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PREPARATION AND FORMULATION OF SUSTAINED-RELEASE TERBUTALINE SULPHATE MICROCAPSULES

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في محاولة للحصول على مستحضرات لها تأثير ممتد المفعول لعقار "التربيوتالين" عن طريق الفم تم دراسة التفاعل السطحى العكسى بين العقار وبعض الطفليات المعروفة بخصائصها الإدمصاصية متمثلة فى كل من السابونايت ، البنتونايت ، الاتبولجيت واللابونايت.

ومن دراسة خاصية الإدمصاص لهذه الطفليات وجد أن السابونايت يعطى أعلى درجة أمتزاز للعقار عند الأس الإيدروجينى ٧ ولقد أوضحت الدراسة أن التبادل الأيونى الموجب هو الميكانيكية الرئيسية المسئولة عن التفاعل الإدمصاصى بين العقار والطفليات وبدراسة معدلات الإنطلاق للعقار من هذه المحملات وجد أن تحميل العقار على السابونايت يعطى معدل أنطلاق بطئ.

وقد تم تحقيق أنطلاق ممتد المفعول بواسطة حوصلة العقار المحمل على الطفليات بإستخدام بيوتارات اسيتات السيليلوز كمادة مغلفة.

وبتقييم هذه المحملات المتحوصلة علاجيا فى عدد من مرضى الربو الشعبى أثبتت الدراسة الحصول على تأثير ممتد المفعول للعقار.

In an attempt to achieve sustained action for the oral administration of terbutaline sulphate (TBL), its surface - reversible interaction with several clays such as saponite, bentonite, attapulgite and laponite was studied. Adsorption studies indicated that, saponite showed the greatest adsorption of the drug among the tested clays. The maximum adsorption occurred at pH 7. The cationic exchange was considered as the main mechanism responsible for interaction between the drug and clays. The drug-saponite sorbate showed slight retardation of drug dissolution. Successful sustained release formulation of the drug was achieved by microencapsulation of the drug sorbate using cellulose acetate butyrate as coating material. Sustained bronchodilator responses after administration of this double-barrier formulation was confirmed in patients suffering from reversible chronic air flow obstruction.

INTRODUCTION

Prolongation of the duration of action of bronchodilators has received considerable interest.[1-6] Terbutaline sulphate is a bronchodilator frequently used for long-term treatment of chronic obstructive airway disease as well as acute bronchospasm. It is given in small doses and has a short duration of action.[7] For these reasons formulation of terbutaline in sustained release oral-dosage form is clinically recommended.[8,9] Although the literature contains numerous applications of silicates in pharmaceutical dosage forms due to their useful technological properties,[10-12] few reports had shown the value of silicates in slow release oral formulations.[13-15] Microencapsulation of drug substances is a useful tool in drug delivery for masking the bad taste and odour, for the protection from the environmental conditions and for the control of the release of the encapsulated drug.[16]

Sustained release microcapsule preparations have frequently been prepared by dispersing drug particles in polymer matrices where the polymer is to act as a rate-controlling barrier.[17]

Various microencapsulation processes such as phase-separation coacervation, interfacial

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deposition techniques utilizing complex-emulsion, interfacial polymerization and spray drying have been developed to achieve sustained release action of drugs.[18] The emulsion solvent evaporation method has been widely used for the formulation of different drugs onto microcapsules using various polymeric materials.[19-21]

The purpose of the present work was to develop oral sustained release terbutaline dosage form employing the interaction of terbutaline with silicate carriers followed by microencapsulation of the obtained drug-carrier sorbates.

MATERIALS AND METHODS

Equipment

Shaker with thermostated water bath (Seti Co., Cairo, Egypt); double beam spectrophotometer UV-150-02 (Shimadzu, Japan); X-ray difractometer PW 1700/1710 (Philips, Netherland); vitalometer, (Warren E. Collins Inc., Braintree, Mass, USA); Scanning electron microscope (JSM-25, Jeik Co., Japan); Centrifuge (DT-51, Germany).

Materials

Terbutaline sulphate (TBL), Bentonite (Sigma Co., St. Louis, USA), Saponite (Venderbilt Chemial Co., Norwalk, Conn., USA), Laponite XLS (Laporte Inorganics Co. Ltd., Laporte, UK), Attapulgite (Pharmasorb regular, Engelhard, Edison, USA), Cellulose acetate butyrate [CAB] (Sci. Polymer Products Inc., Ontario, New York, USA). Simulated gastric and intestinal fluids (USP XXI) without enzymes and containing 0.02% tween 80 were prepared. All other materials were analytical grade chemicals.

