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FACTORS INFLUENCING THE RELEASE OF AMINOPHYLLINE FROM TABLETED ETHYLCELLULOSE MICROCAPSULES

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ABSTRACT

Microcapsules containing aminophylline cores in ethylcellulose walls have been prepared and tableted. The mechanical properties and the release characteristics of tablets obtained by direct compression at six different pressures (ranging from 265 to 1060 $Kg.cm^{-2}$) were studied. The release rate of the drug from tableted microcapsules increased with the increase of compression force and was higher than from uncompressed microcapsules, indicating that some damage of the polymeric wall occurred during the compression process. Among the various excipients tested as binding and protective agents, paraffined starch (a mixed system appositely set up) gave the best results, producing the slowest drug release rate. No important effect on drug release rate was found by changing the size of the microcapsules.

INTRODUCTION

In recent years the use of microencapsulation with polymeric materials has received increasing attention as a means of developing pharmaceutical dosage forms for drug sustained release. In particular, tableting of microcapsules has been shown to better slow drug release, so providing a more satisfactory sustained action, in comparison with their suspension or gel formulations [1, 2]. Numerous methods have been described for the microencapsulation process [3-5] and the manufacturing technology has become more and more accurate and reliable. However, the preparation of microcapsule tablets still presents the problem of possible damage of the polymeric coating film, especially when the core-wall ratio

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is particularly high and therefore the polymeric wall very thin. This potential problem is a consequence of the mechanical stress to which the microcapsules are subjected during the compression process. Among the possible elements which may produce or influence such a phenomenon, the compression force and the presence and type of formulation additives are certainly important, but their actual influence have not been adequately investigated.

Therefore, to shed light on the role played by both these factors, we prepared microcapsules of ethylcellulose, containing aminophylline as model drug. Microcapsules, alone or in mixture with several types of excipients, were then subjected to various compression forces (ranging from 265 to 1060 $Kg.cm^{-2}$). The mechanical properties and the drug release characteristics from these tableted microcapsules have been studied.

MATERIALS AND METHODS

Materials - Aminophylline dihydrate was obtained from Boeringher Ingelheim (Germany). Ethylcellulose was purchased by Aqualon Co. (Welmington, DE, USA). Rice starch (Remy Industries, Wijgmaal-Leuven, Belgium), microcrystalline cellulose (Emcocel 90M, Mendell Inc., Carmel, NY, USA), dicalcium phosphate dihydrate (DiTab, Stauffer Chemicals, Westport, USA), mannitol MG (Roquette, Lestrem, France) were sieved and the granulometric 20-60 mesh fraction was used. Paraffined starch was appositely prepared by granulating 75% rice starch and 25% paraffin (Carlo Erba, Milan, Italy) in a Z-arms Dough mixer; the 20-60 mesh fraction was selected. Other chemicals used were of analytical grade.

Preparation of aminophylline microcapsules - The microcapsules were prepared according to the method patented by Eurand International S.p.a. (Milan, Italy). The method used involved the deposition of polymer wall-forming material onto dispersed particles of core by cooling below a critical phase-separation temperature, using polyethylene as a coacervation-inducing agent [6]. Aminophylline was dispersed under continuous stirring in a cyclohexanic solution of ethylcellulose and polyethylene at 80°C. The temperature was maintained constant for about 1 h, and then it was allowed to decline at a controlled rate. The ethylcellulose separated, first as a liquid phase, which deposited round the core particles. When the temperature reached 45°C, the membrane formation was completed. The stirring was stopped and the microcapsules were filtered, repeatedly washed with cyclohexane and finally dried. Aminophylline microcapsules were sieved on a mechanical shaker and the 20-30 mesh (850-600 μm) and 40-50 mesh (425-300 μm) fractions were used for tableting. The aminophylline content was about 850 mg per gram of microcapsule.

Preparation of tableted microcapsules- Tablets were made by direct compression of 600-mg quantities of the dried aminophylline microcapsules. Compression was carried out with an IR spectrophotometric tableting machine (Specac P/N 15.011), equipped with a pressure-gauge, under six different pressures (265, 400, 530, 665, 795 and 1060 $Kg.cm^{-2}$) for 1 min [7], using flat punches of 11.28 mm diameter. Tablets (600 mg) containing mixtures of microcapsules and each of tested excipients (50:50 w/w) were also prepared. All the selected excipients had good flow and compressibility characteristics and it was not added any lubricant.

