Original Article

Formulation and bioavailability of controlled release salbutamol sulphate tablets using natural additives

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ABSTRACT: Salbutamol sulphate granules and physical mixtures were prepared using mastic with various natural additives. The prepared granules and physical mixtures were examined using IR and DSC. The obtained results indicate that there is no interaction between salbutamol sulphate and the formulation ingredients used. The physical properties and release behavior of the formulated tablets prepared from granules and physical mixtures were evaluated and showed good physical properties. The rate of drug release from tablets prepared from granules was found to be lower than that prepared from physical mixtures at fixed mastic concentration and the same additive. The rate of drug release decreased with increased mastic concentration in formulated tablets. Pectin and sodium alginate allowed the best controlled release rate of the drug. On the basis of the results obtained from the controlled release studies, selected sulbutamol formulations were subjected to an *in vivo* comparison with commercial sulbutamol tablets. The pharmacokinetic parameters AUC_{0-24}, C_{max}, and T_{max} of sulbutamol from the selected formulation were determined after administration of a single oral dose of 8 mg and compared statistically using an ANOVA test. There was no significant difference in the AUC_{0-24}. On the other hand, there was a significant difference in the C_{max} and T_{max} between the commercial and the formulated tablets. These results demonstrate that the formulated tablets extended the time of the drug effect.

Keywords: Salbutamol sulphate, natural additives, tablets, dissolution rate, *in vivo* studies

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1. Introduction

Salbutamol sulphate has a selective action on beta-2 adrenergic receptors. It is used as a bronchodilator in the management of bronchial asthma and in some patients with chronic obstructive pulmonary disease (*1*). Control of asthma may be achieved using a controlled-release formulation of salbutamol. This also serves to increase patient compliance (*2*). Several techniques were developed to formulate salbutamol sulphate in controlled release drug delivery systems; microcapsules of salbutamol sulphate were prepared using ethyl cellulose (*3*), beeswax and carnauba wax (*4*) as coating materials. Eudragit RS30D-coated controlled-release pellets of salbutamol were prepared using an air suspension technique (*5*). Prabakaran *et al.* (*6*) have developed an oral osmotic system to deliver both theophylline and salbutamol sulphate simultaneously. This approach helped to produce extended drug release as well as reduce the problems associated with multi-drug asthma therapy. Hydroxy propyl methyl cellulose hydrophilic-matrix tablets containing encapsulated or unencapsulated salbutamol sulfate were investigated (*7*). Also, Sirkia *et al.* (*8*) developed prolonged release press-coated salbutamol sulphate tablets.

Mastic is a natural oleoresin exudate obtained from the stem and main leaves of a cultivated variety of *Pistacia lentiscus* var. (*9*). Panagopoulou and Georgarakis (*10*) and Abd El-Aleem (*11*) used mastic as a binder in tablet production. Also, many authors combined mastic with microcapsule cores in microencapsulation of many substances (*12-14*). The previous studies have proved that mastic results in larger/compact particles with no pores and a much slower release; and consequently controlled drug release.

The aim of this study was to formulate sulbutamol controlled release tablets using mastic as a natural polymer and to find any possible interaction between salbutamol sulphate and mastic. The study was extended to investigate the bioavailability of the formulated tablets compared to commercial brands.

2. Materials and Methods

2.1. *Materials*

Salbutamol sulphate was kindly supplied by Amriya Pharm. Ind. Co., Alexandria, Egypt. Pectin was obtained from Winlab, a division of Wilfrid Smith, UK. Sodium alginate and lactose monohydrate were from El Nasr Pharmaceutical Chemical Co., Cairo, Egypt. Mastic (commercial grade) was from Chios' Gum Mastic Growers Association. Avicel PH 101 was from Fluka AG, Buchs, Switzerland. Bis-(2-ethylhexyl) phosphate (lot No. 05411ED-107) was from Aldrich.

2.2. *Preparation of drug physical mixtures and granules*

In a total of 200 mg of powder mixture 8 mg drug in combination with 40 mg mastic and with the rest made up of pectin were mixed thoroughly in a mortar to prepare a physical mixture. Other proportions of mastic (60 and 90 mg) were used to prepare more physical mixtures. Pectin was replaced by sodium alginate, avicel or lactose individually in the same amounts to prepare other formulations. In each of the formulations, the mastic concentration was equivalent to 20, 30, and 40% of tablet weight.

The granules were prepared by wetting the powder mixtures with the smallest possible amount of chloroform to make doughy masses. The obtained masses were converted into granules by forcing them through a sieve with a No. 2 mm mesh. The granules obtained were dried at room temperature for 24 h in open air and further dried at 40°C for 48 h in a hot air oven.