Methods

Adsorption study

An accurately weighed 200 mg of each clay was transferred to 50 ml glass stoppered conical flask. Nine ml of distilled water was added to each flask. The flasks were shaken for 1 hour then allowed to stand for 24 h for clay hydration. The pH of clay suspension was adjusted to the desired pH (6.7 & 8) by adding 1 ml of HCl solution of appropriate concentration. Drug solutions of varying concentrations (5-25 mg/ml) were prepared in distilled water. Ten ml of each of these solutions were added to the clay suspensions. The flasks were mechanically shaken at 50 rpm in a thermostatically controlled water bath adjusted at 25° for 2 h (the predetermined equilibrium time). Exposure to direct sunlight was avoided through the experiment. At the end of this period the suspension was centrifuged at 5000 rpm for 5 minutes. Aliquots were taken from the supernatant and assayed spectrophotometrically at 279 nm against blank similarly treated.

Preparation of drug-saponite sorbate

Nine grams of saponite was hydrated in 10 ml of distilled water in a porcelain dish. The pH of saponite suspension was adjusted to 7 using 0.1 N HCl solution. One gram of the drug (drug/saponite ratio, 1:10) was dissolved in 20 ml distilled water and the solution was added to the clay while kneeding with a pestle. Kneeding was continued for 30 min. The drug-saponite sorbate was dried to a constant weight for 3 days at 30° over P_2O_5 under vacuum. The dried sorbate was ground and passed through 125 μm sieve to ensure uniformity. The product was kept in a desiccator over P_2O_5 until use.

Powder X-ray diffraction

Powder X-ray diffraction patterns of the drug, adsorbent and sorbates were obtained using difractometer, Cu K radiation (1.5418), nickel filter, 50 KV, 40 mA. All samples were kept in a desiccator over P_2O_5 for 3 days before recording the X-rays diffraction patterns.

Microencapsulation of drug-carrier sorbate

Microencapsulation was performed using emulsion-solvent technique[22] for pure drug and drug-saponite sorbate. Cellulose acetate butyrate (CAB) containing 10% w/w polyethylene glycol 4000 was used as a coating material at a core : coat ratio of 1:1. Four grams of the coating material was dissolved in 40 ml acetone. Similar

weights either pure drug or drug-sorbate were dispersed in the coating solution. The dispersion was added while stirring at appropriate rate (500 rpm) to 150 ml of liquid paraffin containing 2% w/v sorbitan monooleate. Stirring was continued under cooled air stream till complete evaporation of acetone (about 5 hours). The formed microcapsules were separated by filtration through 90 μ sieve, washed with n-hexane, collected and left to dry at 30° for 24 h. The dried microcapsules were fractionated into different sieve fractions using a set of standard sieves.

Sealing of microcapsules

Approximately one hundred of microcapsules were added to 50 ml of hard paraffin-n-hexane (2% w/v) mixture in a porcelain dish. The suspension was shaken for 10 minutes at 150 rpm using a small magnet and a magnetic stirrer. The microcapsules were separated by filtration and left to dry overnight.

Yield analysis

The total weight of the dried microcapsules of different fraction size from each batch was determined. The yield (%) was determined using the following equation:

$$\text{Yield \%} = \frac{\text{weight of the collected microcapsule}}{\text{total weight of core and coating materials}} \times 100$$

Determination of drug content of microcapsules

Five samples each of 25 mg were taken from each batch of microcapsules. The microcapsules were crushed separately in a glass mortar. The mortar contents were quantitatively transferred to a centrifuge tube with 10 ml 0.1 N HCl solution. The suspension was subjected to ultrasonic waves for 10 min to ensure complete extraction of the drug. The suspension was centrifuged and the supernatant was transferred to a 100 ml volumetric flask. The extraction process was repeated three times and the extract was collected in the volumetric flask. The volume was adjusted by the same medium and drug concentration was determined spectrophotometrically at 279 nm against blank similarly treated.

Dissolution studies

Appropriate amounts of microcapsules equivalent to 4 mg of the drug were introduced into the cups of USP dissolution apparatus. The dissolution medium was 300 ml of simulated gastric fluid (pH 1.2) or simulated intestinal fluid (pH 7.4). The dissolution medium was kept at 37° ±0.2 and stirred at 50 rpm. Samples of 5 ml were withdrawn at suitable time intervals and immediately filtered using Millipore membrane filter (0.4 um). The drug concentration was assayed spectrophoto-metrically at 279 nm.

