin by 30 percent.Several workers (3,4) compared the dissolution behaviour of indomethacin capsules with their bioavailability, however,the

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correlation between the dissolution rate and bioavailability has not been well established.

Aoyagi et al. (5) demonstrated that the USP XX requirement for the dissolution of indomethacin seemed to be better than the Japanese Pharmacopoeia X. In view of the various reports, the present study was undertaken to evaluate the in vitro performance of commercial indomethacin capsule formulations using the USP XXI rotating basket and the paddle methods.

MATERIALS AND METHODS

Formulation

Six commercial brands (A,B,C,D,E and F) of indomethacin capsules were used in the study,each contained 25 mg indomethacin. Indomethacin powder[1], Indian Pharmacopoeial quality, was used as a reference.

Weight Variation and Drug Content Uniformity

The weight variations were ascertained as per USP procedure. The drug content was determined spectrophotometrically (absorption at 314 nm).

Dissolution Rate

The dissolution rates of the drug from the capsules were determined at 37±1°C by the USP procedure using rotating basket dissolution apparatus I (the basket method) and the paddle stirrer apparatus II (the paddle method)(6). The solvent (750 ml) used for the dissolution was a mixture of phosphate buffer (pH 7.2) and distilled water(1:4). The stirrer speed was 100±2 rpm. In the paddle method,the capsule was made to sink to the bottom of the vessel before starting the dissolution. A small, loose piece of copper wire was attached to the capsule to prevent it from floating. At various time intervals, aliquots (5 ml each) were withdrawn, filtered, and replaced with 5 ml of fresh dissolution medium to compensate for the sample withdrawn. The amount of the drug dissolved was determined using UV-Vis

[1]Supplied by M/s Ranbaxy Laboratories Pvt.Ltd.,New Delhi, India.

TABLE 1

Characteristics of Commercial Indomethacin Capsules

Brand	Weight Variation mg ± SD (n=20)	Content Uniformity mg ± SD (n=5)
A	324.8 ± 0.84	24.35 ± 0.17
B	256.9 ± 1.71	25.20 ± 0.51
C	227.7 ± 0.60	24.47 ± 0.23
D	383.6 ± 0.91	24.60 ± 0.32
E	333.6 ± 1.08	24.19 ± 0.22
F	322.5 ± 1.51	24.58 ± 0.71

spectrophotometer (Perkin Elmer, Model Lambda 3) at 314 nm. The average dissolution rate was obtained after six dissolution runs of each product.

Analysis of Variance

For the analysis of variance (7), the dissolution data in the form of percent drug released at various time intervals were used.

RESULTS AND DISCUSSION

All the products included in the study passed the weight variation test. Average weight (mg) of contents per capsule (± SD) has been shown in Table 1 which assures the chemical equivalence of these products.

Figure 1 shows the mean dissolution curves of indomethacin of six products after six dissolution runs, determined by the basket and the paddle methods at 100 rpm according to USP specifications. A lag period does exist prior to the dissolution of the drug from its encapsulated form into the dissolution medium. This is in general agreement with the findings of Mortada et al.(8) who reported a similar trend in the case of ampicillin capsules.

The data represented in Table 2 show that four of test brands, A,D,E and F completely met the requirement of USP

