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Sustained-release dosage forms of microencapsulated isoniazid

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The preparation and release characteristics of microcapsules of isoniazid have been studied. The differing techniques of microencapsulation are assessed and the dissolution of drug from suspended and tableted microcapsules prepared using the chosen technique has been monitored for in vitro release.

Patients taking isoniazid have been classified as either rapid or slow inactivators of the drug (Boxenbaum & Riegelman 1974). To attain in fast inactivators sustained blood concentrations similar to those produced by ordinary isoniazid in slow inactivators slow release medication has been proposed (Eidus & Hodgkin 1975; Ellard et al 1972, 1973; Naplatanova 1974). The best results were claimed for an isoniazid preparation consisting of 37% ordinary isoniazid and 63% matrix component (with no specifications of a matrix type used) (Eidus & Hodgkin 1975).

Microcapsules of ethyl cellulose prepared by the separation of the polymer, form a solvent as a result of temperature change and behave like plastic matrices (Jalšenjak et al 1976). Since isoniazid is a water-soluble drug it might be expected that the substance could be microencapsulated to obtain sustained-release preparations. We have prepared some new isoniazid dosage forms of matrix type based on the ethyl cellulose microcapsules and have investigated their dissolution properties in vitro.

MATERIALS AND METHODS

Materials

Ethyl cellulose had a viscosity of 50000 Nsm^{-2} when dissolved in toluene-ethanol 80 : 20 w/w. All materials were of reagent grade or Ph. Jug. III purity. The commercially available isoniazid was sieved into fractions that passed through 62·5 μm and 282·5 μm sieves.

Methods

Preparation of microcapsules. Technique A was the same as described previously (Jalšenjak et al 1976). Three modifications from this standard technique were made: the stirring rate was decreased to 100 rev min^{-1} (technique B) and the cooling time of the reaction mixture was prolonged to 6 h (technique C). The required amounts of cyclohexane and ethyl cellulose were divided into two fractions (technique D). The main fraction contained 2/3 of the cyclohexane, 2/3 of the ethyl cellulose and all the isoniazid. The procedure for the main fraction was exactly the same as in technique A until the temperature of 66 °C was reached during the cooling step when the remaining ethyl cellulose dissolved in the remaining cyclohexane was added at 66 °C. The combined fractions were then allowed to cool slowly with continuous stirring until room temperature (20 °C) was achieved. The core to wall ratio was 1 : 2 in all preparations.

Screening of microcapsules. The different sizes of microcapsules present in a batch were separated into suitable fractions by sieving on a mechanical shaker using a nest of standard sieves (DIN 1171) and a shaking time of 10 min.

Preparation of tablets. Individual tablets were made using a hand operated compressor. Flat punches of 10 mm diameter were used and 500 mg of microcapsules were fed into the die. A pressure of 100 MPa was used. Tablets were prepared with no adjuvants.

Dissolution procedure in vitro. The dissolution of 500 mg of microcapsules or a 500 mg tablet into 2000 ml of water at 37° ± 0·1 °C was followed. A round bottomed flask fitted with a PTFE stirrer and a syringe for extracting samples with stirring speeds of 50, 100 and 150 rev min^{-1} was used. Samples of a suitable volume were removed at intervals and filtered before assay.

Assay of isoniazid. Measurements of the absorbance at wavelengths of 267·5 and 307 nm in 1 cm silica cells were made. Suitable dilutions of the

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Table 1. Parameters of microcapsules obtained.

Sample	Isoniazid sample	Drug content[a] in 500 mg microcapsules mg	Mean particle diameters d_s	d_v	d_{sv}	$d_g \pm \sigma_g$[b] s.d.		t50%,[c] min at 50 rev min^{-1}
A1	unsieved	171·5	880	960	1160	513	398	44
A2	unsieved	169·0	830	930	1150	437	360	
B1	62·5 μm	172·5	1160	1220	1340	977	345	57
B2	62·5 μm	178·5	1140	1190	1280	912	344	
B3	282·5 μm	167·0	1090	1140	1230	912	329	56
B4	282·5 μm	168·0	1150	1190	1260	955	282	
B5	unsieved	162·0	1100	1150	1250	955	333	56
B6	unsieved	162·0	1200	1230	1280	977	241	
C1	unsieved	167·0	970	1100	1110	631	278	54
C2	unsieved	175·5	890	930	1000	576	266	
D1	unsieved	169·3	970	1060	1210	732	280	56
D2	unsieved	167·5	990	1095	1280	769	336	

[a] Mean (n = 3). The expected value is 166·7 mg.
[b] Mean with standard deviation. Data graphically determined from their individual logarithmic probability plots.
[c] Mean (n = 6), from Higuchi graph.

original sample were made with 1% hydrochloric acid.