Clinical evaluation

Sealed drug-sorbate microcapsules (200-315 um) were tested clinically to evaluate the sustained-release properties of terbutaline formulation. Amounts of the microcapsules, each containing 4 mg of the drug, were filled into hard gelatin capsules. A uniform mixture of the drug with lactose was prepared and amounts each equivalent to 2.5 mg of the drug were filled into capsules (regular formulation). The preparations were tested in six patients suffering from reversible chronic air flow obstruction. No other medications were taken during the study. Each subject received one capsule of regular formulation three times daily for one week and one capsule of the drug-saponite microcapsule twice daily for another week with an interval of one week between the two medications. The forced expiratory volume in one second (FEV_1) was measured using Collins Vitalometer before drug administration and then through two readings taken at 10 AM and 10 PM every day during medication. The relative FEV% was estimated using the following equation:

$$\frac{\text{Average of 7 days readings of FEV during medication}}{\text{Reading of FEV before medication}} \times 100$$

Any signs of improvement or side effects were observed in patients during the period of treatment.

RESULTS AND DISCUSSION

Adsorption of TBL onto various clays

For selection of the most appropriate clay and optimum conditions for loading the drug adsorption study was conducted. Figure 1 demonstrates the adsorption isotherms of TBL to various clays at pH 7 and 25°. The amount of the drug adsorbed x/m (mg/g) is plotted against the equilibrium concentration Ce (mg/100 ml). Different extents of drug adsorption onto various clays were observed. The limiting adsorptive capacity (b) of different adsorbents were calculated in terms of Langmuir equation (Figure 2).

$$Ce / y = 1/ab + Ce/b$$

The limiting adsorptive capacities of different adsorbents presented in Table 1 followed the sequence:

saponite > bentonite > attapulgite > laponite

The variation in adsorption efficacy of these clays are attributed to the difference in the structural functional groups of these adsorbents.[23,24]

The pH dependent adsorption of terbutalin sulphate on saponite at 25° is evident in Figure 3. The adsorption of the drug decreases in acidic medium (pH 6). This might be attributed to competition between the hydrogen ions and terbutaline cations on binding sites of silicate surface. These results indicated that the cation exchange is the main mechanism responsible for adsorption of TBL onto saponite.

The X-ray diffraction patterns of TBL, saponite, and drug-saponite sorbate are shown in Figure 4. The X-ray diffractogram of the drug-saponite sorbate shows no diffraction peaks due to drug crystals. This indicated that the drug exists in a molecularly adsorbed state.

Evaluation of TBL sorbate microcapsules

Microencapsulation of drug sorbate was investigated as an effective second dissolution barrier. Electron scanning micrographs of TBL microcapsules prepared by the use of CAB as a coating material and drug loaded onto saponite as a core, in 1:1 ratio showed spherical microcapsules with continuous wall and smooth surface (Figure 5). The microcapsules of terbutaline-saponite sorbate exhibited a higher encapsulation efficiencies (>98.0%) than those of microcapsules prepared with pure drug (Table 2) and produced good yield (about 94%) in comparison with the yield of drug loaded-microcapsules (about 87%).

In-vitro release studies

Dissolution from different size-range microcapsules indicated that the microcapsules of size range (200-315 um) exhibit a slower drug release than those having larger size range (315-400 um) (Figures 6,7). This can be attributed to the fact that smaller microcapsules have a more thicker polymer coat.[25] Microcapsules of drug-saponite sorbate showed a slower drug release than those of pure drug (Figure 8) because of the presence of double barrier for drug dissolution. There was no significant difference between the extent of drug dissolution in simulated gastric fluids (pH 1.2) compared to that in simulated intestinal fluids (pH 7.4). This can be explained in view of independence of the permeability of the coating material on the pH of the dissolution medium.

In-vivo evaluation of TBL microcapsules

The FEV_1 was reported as the best single test for assessing bronchodilator responses.[26] Figure 9 shows the relative forced expiratory volume (FEV%) after oral administration of TBL regular (2.5 mg twice daily) and sustained release formulations (4 mg twice daily). There was no significant difference between the improvement in respiratory function due to administration of the drug in regular or sustained release formulation. The patients do not suffer from any unpredictable side effects nor attacks during treatment with the investigated sustained-release formulation.