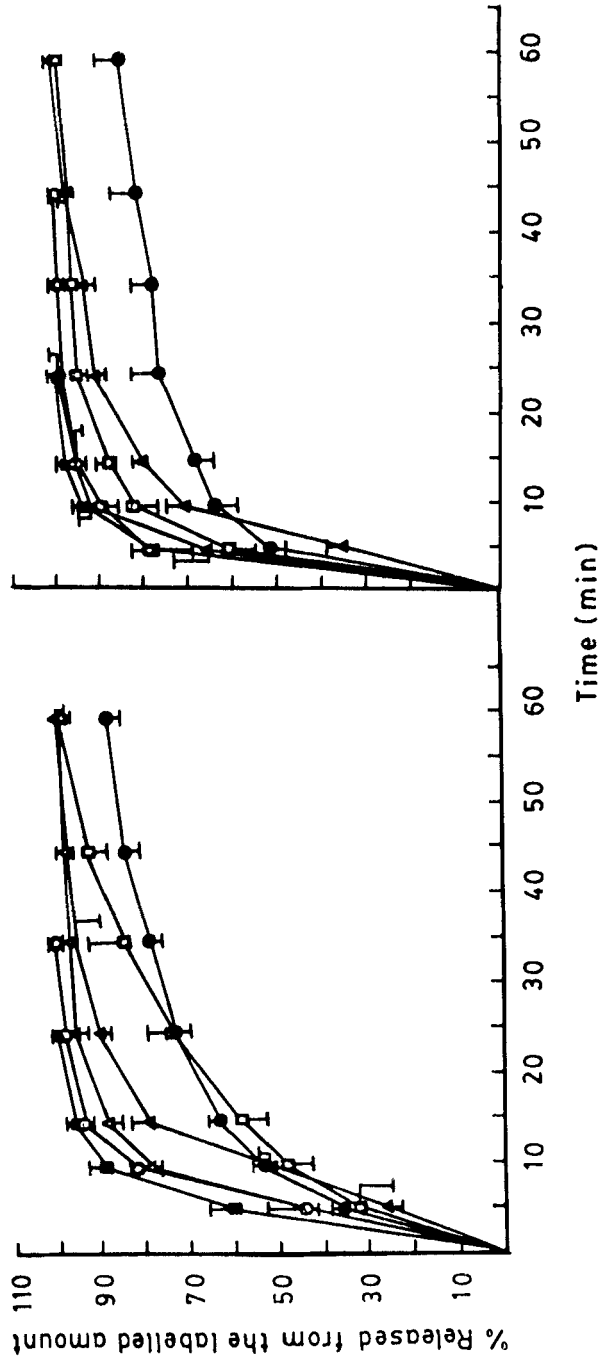

FIGURE 1

Dissolution rate profiles of different brands of indomethacin capsules using (A) the rotating basket and (B) the paddle methods. The vertical lines show SD. (○) brand A, (●) brand B, (□) brand C, (■) brand D, (△) brand E, (▲)brand F.

TABLE 2

Percent Drug Dissolved from Various Brands of Indomethacin Capsules (n=6)

Method	Brand	Time, min.						
		5	10	15	25	35	45	60
Rotating Basket	A	43.94±2.02	82.14±1.65	93.41±1.06	98.43±1.01	99.64±0.80		
	B	36.07±2.74	53.53±2.35	63.54±1.85	73.29±3.57	78.87±2.64	84.16±2.91	88.06±1.92
	C	32.35±6.97	48.16±5.11	58.57±6.27	73.37±6.57	84.50±7.69	92.26±4.63	99.25±1.89
	D	59.64±6.33	88.73±4.61	95.83±2.04	99.79±0.82			
	E	43.98±7.65	78.47±1.65	88.64±3.71	95.52±2.49	96.89±1.73	98.54±1.44	99.58±1.07
	F	26.16±3.21	51.51±3.54	78.96±4.32	90.50±2.46	95.65±2.97	97.21±1.31	99.66±0.90
Paddle	A	78.02±4.75	89.70±4.40	95.04±1.33	97.47±1.05	98.87±0.92	99.98±0.88	
	B	50.75±2.65	63.65±4.72	68.40±3.65	76.23±6.27	77.96±5.24	81.94±5.74	85.81±5.23
	C	60.57±6.57	81.76±4.98	88.32±3.16	95.09±2.06	96.59±1.37	97.72±0.97	99.20±0.68
	D	77.50±8.53	93.93±2.04	97.65±1.73	99.59±0.85			
	E	65.28±8.17	92.37±2.93	96.41±1.32	99.66±0.59			
	F	25.88±3.12	70.76±4.64	80.41±1.86	91.21±2.68	93.83±2.08	98.32±0.76	99.36±0.76

