DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 16(11), 1829-1842 (1990)

A STUDY ON THE MANUFACTURE AND IN VITRO DISSOLUTION OF TERBUTALINE SULFATE MICROCAPSULES AND THEIR TABLETS

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ABSTRACT

Microcapsules of terbutaline sulfate with cellulose acetate butyrate and ethylcellulose were prepared using an emulsion-solvent evaporation technique. The in vitro dissolution of terbutaline sulfate was studied using the USP rotating basket method. As the polymer to drug ratio increased, the microcapsule size distribution shifted to the smaller size and the release of terbutaline sulfate decreased. The release of terbutaline sulfate was independent of the dissolution medium pH for both polymers. The release kinetics from the microcapsules was dependent on the polymer type and polymer to drug ratio. The release of terbutaline sulfate from cellulose acetate butyrate and ethylcellulose microcapsules formulated with a 1:1 polymer to drug ratio was complex and could not be differentiated between the square-root of time and first-order release models. However, the square-root of time model was followed by microcapsules formulated with a 2:1 or a 3:1 cellulose acetate butyrate to drug ratio. When the ethylcellulose to drug ratio was increased to 2:1 the square-root of time model was followed. At an ethylcellulose to drug ratio of 3:1 the release kinetics could not be differentiated between the Hixon-Crowell and first-order release models. The

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T50% from ethylcellulose microcapsules was decreased when the microcapsules were compressed into tablets with the addition of Avicel^{R}/Emcompress^{R} (2:1) or Avicel^{R}.

INTRODUCTION

Terbutaline sulfate, an adrenergic agonist, is an effective bronchodilator following peroral administration. Terbutaline sulfate is a potential candidate to be formulated in a sustained release dosage form because of its short half-life of 3-4 hours (1-2) and a low daily peroral dose of 5 mg three times a day.

Microencapsulation is used to modify and retard drug release. Microencapsulation offers the advantage over other sustained release systems that the coated particles can be widely distributed throughout the gastrointestinal tract. This potentially improves drug absorption and reduces side effects related to localized buildup of irritating drugs against the gastrointestinal mucosa (3).

Many different coating materials and microencapsulation processes can be used. The emulsion-solvent evaporation technique has been described in the literature, and has been applied to polymers like ethylcellulose (4-5) and Eudragit (6).

The purpose of this study was to (a) prepare terbutaline sulfate microcapsules using cellulose acetate butyrate and ethylcellulose by an emulsion-solvent evaporation technique, (b) study the effect of polymer to drug ratio on the *in vitro* dissolution, (c) study the effect of dissolution media pH on the *in vitro* dissolution, (d) fit the data to various postulated drug release models, (e) obtain microcapsules with a drug release of approximately not more than 60 % terbutaline sulfate release in 6 hours and not less than 80 % in 12 hours, and (f) study the effect of tableting on the *in vitro* dissolution of the microcapsules.

MATERIALS AND METHODS

Materials

Terbutaline sulfate (Merrell Dow Pharmaceuticals), cellulose acetate butyrate (CAB) (Scientific Polymer Products), ethylcellulose (EC), 100cps (Hercules Incorporated), light mineral oil, acetone, hexanes, methanol, ethylacetate, Avicel^{R} (FMC Corporation), Emcompress^{R} (Edward Mendell Co.) and magnesium stearate (Mallinckrodt).

Preparation of microcapsules

Microcapsules were prepared by an emulsion-solvent evaporation technique. Acetone was used as the polymer solvent and light mineral oil as the microencapsulating vehicle.

To prepare a batch with a 1:1 polymer to drug ratio, 3 grams of cellulose acetate butyrate (CAB) or 1.8 grams of ethylcellulose (EC) were dissolved in 30 mL of acetone. Three grams or 1.8 grams of terbutaline sulfate, depending on the polymer used, were dispersed in this solution and stirred for 30 minutes. This dispersion was poured into 100 mL of light mineral oil containing 1.3 % sorbitan monooleate and stirred at 1100 r.p.m. for 6 to 8 hours. The light mineral oil was decanted and the collected microcapsules were washed twice with 100 mL of hexanes, thereafter filtered and air dried for 12 hours.