Table 1: Calculated values of Langmuir constants (a) and (b) of TBL onto various clays at pH 7 and 25°.

Clay	r	$ax10^2$	b (mg durg/g clay)
Laponite	0.91	20.10	89
Attapulgite	0.99	19.71	136
Bentonite	0.97	24.79	213
Saponite	0.99	23.63	304

r: regression coefficient of the line (Ce/Y vs Ce).
a: activity coefficient.
b: limiting adsorptive capacity.

Table 2: Drug content of TBL microcapsules prepared using CAB as a coating material and either pure drug or drug loaded onto saponite as a core (1:1) [100 mg samples].

Fraction size	Pure drug		Drug sorbate	
	Theoritical	Found	Theoritical	Found
90-200 μm	50 mg	46.42 mg (2.41)*	10 mg	9.89 mg (0.28)*
200-315 μm	50 mg	48.15 mg (2.26)*	10 mg	9.94 mg (0.17)*
315-400 μm	50 mg	48.89 mg (2.94)*	10 mg	10.08 mg (0.23)*

* Standard deviation.

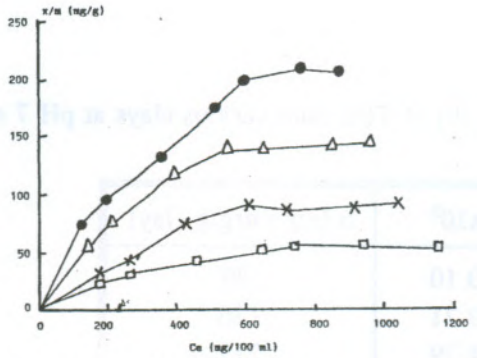

Fig. 1: Adsorption isotherm of TBL onto various clays at pH 7 and 25°.
(●) saponite; (Δ) bentonite; (x) attapulgite; (□) laponite.

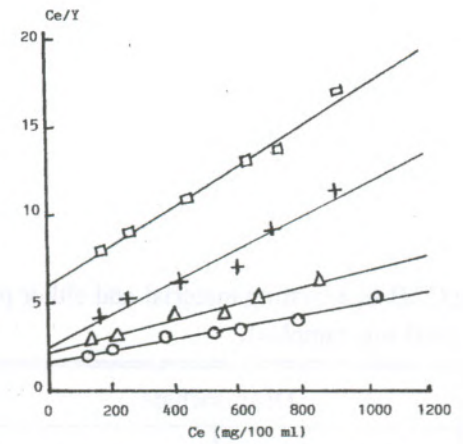

Fig. 2: Langmuir adsorption of TBl onto various clays at pH 7 and 25°.
(○) saponite; (Δ) bentonite; (x) attapulgite; (□) laponite.

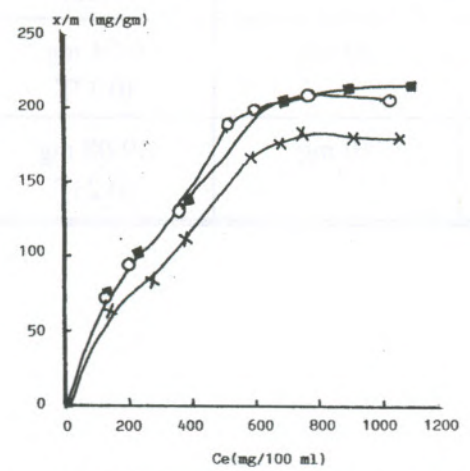

Fig. 3: Adsorption isotherm of TBL onto saponite at various pHs and 25°.
(x) pH 6; (■) pH 7; (○) pH 8.