TABLE 3

Time (min) for 50% and 80% Dissolution of the Different Brands of Indomethacin Capsules using the Two Dissolution Methods

Brands	Rotating basket		Paddle	
	$t_{50\%}$	$t_{80\%}$	$t_{50\%}$	$t_{80\%}$
A	6.0	9.8	3.0	6.0
B	9.0	37.6	5.0	40.4
C	11.0	31.0	4.0	9.8
D	4.5	8.8	3.0	6.0
E	6.0	11.0	3.8	7.6
F	9.8	16.0	7.0	14.8

for indomethacin dissolution (more than 80% of the drug to be dissolved in 20 min) but product B did not. Brand C, on the other hand, met the USP requirement by the paddle method and failed to do so by the other method. Although brands A,D and E showed relatively higher initial dissolution rate after 5 min compared to brand F, all these brands exhibited almost similar dissolution rate patterns with time.

Table 3 shows the dissolution rates data (expressed as the time required for 50% and 80% dissolution, respectively) determined by different *in vitro* methods. The average $t_{80\%}$ for product B, using both the apparatus, is more than 37 min which again emphasizes the slow dissolution rate of this brand. The variation in drug release from the capsules may be attributed to various factors such as particle size of the drug contained in them, variation in storage conditions and manufacturing procedures and/or variations in the types and levels of the additives. Product B formed a compact mass that remained till the end of the dissolution run after the capsule had been dissolved using both the methods. Cementing of the powder content and consequent slug formation due to either

improper storage condition (e.g. high relative humidity) or manufacturing procedure (capsule filling pattern) may probably account for the large variation in the dissolution rates of the drug from the brand B. On the other hand, rapid deaggregation of capsule D content, after the dissolution of its gelatin shell, resulted in a large exposed surface of capsule D content and caused it to dissolve more rapidly than B. Therefore, the dissolution of indomethacin for the capsule D seems to depend mainly on disintegration of the aggregates released from the capsule.

Comparison Between Methods

Differences in dissolution in various apparatus used (Figure 2) may be due to different mechanisms involved in movements of the dissolution fluid from the rotating basket and paddle methods. Withey (9) has shown that the flow obtained in the former assembly is primarily radial from the basket and is with very little vertical mixing. Further the fluid at the surface is barely moving. In the latter assembly, a consistent effect of the stirring movements predominates and the capsule content always comes to lie centrally under the stirrer. In addition, the wire mesh of the basket was easily clogged by the gelatin shell or other insoluble or gummy components, resulting in a non-uniform solvent flow around the capsule inside the basket.

Ranking of the apparatus according to their discriminating capacity using the ratios of the area under dissolution curves for the fastest (D) and the slowest (B) dissolving brands shows that the rotating basket apparatus gave the ratio (1.52) compared to the ratio (1.42) by the paddle method. The finding agrees with the official requirements. Aoyagi et al. (5) also observed that the USP requirement for the dissolution of indomethacin from the capsules seems to be better than the Japanese Pharmacopoeia X.

