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DESIGN OF SUSTAINED RELEASE FORMULATIONS OF SALBUTAMOL 1- ION-EXCHANGE RESIN SYSTEMS

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ABSTRACT

Ion-exchange resins were used in an attempt to prepare sustained release products of salbutamol. Different types of cation-exchange resins were tested namely; Amberlite IRP-69, Amberlite IR-120, Amberlite MB-1, Amberlite CG-50 and Amberlite IRC-50. The drug was loaded onto resins using the batch process. The effect of drug concentration and the resin forms on the loading capacity of resins were tested. The drug release patterns from its resinates were studied. The release rates were too high to bring about sustained action properties. The drug resinates prepared by the use of each Amberlite IRP-69 (H^+ and Na^+- form) and Amberlite IR-120 (Na^+-form) were subjected to coating treatment adopting emulsion-solvent evaporation microencapsulation. Cellulose acetate butyrate was used as the coating material. A sustained release formulations of the prepared microcapsules were clinically evaluated. The treatment with the sustained release formulation given twice daily was found to be clinically the same or better than of the plain drug given three times a day.

INTRODUCTION

Salbutamol is a direct sympathomimetic agent with predominantly beta adrenergic activity and selective action on B_2 receptor [1]. This provides the benefits of bronchodilation without myocardial stimulation. The drug has become established since early 1970 as a bronchodilator for the treatment of obstructive airways diseases [2].

Ion-exchange resins have found many medicinal applications [3,4]. The loading of drugs onto such materials was reported to be valuable in the design of controlled release products, in the enhancement of stability profiles and in overcoming the taste problems [4-8]. Generally, the drug release rates from unmodified resins are too great for adequate control of drug delivery. Coating of the drug resinates with a diffusional barrier to delay the drug egress was employed in commercial products [9].

The regular administration of salbutamol may prevent the degranulation of mast cells and the liberation of vasoactive amines [1]. Also, controlled release preparations of the drug will enable well-tolerated continuous drug therapy and assist patient compliance [10]. Hence, the objective of this study was to utilize cation-exchange resins as a carrier for salbutamol and to coat the drug resinates to get a controlled release pattern of the drug. Dissolution testing and clinical evaluation were carried out on the formulated sustained release products of the drug.

EXPERIMENTAL

Materials:

-Salbutamol sulphate (Sigma Co., St. Louis, U.S.A).

-The ion-exchange resins; Amberlites of different grades (Aldrich Chem. Co., Inc., Milwau-

kee, Wis., U.S.A.) compiled in Table 1.

-Cellulose acetate butyrate; CAB (Sci. Polymer Products Inc., Ontario, New York, U.S.A.).

-Simulated gastric and simulated intestinal fluids (USP XXI, 1985) were prepared without enzymes but containing 0.02% w/v Tween 80.

Apparatus:

-Double beem spectrophotometer UV-150-02 (Shimadzu, Japan).

-Dissolution apparatus; USP rotating paddle type, model DT-06 (Erweka, Germany).

-Thermostatically controlled water bath fitted with horizontally moved mechanical Shaker (GFL, D. Burgwedel).

-Mechanical stirrer fitted with two blade propeller (D.D.R.).

-Vitalometer (Warren E. Collins. Inc., Braintree, Mass., U.S.A.).

-Wright peak flow-meter (Airmed Limited, Harlow, England).

Procedure:

1-Treatment of the tested resins:

The used resin size was obtained by grinding the delivered resins and collecting the fraction of 63-90 um. The H^+ and Na^+ forms of the resin were reactivated or regenerated by agitating the resin with 500 ml of 0.1 N HCl or 0.1 N NaOH for 12 hours respectively. The resins were then separated by filtration, washed with deionized water and dried in an oven at 50°C for 24 hours. The dried resins were triturated and passed through sieve (90 um).