2.3. *Infrared (IR) studies*

Using an infrared spectrophotometer (UV 150-02, double beam spectrophotometer, Shimadzu, Kyoto, Japan), the IR spectra of each salbutamol sulphate, mastic, pectin, sodium alginate, avicel, and lactose were investigated using a KBr disc method from 4,000-400 cm^{-1}. Also, the IR spectra of the physical mixtures and granules of 1:1 ratio of drug to each of mastic, pectin, sodium alginate, lactose, or avicel were studied.

2.4. *DSC studies*

Using a differential scanning calorimeter (Model DSC-50, Shimadzu), DSC thermograms of all samples tested by IR were performed at a heating rate of 10°C/min in a nitrogen atmosphere. The sample (5 mg) was placed in the aluminum pan of the instrument and the scanning started up to 500°C against indium in the reference pan.

2.5. *Formulation of tablets*

Salbutamol sulphate physical mixtures and granules were mixed with 1% magnesium stearate as a lubricant and compressed into tablets each weighing 200 mg. All batches were prepared using a single punch Eraweka tablet press (G.M.B.H., Germany) at constant pressure.

2.6. *Evaluation of tablets*

The prepared tablets were tested for uniformity of weight, thickness, content, friability percent, hardness, tensile strength, and disintegration time.

2.7. *Release study*

Sulbutamol sulphate release from different formulated tablets was performed using the USP basket six jar dissolution apparatus. A round bottom dissolution container containing 250 mL of phosphate buffer, pH 7.4, was immersed in a constant temperature water bath and allowed to equilibrate at 37 ± 0.2°C. A single tablet was placed in the basket and the position of the basket stirrer was kept at a fixed position from the bottom of the dissolution container and rotated at a speed of 50 rpm. Two mL samples were withdrawn at different time intervals. The withdrawn sample was replaced with the same volume of fresh dissolution medium after each sampling. Samples were measured spectrophotometrically at 276 nm. Mean values for six experiments were taken for each batch.

2.8. *Analysis of the release data*

The release data were analyzed according to zero, first order, a diffusion model, and the Peppas equation.

2.9. *Bioavailability study*

Tablet formulations containing 40% mastic with pectin (formula **A**) or sodium alginate (formula **B**) which gave acceptable physical characteristics and best controlled drug release behavior, were chosen for the *in vivo* study. These formulations were compared with commercial tablets (2 tablets of Salbovent Forte each contains 4 mg of salbutamol sulphate).

Male albino rabbits weighing 2.0-2.5 kg were randomly selected for the bioavailability study. The animals were divided into three groups and each group was comprised of six rabbits. Each group received one of the tested formulas namely, formula **A**, formula **B**, or the commercial one. The animals were fasted over night before tablet administration and during the experiment and had free access to water. A single dose (8 mg sulbutamol) of the tested tablets was given orally to the each rabbit using a balling gun to deliver the tablets to the animal stomach. The ear vein was cannulated with a butter fly scalp No.19 needle and blood samples (2 mL) were withdrawn from the vein before dosing (zero time) and at different intervals after dosing *viz.* 1, 2, 3, 5,

8, 12, and 24 h using heparinized tubes. The collected samples were immediately centrifuged and plasma was separated and stored at -20 °C until analysis.

2.10. *Analysis of plasma levels of salbutamol sulphate*

The high performance liquid chromatographic method using chloramphenicol as the internal standard (*15*) was applied in this study. The HPLC system consisted of Series 200 LC pump, sidewinder column heater, Series 200 vacuum degasser, 600 Series LINK interface, Series 200 UV/visible detector (Perkin Elmer, Waltham, MA, USA) and a reversed-phase column Bindapak RP-C18 (5 µm particle size, 300 × 3.9 mm, i.d., Waters, Milford, MA, USA).

To 0.5 mL of plasma sample, 20 µL of internal standard (100 µg/mL) was added. The drug was extracted from plasma using 5 mL chloroform containing 0.1 M bis-(2-ethylhexyl) phosphate. The chloroform layer was subsequently extracted with 1 mL of 0.5 M HCl. The mobile phase was 70:20:10 (v/v) of water, methanol, and acetonitrile, respectively. The pH was adjusted to 2.5 using 10% phosphoric acid and samples were degassed using sonication. Fifty µL of the sample was injected manually. Peaks were monitored using UV absorbance at 276 nm. Quantification of salbutamol sulphate was obtained by plotting salbutamol sulphate to the internal standard peak area ratio as a function of sulbutamol sulphate concentration.

2.11. *Statistical analysis*

The one way analysis of variance (ANOVA) statistical analysis (F-test) at a confidence interval of 5% was applied to estimate any difference between the tested tablets with respect to AUC, C_{max} and T_{max}. A statistics *t*-test was also performed between each pair of the formulations at a confidence interval of 5% (*16*).

