International Journal of Pharmaceutics, 1 (1978) 197–204

INVESTIGATIONS INTO THE ACCURACY OF DOSAGE AND RELEASE OF ACTIVE DRUG FROM SUSTAINED RELEASE PREPARATIONS OF ISOSORBIDE DINITRATE

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(Received October 39th, 1977)
(Accepted January 31st, 1978)

SUMMARY

Six isosorbide dinitrate sustained release preparations have been tested for uniformity of content and average content of active ingredient. All preparations were found to conform to the standards of the DAB 7 and the USP XIX.

The release of active ingredient was investigated using two in vitro techniques (Rotation Method of the NF XIV and the Diffutest) and the results compared.

The variability of drug release within samples of the same batch was evaluated by calculating the limits of error at the 95% probability level. Results showed that Preparation F showed the least variability and Preparations C and D the greatest.

All products tested released 75–100% of their active ingredient during the duration of the test, preparations A, D, E and F did so in a linear fashion. However, with products B and C a steeply increasing pattern, approaching a logarithmical curve, was observed.

INTRODUCTION

Isosorbide dinitrate, in common with a number of other nitric acid esters, is used in the prophylaxis and treatment of angina pectoris. Of the solid dosage formulations available, chewable capsules and tablets are intended for sublingual application for the treatment of acute attacks, whilst sustained release preparations are now on the market for longer term treatment and prophylaxis.

Assinder et al. (1977a, b) have reported a relatively short biological half-life for isosorbide dinitrate of about 45 min after oral application of a non-sustained release preparation. Non-sustained release isosorbide dinitrate tablets of the United States Pharmacopoeia XIX contain 2.5 or 5 mg isosorbide dinitrate.

Long-term treatment with isosorbide dinitrate is generally carried out with sustained release preparations because of the relatively short half-life of this drug. Further, on clini-

cal testing we know about the pharmacological action of mononitrate metabolites (Wendt, 1972).

Manufacturers claim that the duration of action can be prolonged to 10–12 hr by treating the drug so as to produce a depot effect. Twice daily administration (morning and evening) is recommended for all sustained release preparations, which should ensure adequate prophylaxis of angina pectoris during both day and night.

In the investigations described below, 6 of the most commonly prescribed sustained release preparations of isosorbide dinitrate were tested:

	Batch numbers, Company
Corovliss (20 mg)	717063 Boehringer Mannheim GmbH
Isoket retard (20 mg)	07664 Pharma-Schwarz GmbH
Iso Mack retard (20 mg)	61024 (102) Heinrich Mack Nachf.
Iso Mack retard forte (40 mg)	61024 (102) Heinrich Mack Nachf.
Maycor retard (20 mg)	65 S/22006-N Parke-Davis and Co.
Sorbidilat (20 mg)	7106 (12101) Deutsche Kabi GmbH

The dosage form and the technique used to prolong the duration of action are tabulated in Fig. 1.

In 4 of the preparations, the active ingredient is contained as diffusion pellets in hard gelatin capsules, from which it is slowly released.

In the coated and uncoated tablets, isosorbide dinitrate is embedded in an insoluble matrix from which it is slowly released. Our results indicate that these two dosage forms are excreted largely unchanged after release of the active ingredient during passage through the gastrointestinal tract.

It should be pointed out here that the stability of the matrix of many of the embedded drug forms is very high. The Zentrallaboratorium have received many unwarranted objections suggesting that in some tests, the tablets had not 'disintegrated' properly.

Deviation of the weight of single tablets from the average weight and the disintegration time were measured according to the Tablet Monograph of the DAB 7 (Second Addendum).

Experience over the last 15 years, especially in the U.S.A. (Jost, 1972) has shown that checking the average content of solid preparations of drugs is often not satisfactory. For low dosage tablet and capsule preparations with a high proportion of excipients, the homogeneity of active ingredient and additives is only ensured if the preparation of the

	Techniques used to prolong the effect			After 1 hours in gastric fluid USP XIX	After 7 hours in intest.fluid USP XIX
Corovliss[R]			Coated Tablet Embedded		
isoket[R] retard			Tablet Embedded		Disintegration possible
Iso Mack[R] retard			Hard Gelatin Caps No.4 Contents Diffusion pellets		Disintegration
Iso Mack[R] retard forte			Hard Gelatin Caps.No.4 Contents Diffusion pellets		
MAYCOR[R] RETARD			Hard Gelatin Caps.No.4 Contents Diffusion pellets		
SORBIDILAT[R]			Hard Gelatin Caps No.2 Contents Diffusion pellets		Disintegration

Fig. 1. Sustained release preparations of isosorbide dinitrate – techniques used to prolong the duration of action.

tablet has been extremely careful. The USP XIX thus lays down tests for content uniformity for all solid dosage drug forms with less than 50 mg active ingredient per single dose.