RESULTS AND DISCUSSION

The influence of different parameters on preparations is shown by the data in Table 1. Mean particle diameters are defined in the usual manner: the surface mean diameter, d_S, the volume mean diameter, d_V, the surface-volume mean diameter, d_{SV}, and the geometric mean diameter, d_g (Allen 1974). The presentation of data on a log-probability graph was particularly useful because the range of sizes was broad. Although the geometric standard deviations, σg, were rather large, it appears that the techniques A and C produced somewhat smaller microcapsules. The particle size of isoniazid taken into a preparation had no significant influence on the mean particle sizes of microcapsules obtained. The isoniazid content in each fraction and for different techniques was substantially the same; the only difference was the time for 50% release of the drug from microcapsules, the smaller microcapsules releasing their contents more rapidly. This fact could be explained in the same way as previously (Jalšenjak 1976) i.e.: the larger microcapsules are composed of aggregates of smaller microcapsules, rather than single capsules with thicker walls. This would appear to suggest that dissolution was confined to the outer surface, possibly due to incomplete wetting or formation of a static concentrated film of dissolved material towards the centre of the aggregate.

The study of the release of isoniazid from microcapsules and tablets is shown in Table 2 for the two most promising samples. The dissolution was carried out under sink conditions (the solubility of isoniazid is 130 mg ml^{-1}, the volume of water was 2000 ml). The dissolution of isoniazid from microcapsules followed zero-order release up to about 50% release of the core material, and no time lag was observed. There was no isoniazid left either in microcapsules after 5 h or in tablets after 24 h. The release rates obtained for different stirring speeds indicate that a diffusion mechanism operates for the release of isoniazid, the greater the stirring speed used, the shorter the t50% values obtained. This fact was due to the relative thickness of the boundary layer surrounding individual microcapsules. The time for 50% from the tablets was significantly prolonged in comparison with the release time from microcapsules at the same stirring speed (50 rev min^{-1}). Microcapsules obtained by technique D gave tablets with the most promising sustained release properties. It appears that the fractional additional of dissolved ethyl cellulose produces a microcapsule wall which is firstly, strong enough not to break during tableting, and secondly, prolongs the release of the core very well.

All the tablets prepared exhibited good physical properties and when used in dissolution tests remained intact at the end of the experiment. The skeletons of tablets when all of the drug had been released were dried and no more than 4% of ethyl cellulose was lost. The percentage of the drug released was plotted against $(time)^{\frac{1}{2}}$ (Fig. 1). The dissolution from microcapsules and tablets showed a straight line relationship up to 90 and 70% release,

Table 2. Percentage of isoniazid released from microcapsules and tablets.

	Sample (B_5 + B_6)				Sample (D_1 + D_2)	
	Microcapsules			Tablets	Microcapsules	Tablets
Time, min	150[a]	100	50	50	50	50
5	5·8	4·0	3·3	—	4·0	—
10	11·8	8·1	7·7	—	8·6	—
15	17·1	13·4	12·2	13·2	13·0	15·2
30	34·2	29·8	26·9	23·8	29·4	25·0
45	48·5	45·0	42·4	33·4	43·2	31·2
60	61·1	58·2	53·7	40·8	56·0	36·4
120	87·8	86·7	84·4	60·2	83·6	53·7
180	97·6	96·5	96·0	70·9	94·2	65·9
240	99·2	98·9	98·8	78·6	97·1	75·8
300	—	—	—	82·8	—	84·1
360	—	—	—	86·7	—	89·2
420	—	—	—	88·9	—	91·5
(24 h)	(100)	(100)	(100)	(100)	(100)	(100)
t50% min[b]	46	52	56	86	56	110

[a] rev min^{-1}
[b] from Higuchi graphs.

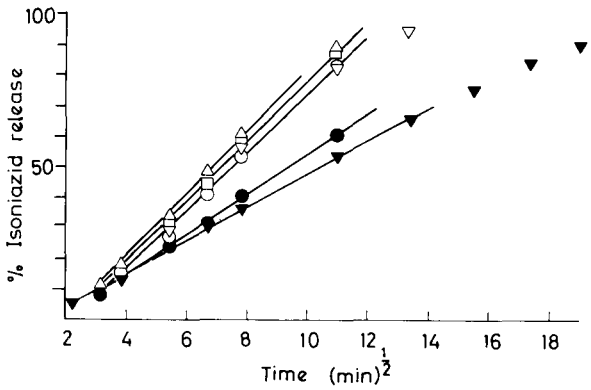

FIG. 1. The percentage of isoniazid released against (time)$^{\frac{1}{2}}$ as a function of the stirring speeds. Sample (B_5 + B_6)—microcapsules △ 150, □ 100, ○ 50 rev min^{-1}, tablets ● 50 rev min^{-1}; Sample (D_1 + D_2)—microcapsules ▽ 50 rev min^{-1}, tablets ▼ 50 rev min^{-1}.

respectively, indicating a diffusion process similar to that postulated by Higuchi for matrices.

Recently it has been found that the absorption of matrix formulated isoniazid continues throughout the enteric tract and is as complete as that of ordinary isoniazid. High dosages of the isoniazid-matrix could be given without encountering toxic reactions because of delayed absorption from a matrix formulation (Eidus & Hodgkin 1975). These facts in conjunction with the data presented here indicate a variety of possibilities for producing simple isoniazid dosage forms using ethyl cellulose microcapsules.

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