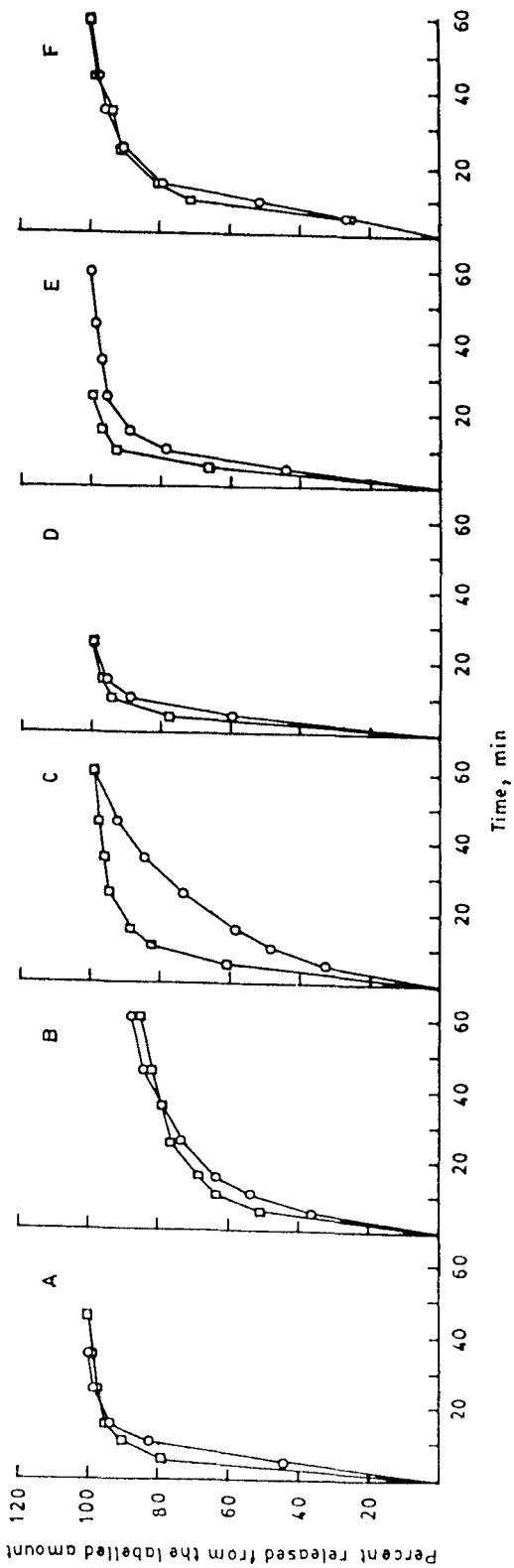

FIGURE 2

Dissolution rate profiles of different brands of indomethacin capsules using the two dissolution apparatus.
(O) rotating basket, (□) paddle.

TABLE 4

Analysis of Variance for Percent Drug Dissolved of the Various Indomethacin Brands

Source of Variance	df[a]	Percent dissolved									
		5 min		10 min		15 min		35 min		60 min	
		MS*	F**	MS	F	MS	F	MS	F	MS	F
Between methods	1	1118.63	15.78	669.46	12.39	186.28	3.08	11.41	0.83	0.87	2.41
Between brands	5	447.14	6.30	422.26	7.81	317.72	5.25	135.05	9.8	54.54	151.53
Error	5	70.88		54.04		60.45		13.78		0.36	

[a]Degree of freedom

*Mean of squares

**F ratio

Table $F_{1,5} = 6.61$; $F_{5,5} = 5.05$

Analysis of variance was performed to determine if the methods actually produce significantly different dissolution profiles or the variations in the dissolution profiles are of such magnitude as produce overlapping curves that are essentially similar. The data represented in Table 4 show that at all the times studied the calculated F value for the brands exceeds the tabular F value (10) at 5 percent level of confidence. Therefore, significant differences between them can be interpreted. Calculated F value for the different methods, however, exceeds the tabular F value (at 5% level) upto 10 min. It is evident from this analysis that indomethacin capsules of a particular brand releases significantly different amount of the drug upto 10 min.

CONCLUSION

The work reported here suggests that four brands (A,D,E and F) of conventional indomethacin capsules have satisfactory *in vitro* dissolution characteristics, one brand (B) dissolving relatively slowly using both the methods while the other (C) dissolved rapidly by the paddle method but failed to do so in the other. Comparison of the rotating basket and paddle methods indicate that the former showed the higher discriminating capacity while the latter showed the lowest discrimination although there was rapid dissolution in the beginning. Generally, dissolution testing is considered as a valuable adjunct to good formulation development as well as an excellent tool capable to monitor the consistency of drug delivery from a product. The official USP rotating basket method can successfully be employed in routine batch-to-batch quality control analysis for testing indomethacin capsules. As yet it is not possible to develop a universal dissolution apparatus which can replace the necessity of biological evaluation of a formulation of pharmaceutical products.

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