Five of the preparations we tested contained 20 mg and one had 40 mg isosorbide dinitrate per single dose. We therefore considered it appropriate to test all preparations for content uniformity so that the evaluation of these products was based on the standards of the USP XIX.

The time release of active ingredient was also tested as this is a further important criterion of the standard of a sustained release preparation. Painstaking pharmaceutical research and development and extensive in vitro and in vivo investigations are required to achieve a continual and pharmacokinetically controlled release of a drug. Great differences in the therapeutic equivalence of sustained release preparations can occur depending on the quality of this development work.

MATERIALS AND METHODS

(1) Colorimetric estimations

Colorimetric techniques have proved to be the best method for the quantitative estimation of isosorbide dinitrate.

In all investigations, the substance was subjected to saponification with alkali and then diazotized with sulfanilic acid and α-naphthylamine. The content of the product of diazotization is measured spectrophotometrically.

Apparatus. Spectrophotometer PMQ 2, manufactured by Carl Zeiss, Oberkochen.

Reagents. Sulfanilic acid reagent: 0.5 g sulfanilic acid is dissolved in 50 ml acetic acid and diluted to 150 ml with water. α-Naphthylamine reagent: 0.2 g α-naphthylamine is dissolved in 50 ml acetic acid and diluted to 150 ml with water. 1 N Sodium hydroxide. 1 N Hydrochloric acid. Acetone.

Estimation procedure. One ml of test solution, or 1 ml acetone as blank, were placed in 25 ml volumetric flasks; 5 ml 1 N NaOH were added and the flasks heated for 45 min at 100°C. After cooling in a refrigerator to 7–10°C, 6 ml 1 N HCl, 1 ml sulfanilic acid reagent and 1 ml α-naphthylamine reagent were added, the flasks were shaken and after being left to stand for 25 min at room temperature, diluted to 25 ml with water.

Samples of test or blank mixtures were transferred to 1 cm cuvettes and extinction measured at 520 nm. The content was estimated by reference to a standard curve.

Statistical evaluation of the method. Analysis of 10 drug solutions of identical concentration gave an average reproducibility rate of 98.55% (confidence limits 95%: 96.65%; 100.55%). This gave a variation coefficient (v) for the method of 2.75.

(2) Assay of drug content

The average content of drug was measured by triturating 20 single doses (for capsules, the contents of 20 capsules) in a porcelain mortar and then transferring aliquots containing about 20 mg of active ingredient to 50 ml volumetric flasks containing 45 ml acetone.

The mixture was kept at 37°C for 15 min and then dispersed in an ultrasonic shaker for 5 min at 40 kHz. After cooling to 20°C, the mixture was diluted to 50 ml with acetone and then filtered. One ml samples were removed and the content of drug estimated as in section (1) above. The content of single doses was then calculated.

(3) In vitro studies of the release of drug

In vitro studies of the release of active ingredient were carried out according to the Rotation method described in the NF XIV and the Diffutest (Chiraramonti et al., 1970).

Rotation method NF XIV

Estimation procedure. The estimation is carried out according to the NF XIV. Single doses were placed in 60 ml extraction fluid in stoppered bottles which were then rotated at 40 rpm in a water bath maintained at 37°C. At the end of the periods specified below, the extracting fluid was decanted, and replaced with the next extraction fluid. The individual fractions were diluted to 100 ml with acetone and then 2 ml samples of this solution taken for assay as in section (1) above.

Diffutest

Estimation procedure. The estimation was carried out according to the method described by Chiaramonti et al. (1970).

