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Evaluation of maltodextrins as excipients for direct compression tablets and their influence on the rate of dissolution

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Summary

The maltodextrins Maltrin M700, M500 and M150 have been evaluated as excipients for direct compression tablets and their influence on the rate of dissolution was examined. The amount of lubricant appears to play an important role and significantly affects and rate of release of drug from the tablet, particularly when the drug is insoluble in water, while the release rate of a soluble drug remains unaffected. All the formulations prepared showed excellent flow and compressibility. Storage of the tablets for 90 days at 45°C was found to have almost no influence on their properties.

Introduction

Maltodextrins are carbohydrate products obtained from the reaction of starch with acid and/or enzymes in the presence of water. They are used as excipients in direct tablet compression, a method with well-documented advantages (Sheth et al., 1980), since they exhibit free flow properties and compressibility characteristics comparable to those of other excipients.

In this investigation the maltodextrins Maltrin M150, M500 and M700 were evaluated. Maltrin M500 and M700 are both in the agglomerated forms. Maltrin M700 exhibits good dissolution while Maltrin M500 and M150 show binding properties. Agglomeration increases the extent of functioning of the maltodextrins, since the particles are more porous and of greater size; therefore the powder flows easier, generates less dust, is directly compressible and dissolves more rapidly.

Since there is a lack of published data on the effect of maltodextrins on the rates of release from solid dosage forms (Parott, 1989), the purpose of the present investigation was to evaluate the influence of the three maltodextrins, namely, Maltrin M500, M700 and M150, on the rate of release from direct compression tablets in vitro, from two model drugs, naproxen (rather insoluble) and tolmetin sodium (soluble in water).

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TABLE 1

The formulations used in the study

	Percentage of ingredients													
Formulation:	A1	A2a	A2b	A2c	A2d	A3	A4	A5	A6	A7	A8	B1	B2	B3
Naproxen	65	65	65	65	65	65	65	65	65	65	65			
Tolmetin sodium												65	65	65
Maltrin M700	34.5								35			34.5		
Maltrin M500		34.5	34	34.75	35					35			34.5	
Maltrin M150						34.5					35			34.5
Lactose							34.5							
Dextrose								34.5						
Magnesium stearate	0.5	0.5	1	0.25	–	0.5	0.5	0.5	–	–	–	0.5	0.5	0.5

Materials and Methods

Materials

For the preparation of the tablets the following materials were used: tolmetin sodium (kindly provided by Knoll), naproxen (kindly donated by Syntex), Maltrin M700, M500 and M150 (kindly provided by Grain Processing Corp., Iowa), lactose (kindly donated by BASF), dextrose (Magglie) and magnesium stearate (BDH).

Methods

The mixture, i.e., the drug, the maltodextrins and magnesium stearate were thoroughly mixed in a blender for 15 min. The tablets (380 mg) were compressed using the direct compression technique on an instrumented single punch tablet machine (Korsch-Erweka, Berlin). The formulations prepared are listed in Table 1.

The ratio between the diameter and thickness of cylindrical tablets was within the range 0.7–0.9. The tablets were compressed to a hardness level of 5 kg, and in particular formulation A6 and A7 to 8 kg, 10 kg and 12–15 kg (measured in the Erweka hardness tester).

For the weight uniformity test, the USP method was adopted for use. Friability was determined according to the Roche friabilator method. As the sample, 10 tablets were selected from each batch. The weights before and after the test were used to calculate the friability.

The dissolution test for naproxen and tolmetin sodium tablets was conducted using the USP dissolution apparatus (paddle method) in 900 ml of intestinal fluid (pH 7.4) or gastric fluid (pH 1.2) maintained at 37 ± 0.2°C and rotated at 50 or 100 rpm. Naproxen and tolmetin sodium were assayed spectrophotometrically at 332 and 322 nm, respectively, using a Perkin Elmer Lambda 6 spectrophotometer. Each data point represents the mean of measurements from three tablets.

Results and Discussion

The experimental results demonstrated excellent flow ability and compressibility with maltodextrins and naproxen or tolmetin sodium. The physical characteristics, i.e., mean weights, breaking strength, diameter and friability, of a number of model batches of naproxen tablets tested are detailed in Table 2. As can be seen, no significant differences were observed. Naproxen tablets containing Maltrin M700 or M500 (hardness levels: 5, 8, 10, 12 and 15 kg) were prepared and tested, however, no effect on the release rate of the drug was observed. Subsequently, only tablets with a hardness strength of 4–5 kg were prepared and investigated.