Determination of tablet thickness and crushing strength - The thickness of the microcapsule tablets with or without excipients was measured by a centesimal caliper. For each tablet, five different measurements were taken and mean values were calculated. The crushing strength of the tablets was determined by a hardness tester (Schleuniger, Mod 2E, Germany). Ten tablets were used for each determination, and the mean was calculated.

Release studies - The release studies were carried out with the Diffutest apparatus (Eurand International S.p.a., Milan, Italy), according to the procedure used by Chiaramonti et al. [8]. Test samples were added to 25 mL of dissolution medium in sealed glass tubes which were rotated at 30 r.p.m. inside the thermostated cell (37±0.5°C). After a suitable interval time, the dissolution medium was removed, and, after dilution, the drug concentration was determined spectrophotometrically at 270 nm (Spectrophotometer UV-Vis Perkin Elmer, Mod. Lambda 3). An equal amount of new dissolution medium was added to continue the experiment. The pH of the medium was changed during the test, to simulate the pH variation on the surface of the tablets exposed in the gastrointestinal tract, according to the following scheme: 1 h at pH 1.5; 1 h at pH 4.5; 2 h at pH 6.9; 2 h at pH 7.2. The composition of simulated gastric and intestinal fluids was the same as described in [8]. Each experiment was performed at least four times and the results were averaged. The relative standard deviation was always less than 4%.

RESULTS AND DISCUSSION

The effect of applied compression force on the thickness of aminophylline tableted microcapsules without excipients is shown in Figure 1. As may be observed, the tablet thickness considerably decreased with increasing the compression force.

Slightly lower thickness values and higher strengths were obtained for the tablets containing the larger microcapsules. A similar effect was observed by Nixon and Agylirah [9], and attributed to breakdown of microcapsule aggregates during compression, resulting in smaller particles which would fill in the gaps between the larger particles, thus producing a more compact and thinner tablet. With regards to the tablet strength, with both the granulometric fractions of microcapsules examined, a valuable hardness (higher than 2 Kp) was obtained only for the highest value of applied compression force (1060 $Kg.cm^{-2}$).

The release profiles of aminophylline from tableted microcapsules at various compression forces are shown in Figure 2 (A and B). It would be expected that, by compacting microcapsules, a slower dissolution rate would result, as a consequence of greatly reduced surface area available for drug release [9-12]. On the contrary, higher drug release rates than from the untableted microcapsules were in all cases observed, showing that microcapsules were susceptible to the mechanical stress undergone during the compression process.

Probably, due to the high core-wall ratio used (>80% drug), the ethylcellulose wall was not strong enough and it underwent some damage during tableting. The slight increase of drug release rate observed by varying the microcapsule size from 40-50 to 20-30 mesh was attributed to the thinning of the polymeric wall by increasing the microcapsule diameter [9, 13]. This effect could cause both a higher drug diffusion rate and a greater facility in wall breakage during the compression process. Interestingly it appeared that the drug release increased with the increase in the

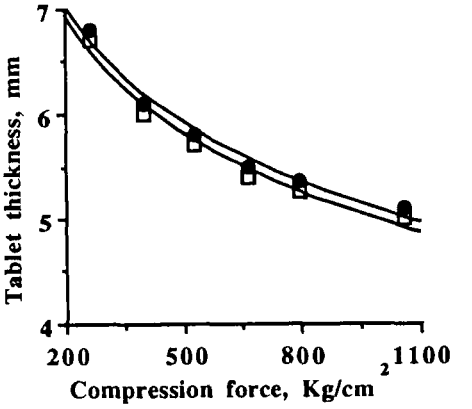

FIGURE 1
Effect of compression force on tablet thickness: (□) 20-30 mesh; (●) 40-50 mesh.