2-Equilibrium studies:

Five bottles of 125 ml, each containing 50 mg of salbutamol sulphate dissolved in 100 ml of deionized water were prepared. The tested resin was added to each of these bottles (0.1 g. / bottle). The bottles were transferred to a thermostatically controlled mechanical shaker adjusted at 25°C and at 30 stroke / minute. After 2 hours-time intervals a bottle was taken and the resin was separated by filtration using filter paper. Sample of filtrate was suitably diluted by 0.1 N NaOH and assayed spectrophotometrically at 296nm. The amount of drug loaded by the resin was calculated by subtracting the amount in filtrate from the initial amount of added drug. The time required for constant amount of drug to be taken by the resin was recorded as the equilibrium time. It was found that 4 hours is a sufficient period to attain equilibrium.

3-Preparation of drug resinates:

Loading the drug onto the resin was accomplished by the batch process. The resin particles were stirred along with 100 ml of drug solution in deionized water for a time period equal to the equilibrium time. The dispersion was then filtered and washed with deionized water to remove unassociated drug and other ions. The resin particles were dried at 50°C in an oven for 24 hours.

Different drug concentrations were used to prepare drug resinates at different loading ratios.

4-Coating of drug resinates:

Drug resinates, prepared by the use of each of Amb. IRP-69

(H^+ and Na^+-form) and Amb. IR-120 (Na^+-form) at drug / resin ratio of 0.25 : 1 were subjected to the coating process. Cellulose acetate butyrate, containing 10% w/w PEG 4000, was used as the coating material. The solution of coating material was prepared at 10% w/v in acetone. The drug resinates were dispersed in the coating solution. The dispersion was then emulsified in paraffin oil (1:3) containing 1% w/v emulsifier. Stirring was continued until the evaporation of acetone and the formation of microcapsules. The formed microcapsules were separated, washed with n-hexane and dried at room temperature. The microcapsules were prepared at resinate: coating material ratio of 1:1. An additional batch was prepared at the ratio of 2:1 in case of drug resinates of Amberlite IRP-69 (H^+-form). The prepared microcapsules were fractionated into different sizes using a set of standard sieves.

5-Determination of microcapsule drug content:

100 mg-sample representing the different sieve fractions were crushed in a mortar. Due to the high release rate of salbutamol in acidic medium, simulated gastric fluid was added to the mortar content. The content was transferred quantitatively to a volumetric flask and was left for 24 hours. The flask content was filtered to remove coat fragments and transferred to another volumetric flask. The flask was completed to volume by simulated gastric fluid. The drug concentration was assayed spectrophotometrically at 276nm[11].

6-*In vitro* release studies:

Release studies were carried out at 37°C in 200 ml of dissolution media. The USP standard apparatus with teflon-coated paddle stirrers at 50 rpm was used. Both simulated gastric fluid and simulated intestinal fluid were used separately as the dissolution media. Each medium was used without enzymes but 0.02% w/v Tween 80 was added to overcome the poor wettability of tested samples and to make the solution more closely resemble the surface tension of gastrointestinal fluid.

Accurately weighed samples of 50 mg of uncoated resinates or 100 mg of microcapsules were added to the dissolution medium. After predetermined time intervals, 5 ml aliquots were withdrawn and replaced with fresh medium. The amount of drug in the withdrawn samples was determined spectrophotometrically at 276 nm in simulated gastric fluid and at 296nm [11] in simulated intestinal fluid after dilution with 0.1 N NaOH.

7-Clinical evaluation of the microencapsulated salbutamol resinates:

The *in vitro* tested formulation of salbutamol which gave sustained release pattern was prepared. The formulation was prepared to contain 1.32 mg of plain drug as initial dose and an amount of microcapsules equivalent to 4 mg of drug as a maintenance dose. The calculation was based on that the formulation contains 4 mg of each of the plain and the microencapsulated drug. The amount of plain drug was corrected taking in consideration the fraction released after 3 hours (time to peak) [12] from microcapsules in simulated gastric fluid. The maintenance dose was an encapsulated product prepared by using CAB as the coating material and drug loaded onto Amb. IRP-69, Na^+ form as the core

at 1:1 core/coat ratio. The sustained release formulation was filled into hard gelatin capsules. Also, hard gelatin capsules, each contains 4 mg of plain drug was used as the control. Six patients suffering from reversible chronic airflow obstruction participated in this study. Each subject received one capsule of the plain drug (control) 3 times daily for one week. Then, the same subject received one capsule of the sustained release formulation twice daily for another week. The forced expiratory volume in one second (FEV_1) was measured by Collins vitalometer. The peak expiratory flow rate (PEFR) was measured by Wright peak flowmeter. The degree of airflow obstruction was determined before drug administration and then through three readings taken at 8 A.M., 2 P.M. and 8 P.M. during medication. Also, the subjective improvement of dyspnea and wheezing, rate of occurence of asthmatic attack and the appearance of any side effects were observed.