The collected microcapsules were sized through standard sieves no. 20, 30, 40, 50 and 70 mesh. The fraction of microcapsules remaining on each sieve was collected for further study.

Drug Content

To determine the total drug content of the CAB microcapsules, an extraction method was performed. Twenty five milligrams of microcapsules were added to 20 mL of ethylacetate to dissolve the polymer coating and terbutaline sulfate was extracted with 100 mL of 0.1 N HCl aqueous solution. The amount of terbutaline sulfate in the aqueous phase was assayed spectrophotometrically at 276 nm. Each determination was performed in triplicate.

To determine the total drug content of the EC microcapsules, a common solvent for terbutaline sulfate and polymer was chosen. Fifteen milligrams of microcapsules or a crushed tablet was dissolved in 200 mL of methanol and the amount of terbutaline sulfate was assayed spectrophotmetrically at 280.5 nm. Ethylcellulose nor any of the tablet excipients interfered at this wavelength. Each determination was performed in triplicate.

In vitro dissolution

The USP basket method was used for all the in vitro dissolution studies. Distilled water containing 0.02 % polysorbate-80 was used as the dissolution media. An appropriate amount of microcapsules equivalent to 50 mg of terbutaline sulfate or a 300 mg tablet was transferred into 500 mL of dissolution fluid at 37±0.1°C and stirred at 100 r.p.m. Five milliliters samples were taken at appropriate intervals and filtered through a 0.45 Millipore filter. After the samples were taken 5 mL of fresh dissolution media was returned to the dissolution vessels to maintain a constant volume. The samples were analyzed by measuring the UV absorbance at 276.7 nm. Drug concentration in each sample solution was calculated from a standard curve.

When the effect of dissolution media pH on the release of terbutaline sulfate from the microcrocapsules was studied, the dissolution medium consisted of simulated gastric (pH=1.2), simulated intestinal (pH=7.5), phosphate buffer (pH=5.8), and citric acid buffer (pH=2.8), all containing 0.02 % polysorbate-80.

The in vitro dissolution of terbutaline sulfate microcapsules was performed on triplicate samples of the same batch. The in vitro dissolution from the tableted microcapsules was reported as the mean of 6 determinations.

Release kinetics

A Dissolution Evaluation Program "DISS", developed in our laboratories by W.A. Ritschel and C.K. Oh (7) was used for the evaluation of the microcapsule drug release kinetics.

For this study the amount of drug released (mg) versus time (hours) data was evaluated for zero-order, Higuchi square-root of time, Hixon-Crowell and first-order models. The period of evaluation was the time range where 20 % to 80 % of the drug was released or the entire dissolution test period in cases where less than 80 % was released during the dissolution test.

Preparation of tablets

For the tableting studies ethylcellulose microcapsules with a mean size of 362.5 μm with a polymer to drug ratio of 2:1 were used. These microcapsules had a release profile close to our target of not more than 60 % terbutaline sulfate released in 6 hours and not less than 80 % terbutaline sulfate released in 8 hours.

Tablets were compressed using an instrumented Manesty D3B tablet press. Standard concave punches of 0.9 cm diameter were used. The compression pressure varied from 26.78 MPa to 107.11 MPa depending on the formulation.

The tablet formula consisted of the amount of microcapsules equivalent to 15 mg of terbutaline sulfate, 1 % magnesium stearate, and the appropriate amount of Avicel^{R} or Avicel^{R}/ Emcompress^{R} blend (2:1) for a tablet weight of 300 mg.

Batches of 50 grams were prepared for compression. The microcapsules and excipients were mixed in a Turbula mixer for 12 minutes at 25 r.p.m.

RESULTS AND DISCUSSION

As the polymer to drug ratio was increased the microcapsule geometric mean size decreased (Table 1) and for a given microcapsule size the release of terbutaline sulfate at 6 hours decreased significantly (Figures 1 and 2). The polymer to drug

TABLE 1
Effect of polymer to drug ratio on the microcapsule mean size.