3. Results and Discussion

3.1. *Infrared spectroscopy*

The IR spectrum of salbutamol sulphate alone (Figure 1, trace A) shows the same characteristic peaks as reported in the literature (*17*). The IR spectra of physical mixtures (Figure 1, trace C) and granules (Figure 1, trace D) of 1:1 salbutamol sulphate with each of pectin, sodium alginate, mastic, lactose, and avicel (data not shown), respectively, did not provide any difference compared to that of the drug alone. This finding indicated that there was no interaction between salbutamol sulphate and the applied additives.

3.2. *DSC study*

The DSC thermogram of salbutamol sulphate alone

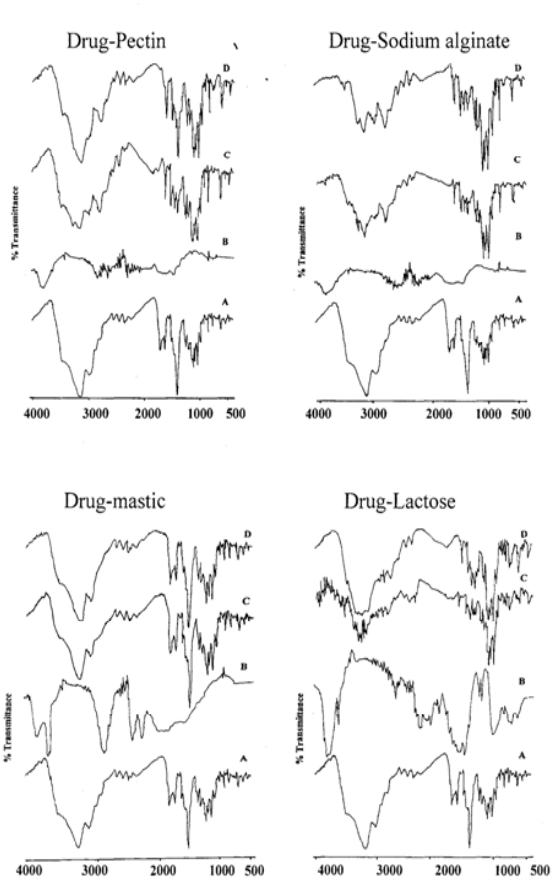

Figure 1. IR spectra of salbutamol sulphate (A), each ingredient alone (B), drug-additive physical mixture (C) and granules (D).

(Figure 2, trace 1) shows an endothermic melting peak with an onset at 190.93°C which reached a maximum peak at 204.58°C. The DSC thermograms of pectin, sodium alginate, mastic, and lactose are shown in trace 2 of Figure 2. The pectin thermal profile demonstrates one broad endothermic peak at 78.41°C (with onset and end set temperatures of 39.54 and 136.26°C, respectively) and an exothermic peak at 258.23°C. This finding is different from that reported by Nurjaya and Wong (*18*). They stated that the thermogram of unprocessed pectin was characterized by two endothermic peaks at melting temperatures of about 148.4 and 163.7°C and exothermic peak at 233.9 ± 0.4°C. Sodium alginate showed a broad exothermic peak at 245.54°C indicating the decomposition of the polymer at that particular temperature (*19*). The thermogram of mastic showed a broad endothermic peak at 71.27°C corresponding to its melting. The lactose thermogram showed two endothermic melting peaks at 145.45 and 219.63°C and agrees very well with literature values (*20*). The thermogram of avicel (data not shown) illustrates a broad endothermic peak at 336.39°C.

The thermal profiles of the drug-lactose physical mixture and granules exhibited two endothermic