TABLE 1

EXPERIMENTAL CONDITIONS OF THE ROTATION METHOD, NF XIV

Time interval (hr)	pH	Simul. gastric fluid USP XIX (%)	Simul. intest. fluid USP XIX (%)	Tonicity (mOsmol)
0–1	1.2	100	0	200
1–2	2.5	46	54	148
2–3.5	4.5	39	61	152
3.5–5	7.0	17.5	82.5	135
5–7	7.5	0	100	120

Single doses were placed in glass bottles containing 75 ml extraction fluid and were then rotated at 30 rpm in a water bath maintained at 37°C; at the end of the rotation period the undissolved residue was filtered through a 30 mesh/cm^2 nylon screen and after washing transferred to the next extraction fluid. Table 2 shows the chronological sequence of extraction fluids used. The single fractions of 75 ml were diluted to 200 ml with acetone and 2 ml samples of this solution assayed as in Section (1) above.

RESULTS of the estimation of average content, content uniformity and measurement of uniformity of weight

Table 3 shows the average content of isosorbide dinitrate in mg/single dose and as a percentage of the declared content. The deviations from the declared content range from −1.7% to +8.0%. The USP XIX specifies that the content of isosorbide dinitrate should be between 90 and 110% of that declared. On this basis, all preparations tested conformed to this standard of uniformity of content.

The maximal deviation in content of the single doses from the declared content for all preparations was within ±15%.

Preparation C had a significantly higher (9.3%) relative standard deviation than the other preparations, i.e. the content of single doses of this product showed the greatest scatter.

TABLE 2

EXPERIMENTAL CONDITIONS OF THE DIFFUTEST

Contact time (hr)	Extraction fluid	Volume (ml)	pH value	Tonicity (mOsmol)
1	Gastric fluid	75	1.5	190
1	Intestinal fluid	75	4.5	95
2	Intestinal fluid	75	6.9	88
2	Intestinal fluid	75	6.9	88
6	Intestinal fluid	75	7.2	90

As shown in Table 3, the deviations in weight of all preparations were within that permitted by the Pharmacopoeia. In no case did the single weight deviate from the mean by more than ±4%. The relative standard deviations were also very low, with all values below 3%.

RESULTS of measurement of drug release and DISCUSSION

The results of these investigations are summarized in Fig. 2.

The release pattern of preparations B and C as shown by the Rotation method differed significantly from those of the other preparations. Thus 70–80% of the active ingredient of preparations B and C were released in the first 3–4 hr of the test, compared to around 40% of that in preparations A, D, E and F. The release pattern of this latter group was almost linear over the entire test period. In all products, on average, at least 80% of the active ingredient was released within 7 hr.

The quicker release from preparations B and C was confirmed in investigations using the Diffutest technique. Preparations A, E and F showed only minor variations in release pattern compared to the marked difference between the pattern of these three products and those of B and C.

The Diffutest, like the Rotation method, showed that the release from preparations A, E and F was almost linear over about 8 hr. The rate of release of isosorbide dinitrate from preparation D in the Diffutest was significantly slower than that in the Rotation method.

After 6 hr, some 50% of the active ingredient had been released and only by 12 hr did the figure reach 80%, whilst the maximal release had occurred in the other preparations after 8 hr. The reasons for this difference in the results of the two techniques are not known, but the techniques differ with respect to several test conditions, such as contact time in various pH solutions, tonicity and volume of test solutions, as well as in the rotation speed.

TABLE 3

AVERAGE CONTENT OF 20 SINGLE DOSES; CONTENT UNIFORMITY OF 10 SINGLE DOSES; MEASUREMENT OF WEIGHT DEVIATIONS

Preparation (content of active ingredient)	Average content (% of declared content)	Content uniformity			Measurement of weight	
		Max. content (% declared content)	Min. content (% declared content)	Relative standard deviation	Mean	Relative standard deviation
A	105.6	111.2	91.9	6.4	252.4	1.83
B	98.3	110.0	94.5	4.7	252.2	1.46
C	103.0	108.0	83.5	9.3	328.9	1.68
D	108.0	106.5	93.5	4.3	201.6	2.17
E	99.9	110.0	95.5	4.2	182.9	2.62
F	103.1	100.7	94.4	2.2	184.0	1.62