Polymer	Polymer: Drug ratio	Geometric mean diameter* (geometric standard deviation)
CAB	1:1	660.89 (1.45)
	2:1	618.25 (1.36)
	3:1	550.22 (1.37)
EC	1:1	728.02 (1.33)
	2:1	563.70 (1.34)
	3:1	491.74 (1.23)

* μm

ratio was varied keeping the amount of polymer and solvent constant in all cases and decreasing the amount of drug used. The reduction in microcapsule size with increasing polymer to drug ratio may be due to a decrease in the viscosity of the internal phase as a result of a decrease in the concentration of solids in the polymer solution. These results agree with results reported by Pongpaibul and Whitworth (8).

The decrease in release of terbutaline sulfate at 6 hours of dissolution testing as the polymer to drug ratio increased may be possibly due to the formation of thicker walls. This is supported by a reduction in the drug content of the microcapsules with higher polymer to drug ratios. In other studies it was observed that thicker walls were obtained as the polymer to drug ratio increased (9-10).

CAB microcapsules released terbutaline sulfate significantly slower than EC microcapsules at 6 hours of dissolution testing at the 2:1 ($p=0.0054$) and 3:1 ($p=0.015$) polymer to drug ratio.

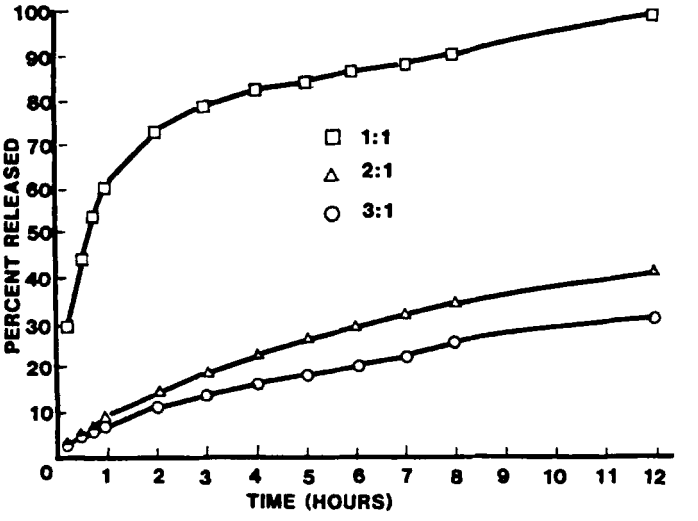

FIGURE 1

Effect of cellulose acetate butyrate:terbutaline sulfate ratio on the drug release from 512.5 um microcapsules.

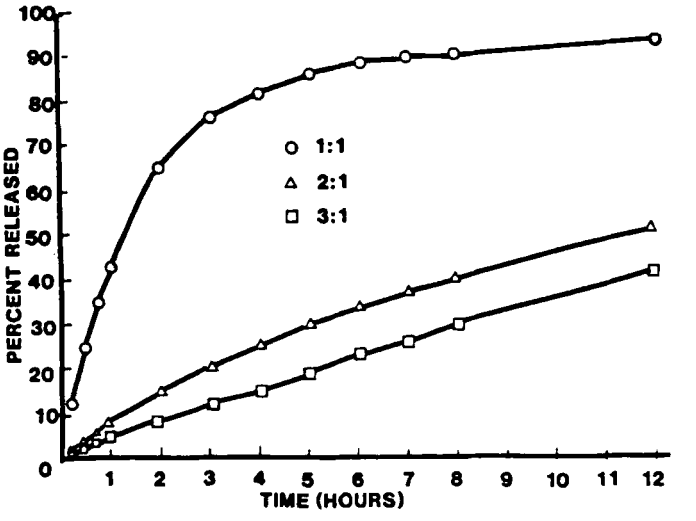

FIGURE 2

Effect of ethylcellulose:terbutaline sulfate ratio on the drug release from 512.5 um microcapsules.