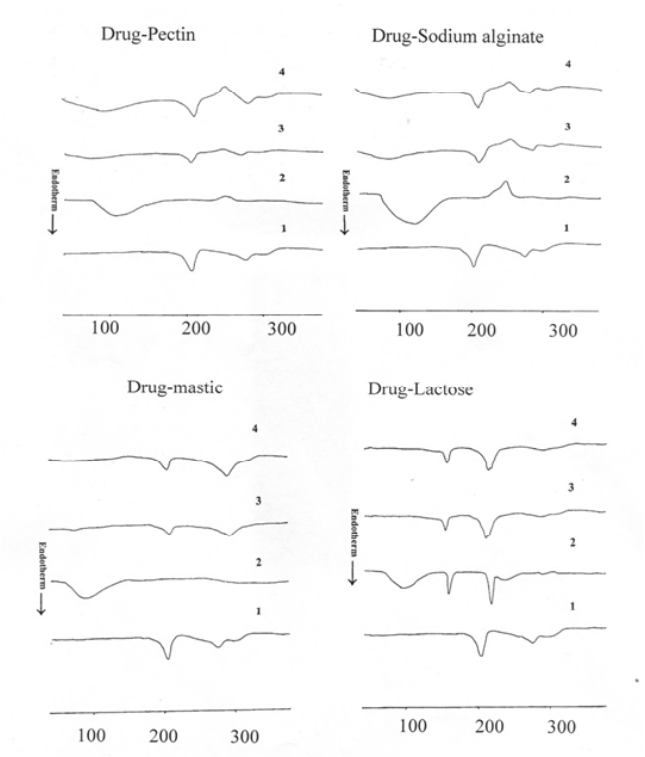

Figure 2. DSC themograms of salbutamol sulphate (1), each additive alone (2), drug-additive physical mixture (3) and granules (4).

peaks corresponding to the dehydration and fusion of lactose, respectively, and no peak was present associated with the melting of the drug. The thermal behavior of both physical mixture and granules of drug in lactose indicated the ease of dispersion and/or dissolution of the drug into the molten mass of lactose. These findings are similar to that reported in the literature (*20,21*).

The DSC thermograms of the granules of salbutamol sulphate with each of mastic, pectin, sodium alginate, lactose (Figure 2, trace 4) and avicel (data not shown) are similar to their respective physical mixtures (Figure 2, trace 3). These results demonstrated that salbutamol sulphate did not interact with the chosen additives.

3.3. *Physical characteristics of salbutamol sulphate tablets*

3.3.1. *Uniformity of weight, thickness, and contents*

All tablets showed a good weight uniformity with CV ranging from 1.26 to 3.52 (Table 1). The thickness of tablets (the range of CV, 0.75-2.96) correlates well with tablet weight. All the prepared tablets showed a good average content (CV, 2.32-4.59) which complies with the requirements of USP XXVII (*22*).

Table 1. Physical characteristics of salbutamol sulphate tablets (8 mg) prepared from physical mixture powders and granules containing different concentrations of mastic and additive

Additive Type	Methods of powder preparation	Mastic (%)	Physical parameter of tablets						
			Mean weight (mg)	Mean thickness (mm)	Average drug content (mg)	Friability (%)	Hardness (kg)	Tensile strength (kg/cm^2)	Disintegration time (min)
Pectin	Physical mixture	20	206.5	2.70	7.44	0.77	5.23	13.69	--*
		30	201.4	2.62	7.36	0.67	5.83	15.73	--*
		40	200.6	2.59	7.87	0.64	7.47	20.39	--*
	Granules	20	202.2	2.67	7.44	0.80	5.68	14.90	--*
		30	198.4	2.35	8.03	0.78	6.93	20.84	--*
		40	202.3	2.66	7.78	0.73	8.09	21.50	--*
Sodium alginate	Physical mixture	20	206.1	2.52	7.69	0.94	4.36	12.23	--*
		30	203.4	2.48	8.01	0.88	5.00	14.25	--*
		40	198.4	2.45	7.48	0.85	5.83	16.82	--*
	Granules	20	205.4	2.59	7.74	0.89	5.23	14.27	--*
		30	200.6	2.50	7.44	0.84	5.66	16.00	--*
		40	203.7	2.54	7.58	0.80	6.82	18.98	--*
Lactose	Physical mixture	20	201.0	2.47	7.62	1.12	3.72	10.64	69.54
		30	203.4	2.51	8.37	0.94	4.62	13.01	76.72
		40	197.3	2.45	8.03	0.90	5.77	16.65	98.30
	Granules	20	205.6	2.53	7.58	0.92	5.24	14.64	--*
		30	198.2	2.45	7.49	0.89	5.82	16.79	--*
		40	200.7	2.48	7.84	0.82	6.12	17.44	--*
Avicel	Physical mixture	20	198.9	2.64	7.78	0.64	8.11	21.71	3.53
		30	203.7	2.78	8.42	0.59	8.23	20.93	5.31
		40	198.5	2.72	8.34	0.53	8.94	23.23	7.23
	Granules	20	201.5	2.80	8.19	0.69	7.95	20.07	11.55
		30	196.3	2.71	8.03	0.62	8.50	22.17	20.57
		40	200.6	2.76	8.26	0.50	9.79	25.07	32.64

* Tablets did not disintegrate for 3 h.

3.3.2. *Mechanical properties*

The obtained results of friability percent and hardness showed that all tablets have friability percents less than 1% and hardness values (Table 1) which comply with USP XXVII (*22*) requirements except the tablets prepared from the 20% lactose physical mixture which showed a friability % of 1.12 and a hardness of 3.72 kg. The friability percent decreased and hardness increased with an increase of mastic concentration in the tablets. This may be due to the increase in the binding effect of mastic with an increase in its concentration. The highest hardness values obtained were for tablets containing avicel. Both the hardness values and tensile strength increased with an increase of mastic concentration in tablets. Small values of friability percent imply much less friability during transportation, which is important in terms of sustained release of tablets (*23*).