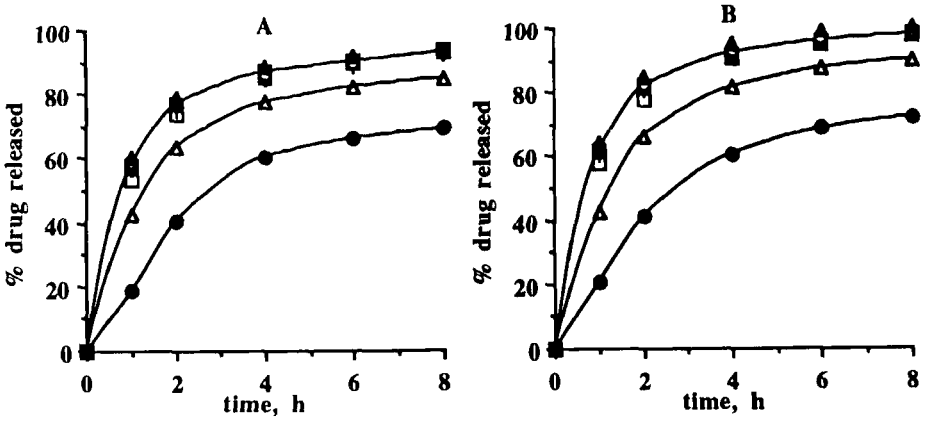

FIGURE 2
Effect of compression force on aminophylline release from 40-50 mesh (A) and 20-30 mesh (B) tableted microcapsules: (●) uncompressed microcapsules; (△) compression force 265 $Kg.cm^{-2}$; (□) 400 $Kg.cm^{-2}$; (+) 530 $Kg.cm^{-2}$; (■) 665 $Kg.cm^{-2}$; (○) 795 $Kg.cm^{-2}$; (▲) 1060 $Kg.cm^{-2}$.

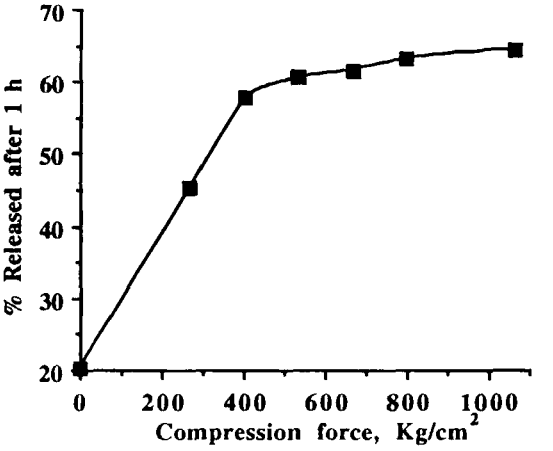

FIGURE 3
Effect of compression force on the amount of aminophylline released after 1 hour from 20-30 mesh tableted microcapsules.

TABLE 1
Thickness and Hardness of Tableted Microcapsules (compress. force: 400 $Kg.cm^{-2}$)

Excipient	40-50 mesh		20-30 mesh	
	Hardness (Kp)	Thickness (mm)	Hardness (Kp)	Thickness (mm)
- - - - - - -	<2	6.1	<2	6.0
Mannitol MG	<2	5.5	<2	5.5
microcryst. cellul.	6.2	6.2	4.6	6.2
Rice starch	<2	6.0	2.1	5.8
DiTab	<2	5.0	<2	4.7
Paraffined starch	3.1	5.4	3.8	5.4

pressure applied, up to a pressure value of about 400-500 $kg.cm^{-2}$, then remained almost constant, even when the compression force was further increased (Figure 3). This behaviour can not be attributable to an increased difficulty of both dissolution fluid penetration and drug diffusion through the narrower permeation channels of the compressed mass, that could counterbalance the damage effect on the microcapsule wall [11]. In fact, in this study, the tablet disintegration time was always less than 15 min, independently of the compression force used.

The effect of addition of different types of excipients on both the tablet properties and the drug release characteristics from tableted microcapsules was then evaluated. Microcrystalline cellulose and rice starch were selected as typical plastic materials, whereas granular mannitole and dicalcium phosphate dihydrate as breakable under pression materials. Paraffined starch was purposely prepared to

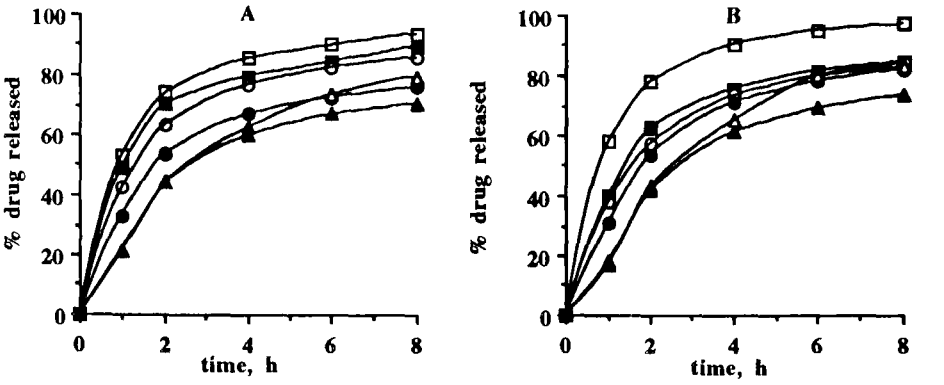

FIGURE 4
Effect of excipients on aminophylline release from 40-50 mesh (A) and 20-30 mesh (B) tableted microcapsules: (□) without excipients; (■) mannitole; (○) microcrystalline cellulose; (●) rice starch; (△) DiTab; (▲) paraffined starch.

combine the plastic properties of starch with the sealing properties of paraffin. Tablets of microcapsule-excipient mixtures (50:50 w/w) were obtained at a compression force of 400 $Kg.cm^{-2}$, because higher values of compression force did not show significant variations of the drug release rate. The tablet properties of aminophylline tableted microcapsules with and without excipients are shown in Table 1.