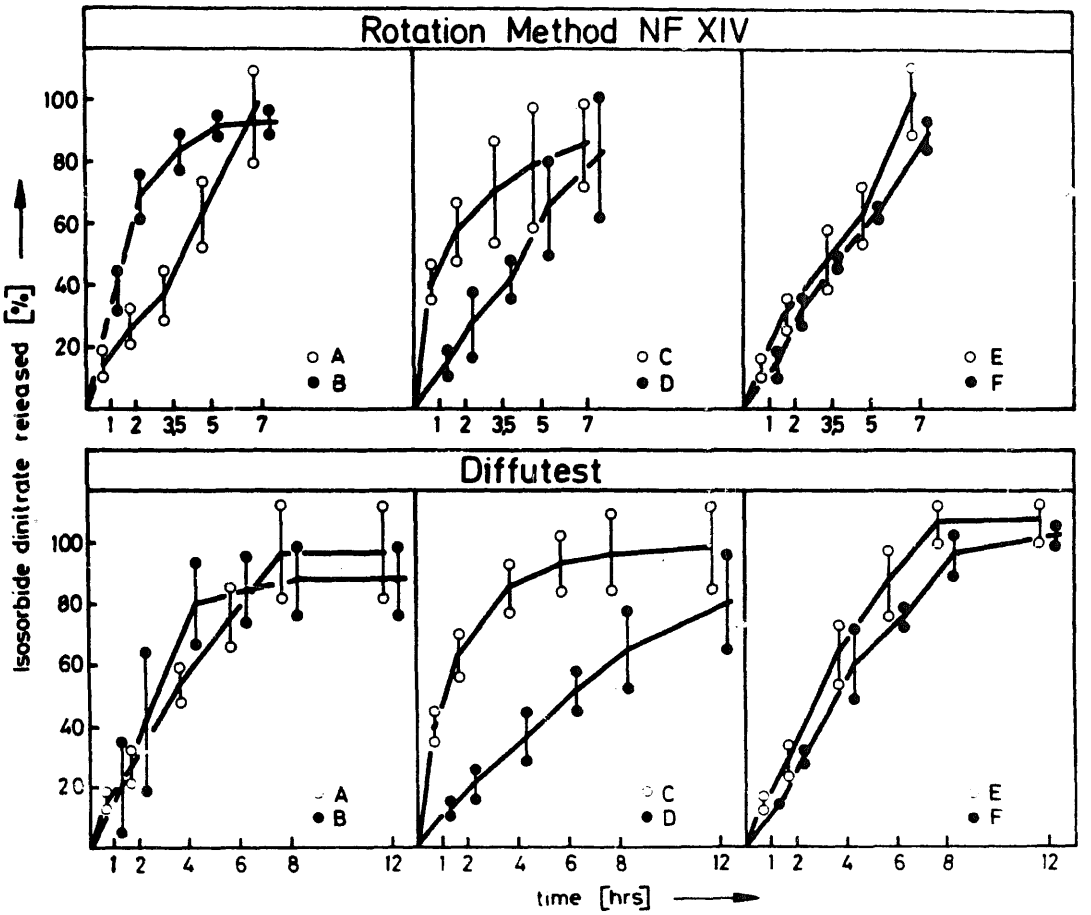

Fig. 2. Release with the 95% confidence limits of isosorbide dinitrate from commercial preparations as measured by the Rotation method of the NF XIV and Diffutest.

To measure the variation in the release between samples of the same preparation, the 95% confidence limits of 4 values were measured for all products using both test methods. Further, Fig. 2 shows the limits of error in the measured release from single doses of the same preparation at the various time intervals at the 95% probability level. Fig. 2 shows that with some preparations the release from single doses of the same batch can, at certain times, vary by up to 40% of the total content.

The results of both test methods showed that Preparations C and D had the greatest variations over the whole period, whilst a smallest scatter occurred with Preparation F.

A complete evaluation of the investigated products with relation to their effectiveness must await the results of in vivo studies.

On the assumption that the in vitro release pattern approximates the release in vivo, preparations A, D, E and F were considered better than preparations B and C.

The results of the release patterns of all preparations with both methods have shown no significant difference, so we are able to draw the conclusion that it is not necessary to have two rotation methods. One standardized method, like the rotating bottle method of

NF XIV, would be enough to investigate the release pattern of sustained release preparations.

The findings for content uniformity and uniformity of weight showed that all preparations tested conformed to the standards of the USP XIX and the DAB 7 (Second Addendum). The results of the test for content uniformity showed that all the preparations complied with the requirements for isosorbide dinitrate-containing products of the USP XIX.

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