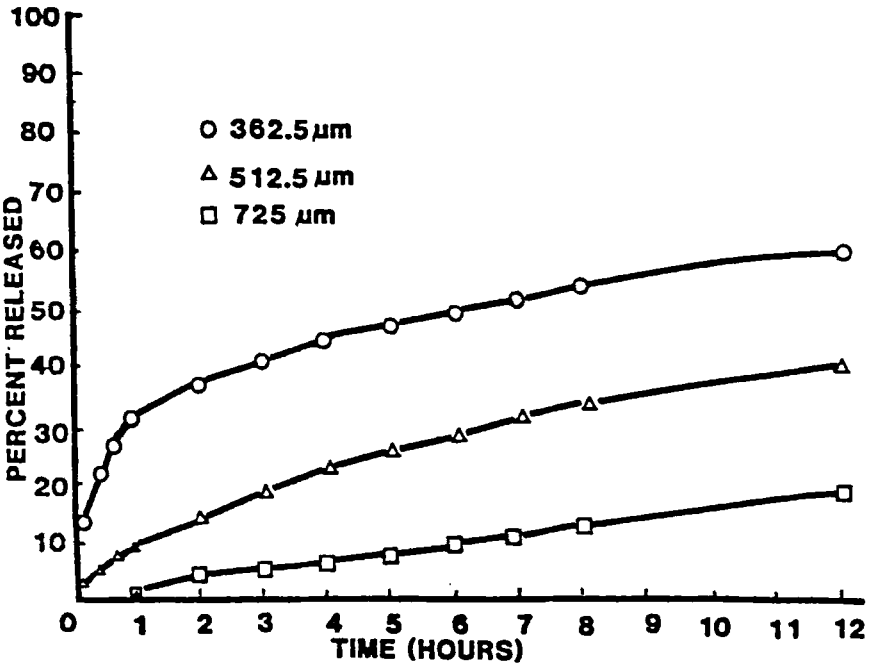

FIGURE 3

Effect of microcapsule mean size on the release of terbutaline sulfate from CAB microcapsules with a 2:1 polymer to drug ratio.

As expected, at a constant polymer to drug ratio of 2:1 the CAB microcapsules with a mean size of 362.5 µm released the drug significantly faster than the 512.5 µm and 725 µm microcapsules (Figure 3). The terbutaline sulfate content of these microcapsules was not significantly different ($p=>0.2968$), therefore the faster drug release from the smaller size microcapsules may be explained by the larger surface area of the smaller size microcapsules. Previous studies (9, 11-12) obtained similar results when microcapsules of different fraction sizes were studied.

For the EC microcapsules the 256 µm microcapsules released the drug significantly slower than the 362.5 µm and the 512.5 µm

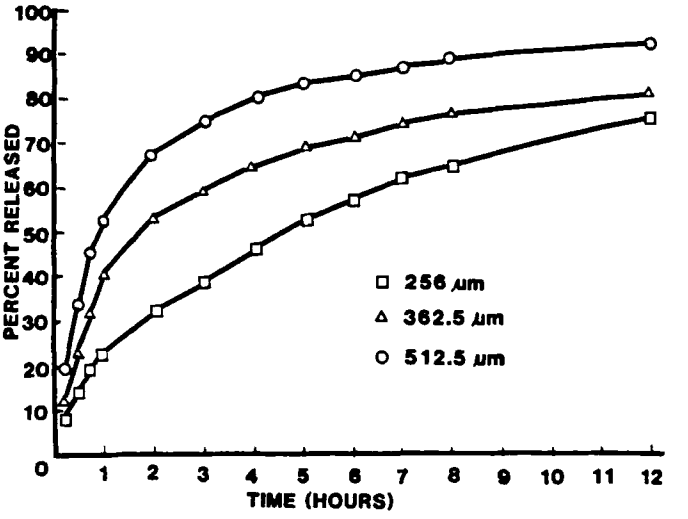

FIGURE 4

Effect of microcapsule mean size on the release of terbutaline sulfate from EC microcapsules with a 2:1 polymer to drug ratio.