The stirring speed appeared to influence significantly the rate of dissolution of the drug from naproxen-Maltrin M500 tablets (Fig. 1), whereas the release of drug from tolmetin sodium-Maltrin M500 tablets remained almost undetectable (Fig. 3). Further, the effect of mixing was examined. Two mixtures were prepared having the same composition as that of formulation A2a. In the first, preblends of naproxen and diluent (Maltrin M500) without the lubricant were mixed for 10 min. Magnesium stearate was then added, followed by mixing for 5 and 10 min. In the second, the mixture was prepared as described in the

TABLE 2

Characteristics of model naproxen tablets

	A1	A2a	A3	A1/T	A2a/T	A3/T
Diameter (mm)	5.40(0.03) [a]	5.20(0.01)	5.00(0.00)	5.40(11.50)	5.20(4.90)	5.10(3.20)
Hardness (kp)	4.42(0.70)	4.34(0.60)	4.12(0.20)	4.14(1.30)	4.11(1.00)	6.5(1.20)
Weight (mg)	378 (5.40)	382 (9.30)	384 (3.10)	375 (5.20)	378 (3.90)	380 (4.60)
Friability (%)	0.98	0.98	0.99	0.58	0.98	0.98
t_{50} (min)	280	350	355	225	370	365

[a] (± SD) values.

A1/T, A2a/T and A3/T stored for 90 days at 45°C.

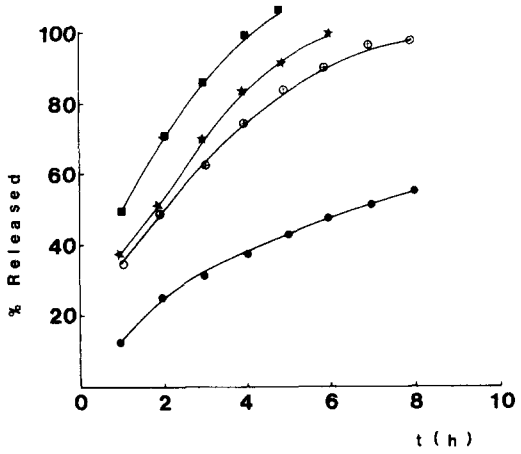

Fig. 1. Dissolution profiles showing the effects of stirring speed and mixing conditions on the rate of naproxen release from the tablets. Stirring speed: (●) 50 and (■) 100 rpm (mixing of ingredients in one step for 15 min); magnesium stearate added and mixed for (○) 10 and (⋆) 5 min at a stirring speed of 50 rpm.

Introduction, i.e., drug, diluent and lubricant were added in one step. The results show that drug release from the second mixture was prolonged compared to the other two cases, while more rapid release was observed after 5 min mixing than after 10 min mixing (Fig. 1). In studying the influence of pH on the release rate of naproxen (formulation A2a), it was found that a fall in pH from 7.4 to 1.2 resulted in a dramatic decrease in release rate with only 10% of the drug being released after 10 h.

To examine the influence of the three maltodextrins and magnesium stearate on the release rate of naproxen, tablets with and without lubricant were prepared. In the tablets without lubricant the dissolution rates (in pH 7.4 buffer) appeared almost identical for the three maltodextrins, and the drug was released completely in 8 h (Fig. 2). Incorporation of magnesium stearate 0.5% resulted in slower release rates for all maltodextrins. Faster release was observed with Maltrin M700 mixtures, while Maltrin M150 and M500 showed intermediate and slow release, respectively. The influence of dextrose and lactose on the release rate was also investigated. Tablets containing dextrose instead of maltodextrins showed more rapid release than Maltrin M700 (Fig. 2), while preparations containing lactose released the drug in less than 90 min.

The faster release of the drug from Maltrin M700 tablets was expected in view of its better dissolution properties. The observed difference in the rate of release of naproxen from Maltrin M150 as compared to Maltrin M500 tablets (although both participate in binding) could be at-