The presence of the excipients improved the mehanical characteristics of the tablets, even if a valuable hardness (higher than 2 Kp) was achieved only using microcrystalline cellulose and paraffined starch. The effect of the excipient addition on the release rate of drug from tableted microcapsules is shown in Figure 4.

Similar release profiles were obtained with the two series of tablets of identical composition, indicating that the size of microcapsules had little effect. The drug release rate, in the presence of each type of excipient investigated, was always lower than from tablets made of microcapsules alone, the compression force being the same. This slowing effect was in no case attributable to an extension, due to the presence of the excipient, of the tablet disintegration time, which remained in all cases under 15 min.

Therefore it may be concluded that all the examined excipients revealed a general protective action on the microcapsule wall, moderating the damaging effect of the compression force. The drug release rate was dependent on the type of formulation additive used, as it is particularly evident in Figure 5, where the times required to release 50% of the drug content from each tablet formulation are reported.

Figure 6 shows the per cent variation of drug amount released at various times from the examined tableted microcapsules with respect to that released at the same times from uncompressed ones. Of the tested excipients, paraffined starch showed the greatest protective power, probably due to the sealing effect of paraffin [14] combined with the plastic properties of starch.

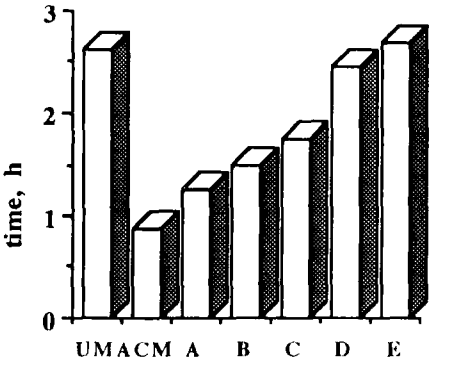

FIGURE 5
Effect of the type of excipient on the time for 50% aminophylline release from 20-30 mesh tableted microcapsules: UM = uncompressed microcapsules; ACM = alone compressed microcapsules; A = mannitol MG; B = microcrystalline cellulose; C = rice starch; D = DiTab; E = paraffined starch.

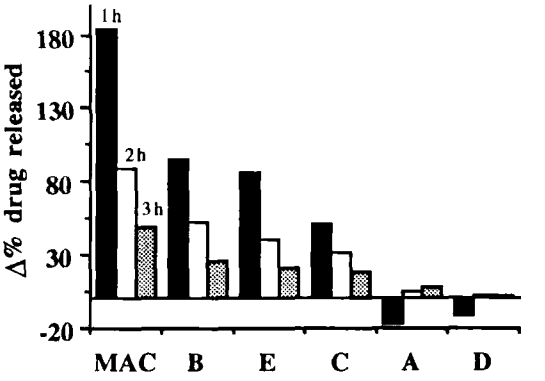

FIGURE 6
Per cent variation of the amount of drug released at various times from 20-30 mesh tableted mmicrocapsules as respect to uncompressed ones: MAC = Microcapsules Alone Compressed; A = mannitol MG; B = microcrystalline cellulose; C = rice starch; D = DiTab; E = paraffined starch.

CONCLUSIONS

Probably because of the high core-wall ratio, the prepared microcapsules were found to be very sensitive to the mechanical stress of the compression process, so that they gave an even higher drug release rate than uncompressed microcapsules. The addition of protective excipients not only improved the mechanical properties of the tablets, but also reduced the damaging effects of compression force, although it appeared evident that in any case, to completely eliminate these negative effects, a lower core-wall ratio should be used, so that a thicker, more resistent ethylcellulose film could be obtained. Anyway, the addition of paraffined starch enabled us to obtain microcapsule tablets with satisfactory mechanical characteristics and the slowest drug release rate, which was very close to that from uncompressed microcapsules.

Interestingly, it was observed that the type of excipients used in tablet preparation appeared to play a very important role in determining the drug release rate from tableted microcapsules. Their effect should be therefore carefully evaluated in each case, considering that a suitable choice could be of great aid to the formulator in obtaining the desired drug release profile.

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