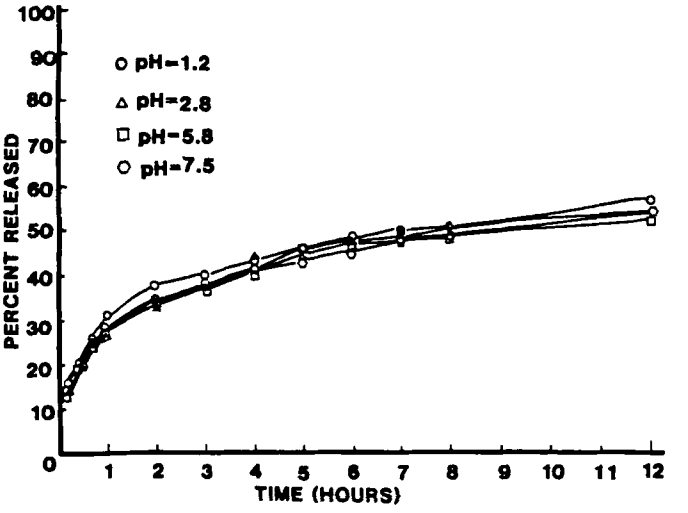

FIGURE 5

Effect of dissolution media pH on the release of terbutaline sulfate from CAB microcapsules with a 2:1 polymer to drug ratio.

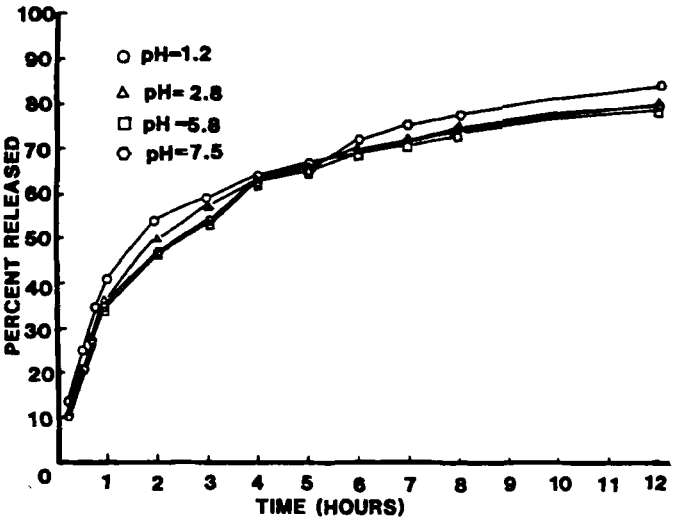

FIGURE 6

Effect of dissolution media pH on the release of terbutaline sulfate from EC microcapsules with a 2:1 polymer to drug ratio.

microcapsules (Figure 4). The drug content of these microcapsules showed that there was significantly more ($p=<0.05$) polymer present in the 256 μm microcapsules. For the EC microcapsules the slower release of terbutaline from the smaller size microcapsules may be due to the effects of increased wall thicknesss surpassing the effects of increased surface area. This behaviour was observed previously by Oya-Alpar and Walter (13) who noticed that the bigger size microcapsules were aggregates of smaller ones and that the dissolution was influenced by the irregular shapes and surfaces. Kawashima et al. (14) attributed the faster drug release of the larger size microcapsules to a decrease in wall thickness.

The release of terbutaline sulfate from CAB and EC microcapsules was independent of the pH of the dissolution media (Figures 5 and 6).

In order to obtain meaningful information for the release models, the drug release profiles were fitted to various models

Table 2
Comparisons of correlation coefficients from dissolution data fit to various release models

Polymer:drug ratio	Range [% released]	I Zero Order	II Square Root	III Hixon Crowell	IV First Order	Statistics α=0.05
Cellulose acetate butyrate						
1:1	0.25-5 hrs. [85]	0.8999 (0.0059)	0.9571 (0.0039)	0.9483 (0.0053)	0.9669 (0.0067)	II/IV p=0.0616
2:1	0.25-24 hrs. [55]	0.9303 (0.0041)	0.9951 (0.0009)	0.9565 (0.0041)	0.9678 (0.0042)	II/IV p=0.0001 III/IV p=0.0051
3:1	0.25-24 hrs. [41]	0.9525 (0.0002)	0.9981 (0.0002)	0.9670 (0.0006)	0.9734 (0.0006)	II/IV p=0.0001 III/IV p=0.0001
Ethylcellulose						
1:1	0.25-5h hrs. [83]	0.9353 (0.0023)	0.9793 (0.0013)	0.9687 (0.0026)	0.9808 (0.0024)	II/IV p=0.4270
2:1	0.25-24 hrs. [70]	0.9443 (0.0036)	0.9971 (0.0004)	0.9777 (0.0021)	0.9894 (0.0014)	II/IV p=0.0029
3:1	0.25-24 hrs. [65]	0.9872 (0.0033)	0.9875 (0.0027)	0.9986 (0.0007)	0.9994 (0.0003)	III/IV p=0.6610