RESULTS & DISCUSSION

Ion-exchange resins were used in an attempt to prepare sustained release products of salbutamol. Loading capacity of the tested resins was in the following order: Amb. IRP-69 > Amb. IR-120 > Amb. MB-1 > Amb. IRC-50 or Amb. CG-50 (Tables 2 & 3). A result which in agreement with the description of the resins as strong or weak exchangers. In this respect, although Amb. MB-1 is a strong exchanger, its maximum capacity towards drug was intermediate. A result which can be attributed to its mixed exchanging properties. The amount of drug loaded onto the weak resins (CG-50 and IRC-50) was too small to be considered in the preparation of sustained release forms. Hence, the study was focused on the drug resinates prepared by the use of Amb. IRP-69 and Amb. IR-120.

Amb-IRP-69 and Amb-IR-120 in their H^+-form were found to hold somewhat greater amount of drug than the corresponding Na^+-form (Table 3). A result which can be attributed to the greater tendency of the resin to exchange H^+ than Na^+. This explanation is based on the fact that hydrogen ion has a smaller molecular size than sodium ion, thus it is easily exchanged [13]. Also, the eluted hydrogen ion enhances the ionization of drug in the loading solution hence it increases the concentration of dissociated drug.

The drug release from its resinates prepared by the H^+-form was highly retarded than those prepared by the Na^+-form (Tables 4-7). This effect is more pronounced at the lowest loading values. This may be attributed to the higher degree of swelling of the Na^+-form [13]. The higher release rates at the lower loading ratios in case of Na^+-form in comparison with that of H^+-form confirms this explanation. Hence, by increasing the degree of loading, both forms of resin approach nearly the same composition, so the release differences decrease. In addition, on drying the loaded resin, the evaporation of water from the more swellable Na^+-form leads to a more porous structure making the diffusion of drug molecules more easier. Generally but not in all cases, the amount released in simulated intestinal fluid was found to be lower than that in simulated gastric fluid (Tables 4-7). This may be attributed to the higher degree of dissociation of salbutamol in the acidic medium than that in the basic one.

As a general conclusion, the drug release profiles from its resinates

were too high to bring about sustained action properties. Hence, it was deemed assential to apply a diffusion barrier to modify the drug release profile. Cellulose acetate butyrate was used as a diffusion barrier to coat the drug resinates at core:coat ratio of 1:1 adopting a microencapsulation techinque. The drug resinates prepared at drug resin ratio of 0.25:1 by the use of Amb. IRP-69 (H^+ and Na^+-form) and Amb. IR-120 (Na^+-form) were used as the core materials. The use of core:coat ratio of 1:1 in case of Amb. IRP-69 (H^+-form) resinates was found to have undesirable release retardation, consequently, core:coat ratio of 2:1 was tried.

The determined drug content (Table 8), and the electron micrographs of the prepared microcapsules (Figure 1), confirm the validity of the adopted procedure.

Increasing the core:coat ratio was found to significantly increase the microcapsule size (Table 9). This may be attributed to the fact that the higher the core:coat ratio, the greater the difficulty to disperse the core material during the emulsification process resulting in large aggregates of the core. The effect which leads to an increase in the microcapsule size. The use of resins in the H^+-form was found to give larger microcapsules than those in case of using the Na^+-form. This effect can be attributed to the higher degree of swelling of H^+-form in acetone [13]. A result which leads to an increase in the microcapsule size.