3.3.3. *Disintegration time*

The tablets containing pectin and sodium alginate as well as tablets containing lactose prepared by granulation did not disintegrate for 3 h (Table 1). Tablets prepared with pectin and sodium alginate did not disintegrate because they form a hydrophilic non-disintegrated matrix. However, the non-disintegration of the tablets prepared from granules containing lactose may be due to the coating of the particles by the mastic.

In contrast, the tablets prepared from physical mixtures containing lactose disintegrate by erosion and those containing avicel prepared from granules and physical mixtures disintegrated. The disintegration time of tablets containing avicel was longer for those prepared from granules (11.55-32.64 min) compared to those prepared from physical mixtures (3.53-7.23 min). The increased disintegration time with the increase of mastic concentrations in tablets may be attributed to the enhancement of the binding action of mastic (*11*).

3.3.4. *Release studies*

The release rate of salbutamol sulphate from tablets made from granules was lower than that of tablets prepared from physical mixtures at fixed mastic concentrations using the same additive such as pectin (Figure 3). The lower release from granules can be explained because mastic solutions act as a binder forming large compact particles which are surrounded by a film of mastic (*11*). When comparing drug release from tablets containing various mastic concentrations, drug release was retarded by an increase in mastic concentration. This may be attributed to the hydrophobic nature of mastic gum which reduces the penetration of solvent molecules into the tablet matrix and therefore retards the wetting and dissolution of drug (*14*,*24*).

The release of salbutamol sulphate from tablets containing 40% mastic with various additives prepared from physical mixtures and granules is shown in Figure 4. The release rate of drug from tablets containing different additives at constant mastic concentration and the method of preparation can be arranged in the following order: Pectin < Sodium alginate < Lactose < Avicel.

The hydrophilic jelly nature of pectin and sodium alginate is responsible for the sustained release of drug from tablets containing them. These polymers upon contact with aqueous medium start to absorb water and as a consequence the polymers swell forming a gel layer. This layer increases in thickness as time passes creating a considerable barrier for both penetration of solvent into the tablets and drug release from it (*25*).

The pectin based tables sustain drug release more than the sodium alginate based tablets due to the difference in viscosity and swelling properties of the

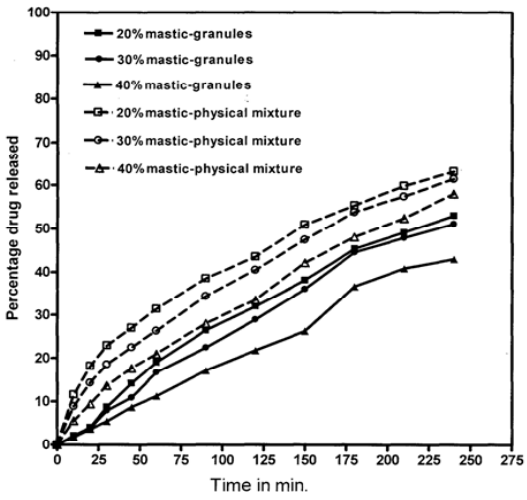

Figure 3. Release profile of salbutamol sulphate tablets prepared from physical mixtures and granules containing pectin as additive and different concentrations of mastic.

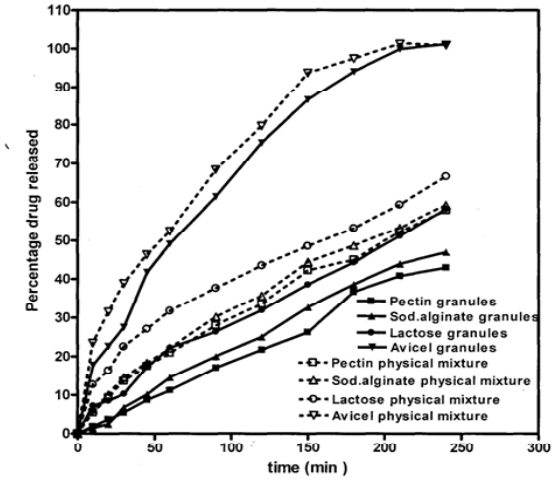

Figure 4. Effect of different additives on the release of salbutamol sulphate from tablets prepared from physical mixtures (---) and granules (—) containing 40% of mastic.