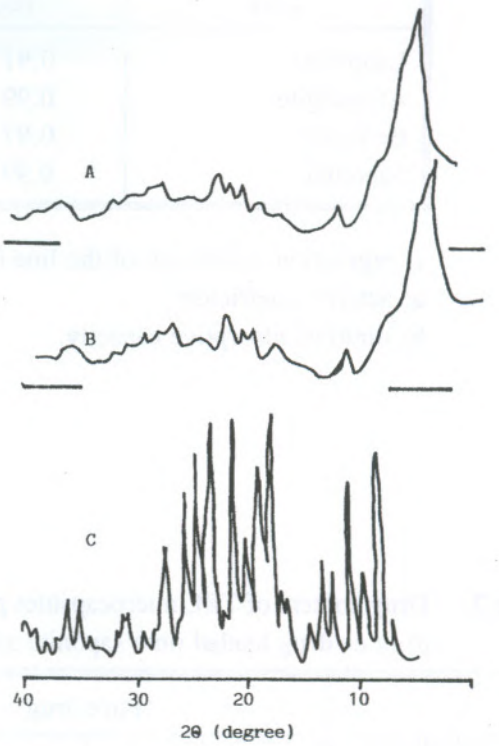

Fig. 4: Powder X-ray diffraction patterns of:
A- terbutaline-saponite sorbate.
B- saponite.
C- terbutaline sulphate.

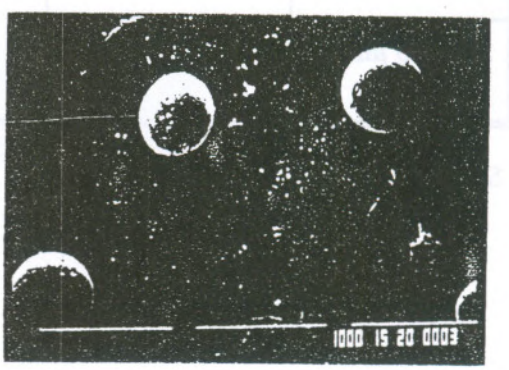

Fig. 5: Electron scanningmicrographs of microcapsules prepared using CAB as a coating material and drug loaded onto saponite as a core (1:1 ratio).

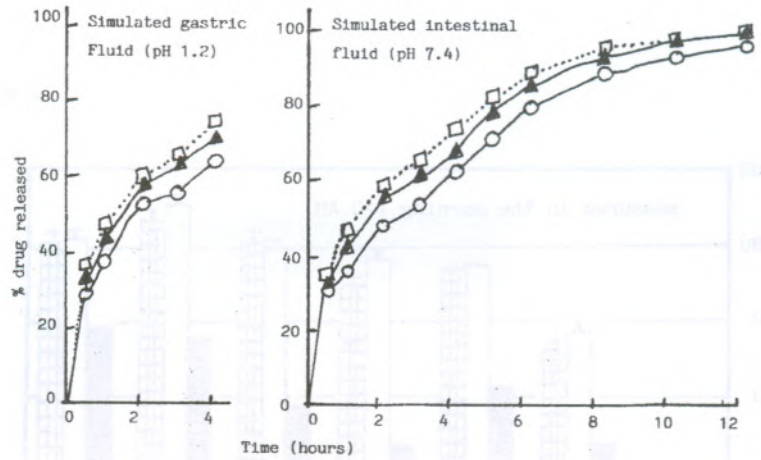

Fig. 6: *In-vitro* release of TBL from its microcapsules prepared using CAB as a coating material and pure drug as a core (1:1). (○) 90-200 μm; (▲) 200-315 μm; (□) 315-400 μm.

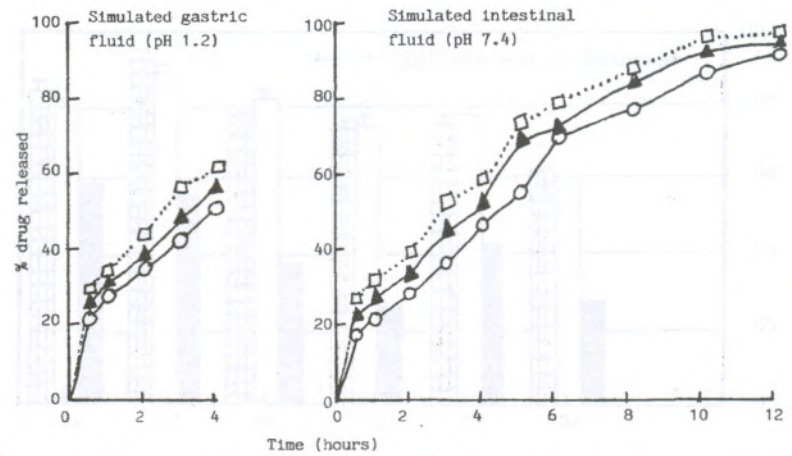

Fig. 7: *In-vitro* release of TBL from its microcapsules prepared using CAB as a coating material and drug loaded onto saponite as a core (1:1).
(○) 90-200 μm; (▲) 200-315 μm; (□) 315-400 μm.