Release studies on the prepared microencapsulated resinates were done (Figures 2-5). The results confirm that, fraction of coarser particle size showed a relatively slower release rate of the drug in comparison with those of finer particle size. A result which can be attributed to the decrease in surface to volume ratio with the increase in the size of the microcapsules.

Increasing the core:coat ratio from 1:1 to 2:1 in case of Amb. IRP-69 (H^+-form) resinates resulted in significant increase in the release rate (Figures 2&3). An effect which can be attributed to the decrease in the coat thickness upon decreasing the coat ratio. Thus, a reduction in the distance of diffusion of drug through the microcapsule wall.

Clinical evaluation of the microencapsulated drug product was done on asthmatic patients. From the data of these studies (Tables 10 & 11) it can be seen that, the improvement obtained during the treatment with sustained release formulation twice daily was the same or better than that obtained with the plain preparation taken three times a day. Clinically, it was observed that there are subjective improvement of dyspnea and wheezing. Also, neither asthmatic attacks nor side effects were observed during the treatment period.

On the basis of the previous findings, we can conclude that loading of the drug onto the Na^+-forms of strong cation exchange resins (Amberlite IRP-69 or Amberlite IR-120) and coating the drug resinates is a valuable approach in the preparation of sustained release products of salbutamol. The H^+-form have to be excluded since the fraction of drug available for release from the uncoated resins is usually small. At the same time coating of such resins resulted in undesirable retardation in the release pattern.

Table 1: Description of the Used Ion-Exchange Resins.

Resin used	Character	Received form	Active group
Amberlite IRP-69	Strong acid	Sodium	$-SO_3^-$
Amberlite IR-120	Strong acid	Hydrogen	$-SO_3^-$
Amberlite MB-1	Mixture of Strong acid and Strong base		$-SO_3^-$ $-N(CH_3)_3^+$
Amberlite CG-50	Weak acid	Sodium	$-Coo^-$
Amberlite IRC-50	Weak acid	Sodium	$-Coo^-$

Table 2: Loading Characteristics of Salbutamol on the Tested Resins as a Function of Time

Time Hours	Amount of Drug Loaded (mg/0.1 g) onto the Following Resins				
	Amb.IRP-69	Amb.IR-120	Amb.MB-1	Amb.CG-50	Amb.IRC-50
2	31.99	34.67	29.84	2.28	3.60
4	31.77	34.55	29.75	3.44	4.07
6	31.37	36.56	30.29	2.46	2.53
8	32.17	35.06	31.31	3.35	3.53
10	31.99	37.90	31.63	3.80	4.26

Table 3: Loading Characteristics of Salbutamol onto the Tested Resins as a Function of Initial Drug Concentration.

Initial Drug Concentration mg/100 ml	Amount of Drug Loaded (mg/0.1 g) onto the Following Resins				
	Amb. IRP-69 H^+	Amb. IRP-69 Na^+	Amb. IR-120 H^+	Amb. IR-120 Na^+	Amb. MB-1
25	22.05	19.82	19.86	18.62	17.41
50	40.65	32.18	34.55	34.85	29.03
75	53.78	45.99	49.35	44.56	30.37
100	66.01	59.53	60.18	57.49	36.73
150	73.23	67.32	67.19	65.89	34.23

Table 4: *In Vitro* Release of Salbutamol from its Resinates Prepared by the Use of Amberlite IRP-69; H^+-Form, at Different Ratios.

Initial Drug/ Resin Ratio		Salbutamol Released (% w/w) after The Following Specified Time Intervals in Hours					
		0.25	0.5	0.75	1	1.5	2
0.25:1	A	20.40	22.70	26.06	27.77	31.96	32.69
	B	31.16	34.26	34.50	37.03	37.25	38.80
0.50:1	A	40.42	49.73	49.73	49.80	64.41	64.41
	B	43.21	43.21	44.40	46.30	63.52	65.84
0.75:1	A	55.58	65.34	72.38	80.67	80.70	80.70
	B	71.49	74.92	76.35	76.52	77.90	79.23
1:1	A	65.54	96.93	99.62	100	100	100
	B	42.32	42.53	54.49	63.60	65.42	65.42
1.50:1	A	76.35	93.15	98.68	98.68	98.68	100
	B	76.45	76.56	78.60	78.80	84.01	85.50

A = In simulated gastric fluid.
B = In simulated intestinal fluid.