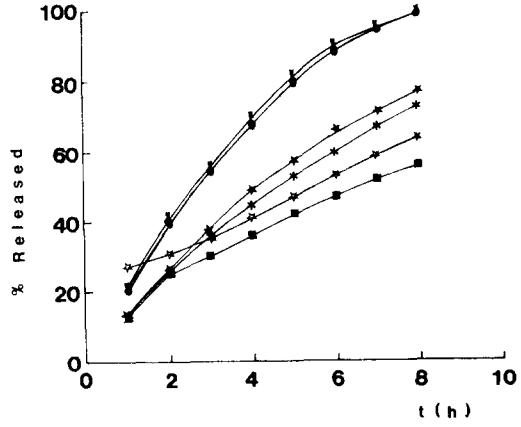

Fig. 2. Dissolution profiles showing the effects of lubricant on the release rate of naproxen, from maltodextrin tablets, before and after the addition of magnesium stearate. (▼) Maltrin M700, (●) Maltrin M500 and (◆) Maltrin M150, without lubricant. (⋆) Dextrose, (∗) Maltrin M700, (■) Maltrin M500 and (☆) Maltrin M150 containing 0.5% magnesium stearate.

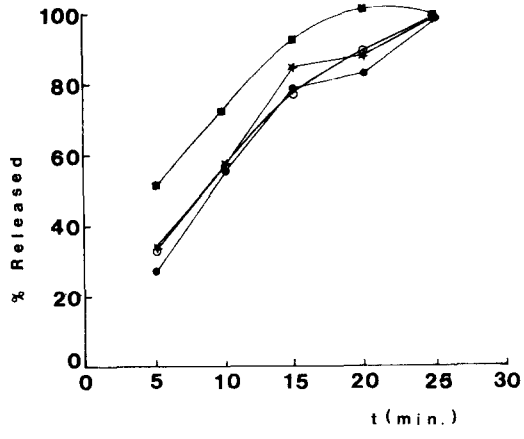

Fig. 3. Dissolution profiles showing the influence of maltrodextrins on the release rate of tolmetin sodium from tablets containing 0.5% magnesium stearate. (■) Maltrin M700, (⋆) Maltrin M150, (●) Maltrin M500 at 50 and (○) 100 rpm.

tributed to the different form of the powder. Maltrin 500 is an agglomerated form, while Maltrin M150 exhibits a greater surface area than Maltrin M500 and therefore, after mixing with magnesium stearate, the lubricant creates a more effective coating around the particles of Maltrin M500 due to their smaller total surface area as compared with that around the M150. Additionally, the particles of Maltrin M500 become more hydrophobic due to the hydrophobicity of magnesium stearate. This results in a decrease in the wetting capacity of Maltrin M500 particles, and eventually leads to retardation of the rate of release of the drug from the tablet.

The incorporation of magnesium stearate 0.5% in tolmetin sodium tablets exerted almost no unwanted effect on the release of this drug, drug release being complete in 25 min (Fig. 3). This was further confirmed when different amounts of magnesium stearate were incorporated (0.25, 0.5 and 1%) in tablets containing Maltrin M500. The addition of different amounts of lubricant was found to have no effect on the release rate of the drug, since complete release of tolmetin sodium again occurred within 25 min in all cases.

In contrast, when similar amounts of magnesium stearate were incorporated into naproxen tablets with Maltrin M500, a significant retardant effect on drug release was noted (Fig. 4). An increase in the concentration of lubricant causes

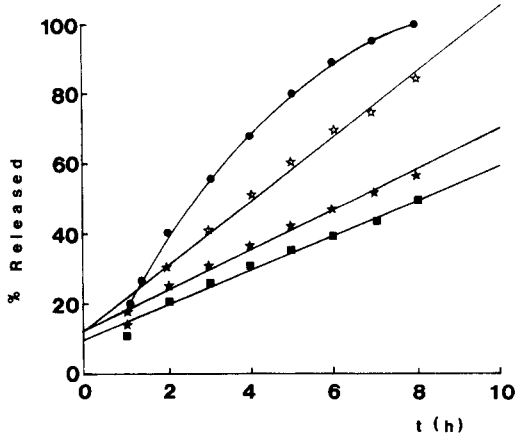

Fig. 4. Dissolution profiles showing the influence of the amount of magnesium stearate on the release of naproxen from tablets. (■) 1%, (★) 0.5%, (☆) 0.25% and (●) 0%.