Table 2. Analysis of release data of salbutamol sulphate tablets from tablets containing mastic with different additives using different kinetic models

Additives	Methods of powder preparation	Mastic (%)	Zero order		Diffusion		Peppas equation	
			K (%) × 100	r^2	K (%/$\sqrt{\text{min}}$)	r^2	n	r^2
Pectin	Physical mixture	20	2.29	0.981	0.416	0.998	0.52	0.997
		30	2.25	0.962	0.415	0.997	0.60	0.998
		40	2.16	0.962	0.339	0.991	0.65	0.997
	Granules	20	2.19	0.933	0.399	0.996	0.84	0.980
		30	2.16	0.989	0.365	0.986	0.92	0.989
		40	1.80	0.992	0.339	0.964	1.00	0.998
Sodium alginate	Physical mixture	20	2.53	0.972	0.456	0.991	0.60	0.994
		30	2.39	0.979	0.434	0.986	0.63	0.993
		40	2.27	0.980	0.416	0.994	0.70	0.998
	Granules	20	2.26	0.979	0.411	0.989	0.88	0.968
		30	2.21	0.993	0.399	0.987	0.97	0.977
		40	1.97	0.993	0.373	0.986	1.00	0.979
Lactose	Physical mixture	20	2.59	0.979	0.470	0.986	0.64	0.998
		30	2.23	0.976	0.405	0.985	0.64	0.981
		40	2.17	0.986	0.397	0.978	0.69	0.978
	Granules	20	2.67	0.892	0.471	0.989	0.53	0.992
		30	2.54	0.941	0.450	0.994	0.48	0.993
		40	2.26	0.945	0.397	0.988	0.51	0.993

polymers (*26*). On the other hand, the tablets containing lactose gave a relatively lower release rate of drug compared to those containing avicel. This is due to the fact that avicel based tablets disintegrated during release and the lactose based tablets were subjected to erosion due to the dissolution of lactose.

Tablets containing 40% mastic prepared from granules containing pectin or sodium alginate produced the most sustained release compared to other tablets. These tablets are a suitable candidate to control the release of salbutamol sulphate and their bioavailability will be studied.

3.4. *Analysis of release data*

Table 2 illustrates the analysis of the release data of salbutamol sulphate from the different tablet formulations using zero and first order kinetics (data not shown), diffusion models, and the Peppas equation. The tablets containing avicel prepared from physical mixtures and granules did not follow any kinetic model because of their disintegration (data not shown).

The results of analysis indicate non-Fickian release ($0.5 < n < 1$) for all tablet formulations except those containing 40% mastic and prepared from granules containing pectin or sodium alginate. The non-Fickian release means that the drug release occurred by diffusion and erosion of the tablet matrix (*27*). However, the tablets containing pectin and sodium alginate prepared from granules at 40% mastic follow zero-order release as indicated by $n = 1$ and high regression coefficients.

3.5. *Bioavailability of salbutamol sulphate*

Sulbutamol mastic tablet formulations that generate the best controlled release pattern were selected for this study. These formulas contained 40% mastic and pectin (formula **A**) or sodium alginate (formula **B**). The bioavailability of the controlled release tablet formulations was studied by administration of a single dose containing 8 mg drug or two commercial tablets (2 × 4 mg) to rabbits (4 mg/kg).

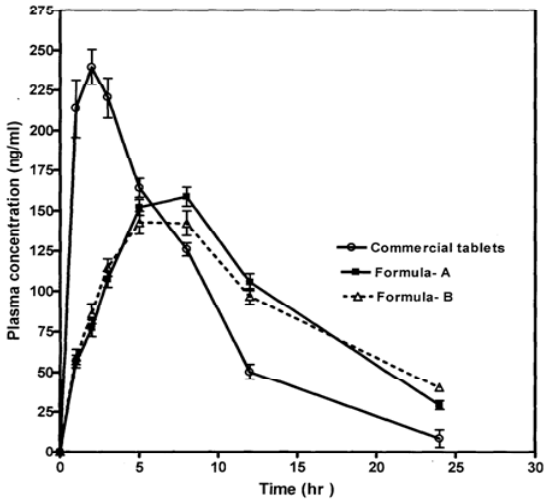

Figure 5. Mean plasma concentration-time curve of salbutamol sulphate after administration of a single dose of formula A, B and two commercial tablets each containing 4 mg.