Table 5: *In Vitro* Release of Salbutamol from its Resinates Prepared by the Use of Amberlite IRP-69; Na^+-Form, at Different Ratios.

Initial Drug/ Resin Ratio		Salbutamol Released (% w/w) after The Following Specified Time Intervals in Hours					
		0.25	0.5	0.75	1	1.5	2
0.25:1	A	89.30	91.88	94.61	98.08	100	100
	B	81.11	83.52	83.52	83.82	86.58	100
0.50:1	A	92.23	92.23	92.50	92.50	98.77	100
	B	78.54	78.63	78.63	79.90	79.90	81.74
0.75:1	A	93.58	94.10	95.07	95.07	95.07	98.77
	B	86.82	86.87	91.70	91.70	95.07	100
1:1	A	91.65	97.10	97.10	97.57	97.75	100
	B	93.11	93.32	95.28	97.90	97.90	97.90
1.50:1	A	96.70	96.70	98.31	100	100	100
	B	98.30	99.00	99.45	99.86	100	100

A = In simulated gastric fluid.
B = In simulated intestinal fluid.

Table 6: *In Vitro* Release of Salbutamol from its Resinates Prepared by the Use of Amberlite IR-120; H^+-Form, at Different Ratios.

Initial Drug/ Resin Ratio		Salbutamol Released (% w/w) after The Following Specified Time Intervals in Hours					
		0.25	0.5	0.75	1	1.5	2
0.25:1	A	26.52	27.69	27.69	27.69	40.63	40.63
	B	19.05	19.18	19.68	23.14	24.75	24.75
0.50:1	A	36.18	39.23	44.87	44.87	44.87	44.87
	B	25.48	26.56	26.56	30.07	33.58	40.59
0.75:1	A	50.23	50.23	58.38	70.33	70.33	70.61
	B	41.75	41.75	45.51	45.51	45.83	45.83
1:1	A	65.19	72.15	73.59	82.10	87.45	94.03
	B	44.30	47.56	48.67	48.67	50.52	52.47
1.50:1	A	65.59	65.59	74.88	93.58	93.58	93.58
	B	57.08	63.67	70.74	72.42	82.61	89.55

A = In simulated gastric fluid.
B = In simulated intestinal fluid.

Table 7: *In Vitro* Release of Salbutamol from its Resinates Prepared by the Use of Amberlite IR-120; Na^+-Form, at Different Ratios.

Initial Drug/ Resin Ratio		Salbutamol Released (% w/w) after The Following Specified Time Intervals in Hours					
		0.25	0.5	0.75	1	1.5	2
0.25:1	A	64.54	69.94	72.90	73.50	82.78	82.78
	B	51.60	54.99	59.09	62.96	65.15	66.83
0.20:1	A	63.13	73.80	75.95	82.78	88.48	88.48
	B	60.40	62.56	67.38	74.25	74.60	76.04
0.75:1	A	66.59	78.02	78.31	83.25	90.39	100
	B	67.66	67.66	72.98	74.05	80.06	85.45
1:1	A	78.04	78.04	83.25	88.96	91.40	100
	B	82.33	82.98	85.00	85.00	88.90	90.92
1.50:1	A	81.12	90.06	90.06	91.81	91.81	100
	B	83.25	85.07	94.07	97.24	100	100

A = In simulated gastric fluid.
B = In simulated intestinal fluid.

Table 8: Drug Content of Microencapsulated Salbutamol Resinates Prepared by Using PEG-Treated Cellulose Acetate Butyrate as the Coating Material at 1:1 Core/Coat Ratio.

Microcapsule Fraction Size um	Drug Content (% w/w) of the Amberlite Resins:			
	IRP-69 H^+-form	IRP-69* H^+-form	IRP-69 Na^+-form	IRP-120 Na^+-form
90-200	--	--	8.29	8.01
200-315	8.77	--	8.24	8.15
315-400	8.89	--	--	8.12
400-630	9.16	11.82	8.34	--
630-710	--	11.87	--	--
710-840	--	11.89	--	--

* Core/Coat ratio 2:1.