( )=±standard deviation

and a Duncan multiple comparison test (α=0.05) was performed on the correlation coefficents to select the model which yielded the best fit. Table 2 summarizes the correlation coefficients for the different release kinetics models for the CAB and EC microcapsules formulated with a 1:1, 2:1 and 3:1 polymer to drug ratio.

Models with higher correlation coefficients were judged to be a more appropriate model for the dissolution data. In comparing correlation coefficients between models, p values larger than the selected significant level (α=0.05) indicate no significant difference between the correlation coefficients.

For the CAB microcapsules with a 1:1 polymer to drug ratio the first-order and square-root of time models were not

distinguishable up to 5 hours of dissolution testing where 85 % of the drug was released. For the CAB microcapsules with a 2:1 and 3:1 polymer to drug ratio the release models were tested for the entire dissolution test of 24 hours because of the slow drug release. The square-root of time release model was followed for the 2:1 and 3:1 polymer to drug ratio.

For the EC microcapsules formulated with a 1:1 polymer to drug ratio there was no significant difference between the square-root of time and the first-order release models. For the 2:1 and 3:1 polymer to drug ratios, the release models were tested for the range up to 24 hours of dissolution testing because of the slow drug release. For EC microcapsules formulated with 2:1 polymer to drug ratio the square-root of time model was followed, whereas for those formulated with a 3:1 polymer to drug ratio drug release could not be differentiated between the Hixon-Crowell and first-order release models.

Ethylcellulose microcapsules with a 2:1 polymer to drug ratio had the release profile closest to our previously described desired target. However, the percent yield of microcapsules in the size range from 300 μm to 425 μm was only 16 %. In order to increase the amount of microcapsules within this range, which was the desired size for the tableting studies, the preparative stirring speed was increased to 1400 r.p.m. This modified method increased the yield of the desired microcapsule fraction to 39 %. These microcapsules had a T50% (time to release 50 % of the drug) of 4 hours and met our release profile target, and were, therefore, used in the tableting studies.

Tablets formulated with an Avicel^R/Emcompress^R blend (2:1) were compressed at 26.78 MPa, 53.56 MPa and 107.11 MPa. Tablets formulated with Avicel^R were compressed at 26.78 MPa, 40.17 MPa and 53.56 MPa. For tablets formulated with Avicel , compression pressures of 53.56 MPa and higher produced capping. All tablets disintegrated in less than 10 minutes during the dissolution test for both formulations.

When the microcapsules were compressed with the blend of Avicel^R/Emcompress^R at 26.78 MPa, 53.56 MPa and 107.11 MPa the T50% was decreased to approximately 1 hour, whereas prior to compression the T50% was 4 hours. Figure 7 shows the effect of compression pressure on the drug release from the tableted microcapsules. A Student Newman-Keuls test on the T50% showed that there was no significant difference between the compression pressures.

Figure 8 shows the effect of compression pressure on the release of terbutaline sulfate from the tableted microcapsules

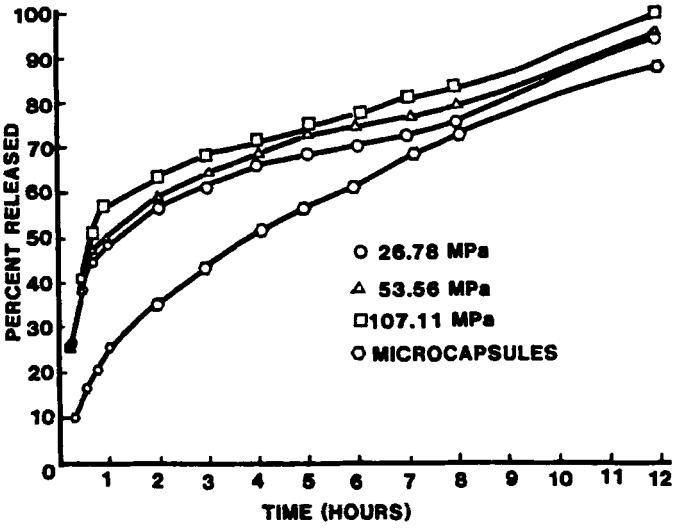

FIGURE 7

Effect of compression pressure on the release of terbutaline sulfate from tablets containing Avicel/Emcompress (2:1).