The mean plasma concentration curve of salbutamol sulphate after oral administration of formulated tablets **A** and **B** was compared with that of the commercial sulbutamol tablets (Figure 5). The plasma sulbutamol profiles of the two mastic formulated tablets were similar and were nearly superimposed, while these

Table 3. Individual numerical values of T_{max}, C_{max}, and AUC_{0-24} of formulated and commercial tablets of salbutamol sulphate in rabbit plasma

Rabbit	Formula **A**			Formula **B**			Commerical tablets		
	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-24} (ng/mL•h)	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-24} (ng/mL•h)	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-24} (ng/mL•h)
I	8.0	158.5	2,203.0	8.0	146.1	1,959.8	1.0	257.8	2,286.6
II	8.0	175.0	2,117.9	5.0	155.5	2,287.9	2.0	264.9	1,981.5
III	8.0	173.0	2,408.8	5.0	148.9	2,137.3	1.0	261.6	1,838.1
IV	5.0	158.3	2,056.8	8.0	161.3	2,352.6	3.0	256.0	2,057.6
V	5.0	172.4	2,261.7	5.0	164.1	2,140.0	2.0	264.6	2,151.6
VI	8.0	160.4	2,442.2	8.0	166.1	2,219.6	1.0	240.2	2,195.2
Mean	7.0	166.2	2,248.4	6.5	157.0	2,182.8	1.66	257.5	2,085.1
S.D.	1.5	7.9	154.4	1.64	8.2	137.7	0.75	9.2	161.0

profiles were completely different from the plasma profile of the commercial tablets (Figure 5).

Pharmacokinetic parameters (C_{max}, T_{max}, and AUC_{0-24}) for each rabbit were calculated on the basis of concentration-time data. From individual pharmacokinetic parameters, their mean values ± S.D. were obtained and are shown in Table 3 for both the formulated tablets and commercial sulbutamol tablets.

The mean sulbutamol C_{max} were 166.2 ± 7.9, 157 ± 8.2, and 257.5 ± 9.2 ng/mL and occurred at T_{max} 7.0 ± 1.5, 6.5 ± 1.64, and 1.66 ± 0.75 h after administration of a single 8 mg dose of formula **A**, formula **B**, and commercial tablets, respectively. The results showed that the C_{max} of the commercial tablets was greater than that of formulated tablets. In addition, the T_{max} of the commercial tablets was shorter than that obtained from the formulated tablets. These results demonstrate that the formulated tablets extended the time of drug effect.

The mean AUC_{0-24} of formula **A**, formula **B**, and the commercial tablets were 2,248.4 ± 154.4, 2,182.8 ± 137.7, and 2,085.1 ± 161 ng/mL•h, respectively. The ANOVA test of the AUC results ($F_{0.05}$ = 1.768) revealed that there is no significant difference in AUC between the different tablets indicating that all tested tablets were equivalent in the extent of drug absorption.

The obtained results revealed that all of the tested sulbutamol sulphate formulas are equivalent in the AUC. The formulated tablets **A** and **B** have a longer T_{max} and smaller C_{max} compared to the commercial tablets. These results demonstrate prolonged salbutamol sulphate plasma concentrations compared to the commercial tablets. Similar results were reported by Hernández *et al.* (*28*) who worked on two sustained formulations of salbutamol sulphate, commerical immediate release formulation, and osmotic pump. Also, Sirkia *et al.* (*8*) found that the bioavailability parameters of salbutamol sulphate prolonged release press-coated tablets and the commercial reference have statistically no difference in AUC but a significant difference in C_{max} values in humans.

4. Conclusion

The incorporation of mastic in the formulation of salbutamol sulphate tablets has a great effect in delaying drug release. Both the method of treatment of powders and type of additives affected the drug release from the tablets. Tablets prepared from granules and containing 40% mastic with pectin or sodium alginate showed the best control of drug release. Formula **A** (containing pectin and mastic), formula **B** (containing sodium alginate and mastic) achieved the targets of the present study in controlling drug release and good bioavailability.

References

1. Parfitt K. Martinale: The complete drug reference, 32nd ed. Pharmaceutical Press, Taunton, MA, USA, 1999; pp. 758-761.
2. Mulligan S, Devane J, Martin M. Pharmacokinetic characteristics of a novel controlled-release sprinkle formulation of salbutamol. Eur J Drug Metab Pharmacokinet. 1991; 3:312-314.
3. Yazan Y, Demirel M, Guler E. Preparation and *in-vitro* dissolution of salbutamol sulphate microcapsules and tabletted microcapsules. J Microencapsul. 1995; 12:601-607.
4. Raghuvanshi RS, Tripathi KP, Jayaswal SB, Singh J. Release kinetics of salbutamol sulphate from wax coated microcapsules and tableted microcapsules. J Microencapsul. 1992; 9:449-455.
5. Govender T, Dangor CM, Chetty D. Microencapsulated Eudragit RS30D-coated controlled release pellets: the influence of dissolution variables and topographical evaluation. J Microencapsul. 1997; 14:1-13.
6. Prabakaran D, Singh P, Kanaujia P, Jaganathan KS, Rawat A, Vyas SP. Modified push-pull osmotic system for simultaneous delivery of theophylline and salbutamol: development and *in-vitro* characterization. Int J Pharm. 2004; 284:95-108.
7. Lin SY, Tau J, Wu WH, Chang HN. Biopharmaceutic evaluation of controlled-release hydrophilic-matrix tablets containing encapsulated or unencapsulated salbutamol sulfate. Current Therapeu Res. 1992; 2:486-492.
8. Sirkia T, Makimartti M, Liukko-Sipi S, Marvola M.