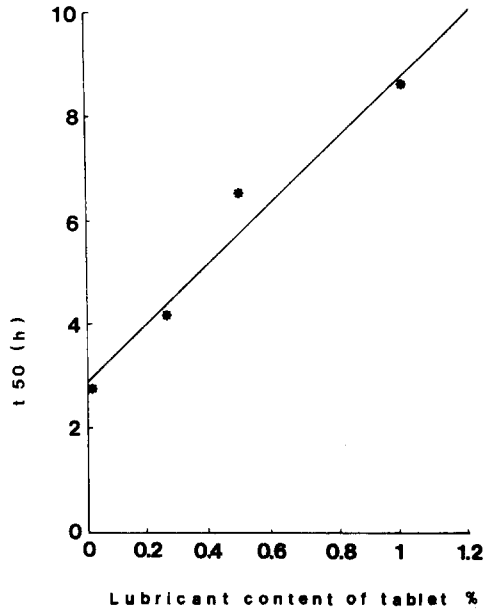

Fig. 5. Time taken for 50% drug release as a function of percentage of magnesium stearate content.

a significant decrease in the release rate of naproxen. The results indicate that a linear relationship exists between the t_{50} value and the percentage of magnesium stearate content in the tablets (Fig. 5). From these results, it appears that Maltrin M500-magnesium stearate mixtures exhibit a strong retardant effect on drug release when mixed with rather water-insoluble materials like naproxen. This effect increases with increase in the amount of magnesium stearate in the mixture. When a water-soluble material, such as tolmetin sodium, is incorporated into a Maltrin M500-magnesium stearate mixture, this retardant effect is not exhibited. This phenomenon could be attributed to the high solubility of tolmetin sodium which appears to counterbalance the retardant effect of Maltrin M500 in the mixture.

Further, the effect of storage conditions on the physical characteristics of naproxen tablets was examined. Formulations A1, A2a and A3 were stored for 90 days at 45°C. The data obtained are listed in Table 2. The tablet properties were apparently unaffected by the conditions of storage and revealed no significant changes (except that on the surface of formulation A1/T where

TABLE 3

Kinetic assessement of release data

	Zero order			First order			Cube root		
	Slope	Inter-cept	r^2	Slope	Inter-cept	r^2	Slope	Inter-cept	r^2
A1	0.150	5.66	0.991	−0.001	2.01	0.997	−0.003	4.62	0.999
A2d	0.206	11.35	0.975	−0.003	2.20	0.946	−0.004	4.71	0.994
A2c	0.168	7.08	0.991	−0.001	2.02	0.993	−0.004	4.62	0.999
A2a	0.110	6.97	0.980	−0.001	1.98	0.996	−0.002	4.55	0.992
A2b	0.095	5.92	0.982	−0.001	1.98	0.994	−0.001	4.56	0.991
A3	0.110	13.00	0.950	−0.001	1.95	0.990	−0.002	4.45	0.975
A1/T	0.192	7.24	0.930	−0.002	2.10	0.976	−0.005	4.71	0.995
A2a/T	0.120	9.21	0.975	−0.001	1.97	0.995	−0.002	4.62	0.991
A3/T	0.119	6.54	0.988	−0.001	1.98	0.996	−0.002	4.56	0.994

cracks were observed), compared to those of the control tablets while release rates were modified. In order to present the dissolution data in a manner that could clearly demonstrate the effect of storage, the t_{50} values were determined (Table 2) using apparent first-order dissolution plots (Wagner, 1969). The results obtained on formulations A2a/T and A3/T indicated slight retardation of the rate of drug release whereas A1/T appeared to have a faster release rate. The latter is probably due to the cracks created on the surface of this formulation, thereby resulting in more rapid dissolution of drug in the penetrating liquid, and thus increasing the release rate of the drug from the tablet.

The data on the release from naproxen tablets suggest that mixtures of naproxen with maltodextrins can produce controlled release products. Therefore, in order to elucidate the mechanism of naproxen release, the data were further analyzed taking into consideration the percent release values vs time for zero order, first order (as log of undissolved percent of drug vs time) and cube root (Bamba et al., 1979). In Table 3 the estimated values of the slope, intercept and correlation coefficient following regression of dissolution data are listed for different formulations. The results indicate that the mechanism of release is influenced by the excipients in the formulation as can be seen from the r^2 values (Table 3). In preparations consisting of Maltrin M700 and M500 (with concentrations of lubricant 0–0.25%), the release mechanism can be explained better by the cube root model, (formulations A1, A2d, A2c and A1/T), while in formulations consisting of Maltrin M150 and M500 (with concentrations of lubricant 0.5–1%) the mechanism can be described better by first-order release (formulations A2a, A2b, A2a/T, A3 and A3/T) (Table 3).

However, determination of the best-fit kinetic equation is rather difficult, since no significant differences were observed which indicate that complex mechanisms influence the release of drug from these tablets.

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