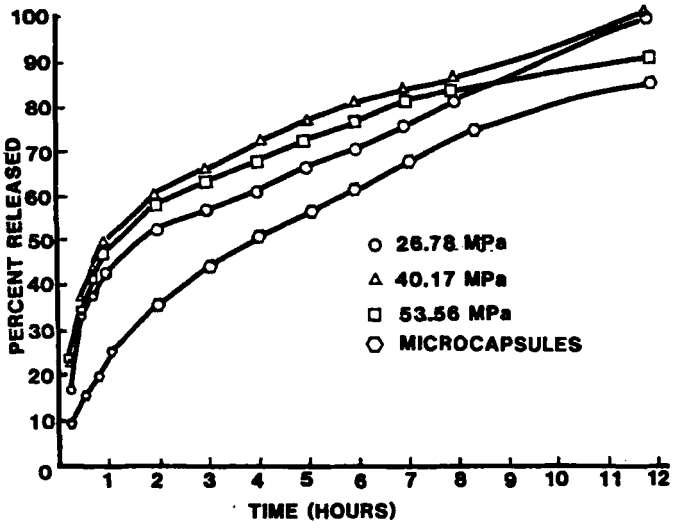

FIGURE 8

Effect of compression pressure on the release of terbutaline sulfate from tablets containing Avicel.

formulated with Avicel^{R}. The T50% was reduced to between 1 and 2 hours compared a T50% of 4 hours for uncompressed microcapsules. A Student Newman-Keuls test showed that there was significant decrease in the T50% when the compression pressure was increased from 26.78 MPa to 40.17 MPa. There was no signficant difference in the T50% between compression pressures of 40.17 and 53.56 MPa.

Other studies showed opposite results. Sayed and Price (15) found that the tablets containing 40 % microcapsules, 55 % microcrystalline cellulose and 5 % carboxymethyl starch, and compressed at pressures ranging from 35.1 MPa to 351 MPa did not exhibit a change in the dissolution charactersitics compared to the microcapsules before compression. Sakr and Oyola (16) found that the release profiles of tablets formulated with either 1:1 or 1:2 Avicel^{R} to microcapsules were not different from that of microcapsules prior to compression, over a range of applied pressures.

CONCLUSIONS

1. Sustained release for terbutaline sulfate was succesfully obtained by microencapsulation using an emulsion-solvent evaporation technique.
2. Higher polymer to drug ratios decreased the microcapsule size and the drug release.
3. Smaller CAB microcapsules released terbutaline sulfate faster, whereas smaller EC microcapsules released terbutaline sulfate slower.
4. In vitro drug release showed no pH dependance.
5. This technique produced CAB and EC microcapsules with a complex release kinetics where it could not be distinguished between the square-root of time and first-order release mechanisms, when formulated with a 1:1 polymer to drug ratio. CAB microcapsules formulated with a 2:1 and 3:1 polymer to drug ratio followed the Higuchi square-root of time release model. EC microcapsules formulated with a 2:1 polymer to drug ratio followed the square-root of time release model but the release kinetics could not be differentiated between the Hixon-Crowell and first-order release models when a 3:1 polymer to drug ratio was used.
6. The T50% was significantly decreased when the microcapsules were formulated into a tablet. An initial burst effect was observed, followed by a slow release second portion. This is indicative that not all the microcapsules were fractured upon compression.

ACKNOWLEDGMENTS

The authors appreciate the assistance given by Dr. W.A. Ritschel in the use of the "DISS" computer program. The authors would like to acknowledge Merrell Dow Pharmaceuticals for the donation of terbutaline sulfate and Hercules Incorporated for providing ethylcellulose to this project.

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