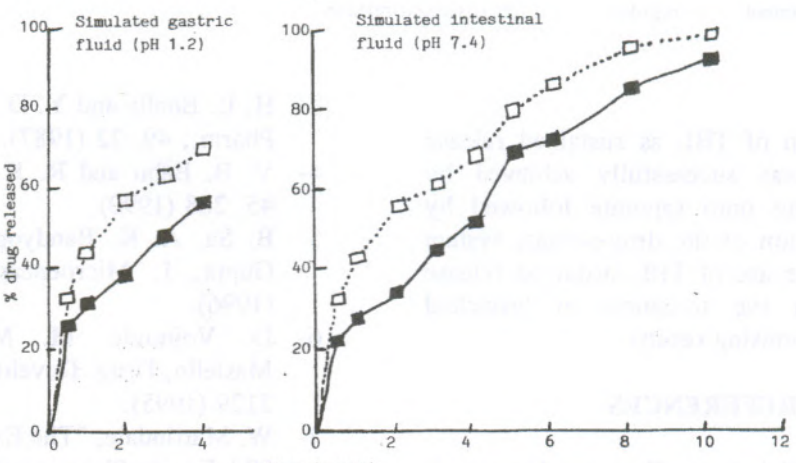

Fig. 8: *In-vitro* release of TBL from its microcapsules prepared using CAB as a coating material and either (□) pure drug or (■) drug-saponite sorbate as a core (1:1), fraction size 200-315 μm.

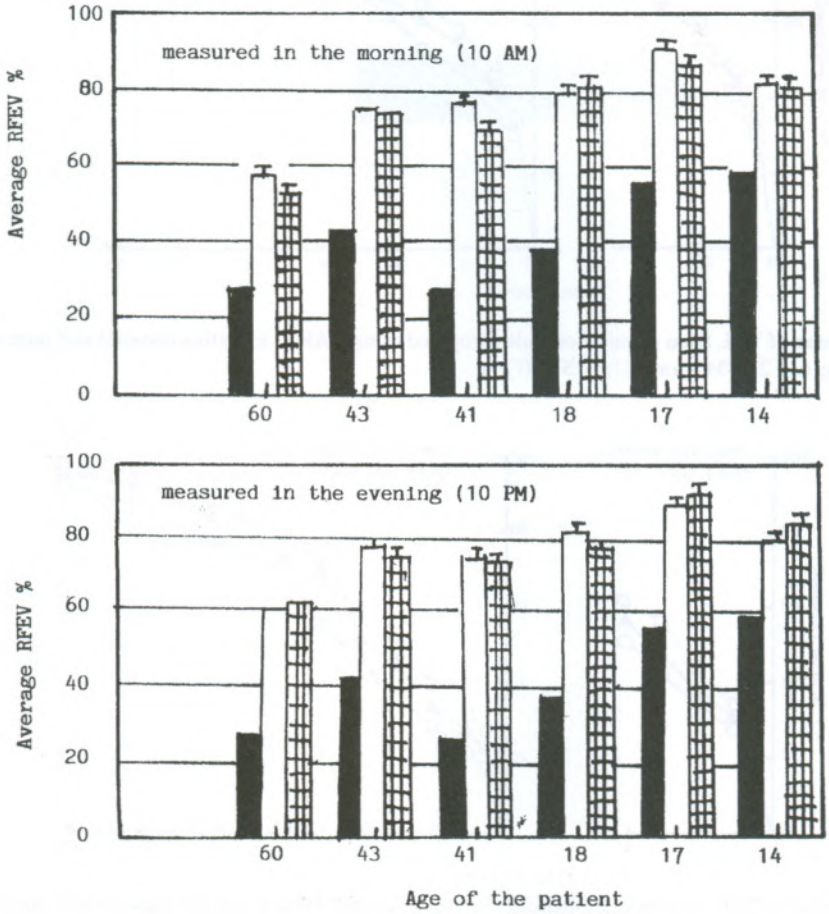

Fig. 9: Relative forced expiratory volume (FEB %) after oral administration of TBL regular and sustained-release formulations.
■ before treatment □ regular ⊞ sustained-release.

Conclusion

Formulation of TBL as sustained release dosage form was successfully achieved by loading the drug onto saponite followed by microencapsulation of the drug-sorbate system using CAB. The use of TBL sustained release formulation for the treatment of bronchial asthma gave promising results.

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