Development and biopharmaceutical evaluations of a new press-coated prolonged-release salbutamol sulphate tablet in man. Eur J Pharm Sci. 1994; 1:195-201.
9. Martindale: The Extra Pharmacopoeia, 28th ed. The Pharmaceutical Press, London, UK, 1982; p. 315.
10. Panagopoulou A, Georgarakis M. Effect of compression and diluent on drug release from mastic matrix tablets. A statistical analysis. Drug Dev Ind Pharm.1990; 16:637-646.
11. Abdel-Aleem HM. Formulation and evalution of mastic in antacid preparations. Alex J Phar Sci. 1996; 10:65-68.
12. Georgarakis M, Groning R, Henzler P. Microencapsulation of potassium chloride with mastic. Pharmazie. 1987; 42:455-456.
13. Assimopoulou AN, Papageorgiou VP, Kiparissides C. Synthesis and release studies of shikonincontaining microcapsules prepared by the solvent evaporation method. J Microencapsul. 2003; 20:581-596.
14. Assimopoulou AN, Papageorgiou VP. Preparation and release studies of alkannin containing microcapsules. J Microencapsul. 2004; 21:161-173.
15. Sutariya VB, Mashru RC, Sankalla MG, Sankalla JM. Liquid chromatographic determination and pharmacokinetics study of salbutamol sulphate in rabbit plasma. Ars Pharm. 2006; 47:185-197.
16. Kirkwood BR. Essential of Medical Statistics. The Blackwell Science Ltd., UK, 1988; pp. 41-57.
17. Moffat AC, Osselton MD, Widdop B. Clarke's Analysis of Drug and Poisons in Pharmaceutical, Body Fluids and Postmortem Material, 3rd ed. Pharmaceutical Press, London, UK, 2004; pp. 1546-1447.
18. Nurjaya S, Wong TW. Effects of microwave on drug release properties of matrices pectin. Carbohydrate Polymers. 2005; 62:245-257.
19. Gonzalez-Rodriguez ML, Holgada MA, Sanchez-Lafuente C, Rabasco AM, Fini A. Alginate/chitosan particulate systems for Diclofenac sodium release. Int J Pharm. 2002; 232:225-234.
20. Cavallari C, Albertini B, Rodriguez L, Rabasco AM, Fini A. Release of indomethacin from ultrasound dry granules containing lactose-based excipients. J Control Rel. 2005; 102:39-44.
21. Fini A, Moyano JR, Gines JM, Perez-Martinez JI, Rabasco AM. Diclofenac salts, II. Solid dispersion in PEG 6000 and Gelucire 50/13. Eur J Pharm Sci. 2005; 60:99-111.
22. U.S.P. The United States Pharmacopoeia, 27th revision. United States Pharmacopeial Convention Inc., The Board of Trustees, Washington, USA, 2004; pp. 2396, 2397, 2621, 2622.
23. Savaser A, Ozkan Y, Isimer A. Preparation and *in-vitro* evaluation of sustained release tablets formulations of diclofenac sodium. J Pharmaco. 2005; 60:171-177.
24. Kuksal A, Tiwary AK, Jain NK, Jain S. Formulation and *in vitro-in vivo* evaluation of extended-release matrix tablets of Zidovudine: Influence of combination of hydrophilic and hydrophobic matrix formers. AAPS PharmSciTech. 2006; 7:E1.
25. Efentakis M, Koligliati S, Vlachou M. Design and evalution of drug coated drug delivery systems with an impermeable cup, swellable top layer and pulsatile release. Int J Pharm. 2006; 311:147-156.
26. Gursoy A, Cevik S. Sustained release properties of alginate microsphers and tabletted microsphers of diclofenac sodium. J Microencapsul. 2000; 17:565-575.
27. Peppas NA. Analysis of fickian and non-fickain drug release from polymers. Pharm Acta Helv. 1985; 60:110-111.
28. Hernández RM, Gascón AR, Calvo MB, Caramella C, Conte U, Domínguez-Gil A, Pedraz JL. Correlation of '*in-vitro*' release and '*in-vivo*' absorption characteristics of four salbutamol sulphate formulations. Int J Pharm. 1996; 139:45-52.

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