Table 9: Frequency Distribution of Microencapsulated Salbutamol Resinates Prepared by Using PEG-Treated Cellulose Acetate Butyrate as the Coating Material at 1:1 Core/Coat Ratio.

Microcapsule Fraction Size um	Microcapsules (% w/w) in each Fraction of the Amberlite Resins:			
	IRP-69 H^+-form	IRP-69* H^+-form	IRP-69 Na^+-form	IRP-120 Na^+-form
63-90	--	--	7.40	3.35
90-200	14.72	37.02	52.74	
200-315	31.45	2.11	20.60	38.55
315-400	21.03	2.11	9.87	5.36
400-630	29.32	10.88	19.85	--
630-710	3.48	68.04	5.26	--
710-840	--	16.86	--	--

* Core/Coat ratio 2:1.

Table 10: Absolute and Percent Predicted Forced Expiratory Volume in One Second (FEV_1) after Oral Administration of Salbutamol.

Day	Formulation	8 a.m.		2 p.m.		8 p.m.	
		Absolute	% Predicted	Absolute	% Predicted	Absolute	% Predicted
1st	P	1.47 ± 0.06	46.79 ± 3.26	1.51 ± 0.09	48.25 ± 3.62	1.58 ± 0.20	50.34 ± 6.08
	S	2.15 ± 0.08	66.78 ± 14.93	2.20 ± 0	70.83 ± 3.54	2.25 ± 0.07	72.50 ± 3.00
2nd	P	1.70 ± 0.10	54.26 ± 5.25	1.79 ± 0.13	57.10 ± 5.12	1.84 ± 0.15	58.68 ± 1.13
	S	2.25 ± 0.07	72.38 ± 1.34	2.35 ± 0.07	75.65 ± 1.58	2.35 ± 0.07	75.60 ± 1.51
3rd	P	2.00 ± 0.10	63.77 ± 4.15	2.04 ± 0.14	65.02 ± 4.78	2.19 ± 0.27	69.87 ± 8.32
	S	2.25 ± 0.21	72.27 ± 3.20	2.25 ± 0.21	72.27 ± 3.20	2.35 ± 0.07	75.60 ± 1.51
4th	P	2.13 ± 0.15	68.00 ± 5.18	2.23 ± 0.23	71.12 ± 6.52	2.30 ± 0.20	73.22 ± 4.32
	S	2.25 ± 0.21	73.94 ± 0.86	2.35 ± 0.07	75.60 ± 1.51	2.34 ± 0.07	75.60 ± 1.51
5th	P	2.27 ± 0.06	72.20 ± 0.98	2.40 ± 0.10	76.44 ± 1.81	2.40 ± 0.10	76.44 ± 1.81
	S	2.35 ± 0.07	73.94 ± 0.86	2.35 ± 0.07	75.60 ± 1.51	2.34 ± 0.07	75.60 ± 1.51
6th	P	2.27 ± 0.06	72.20 ± 0.78	2.40 ± 0.10	76.55 ± 1.81	2.40 ± 0.10	76.44 ± 1.81
	S	2.30 ± 0.14	73.93 ± 0.85	2.35 ± 0.07	75.60 ± 1.51	2.34 ± 0.07	75.60 ± 1.51
7th	P	2.27 ± 0.06	72.20 ± 0.98	2.40 ± 0.10	76.44 ± 1.81	2.40 ± 0.10	76.44 ± 1.81
	S	2.30 ± 0.14	73.93 ± 0.85	2.35 ± 0.07	75.60 ± 1.51	2.34 ± 0.07	75.60 ± 1.51

EFV_1 pre-drug = 1.47 ± 0.06 litre
P : Plain drug

FEV_1 Predicted = 3.14 ± 0.12 litre
S : Sustained formulation

Table 11: Absolute and Percent Predicted Peak Expiratory Flow Rate (PEFR) after Oral Administration of Salbutamol.

Day	Formulation	8 a.m.		2 p.m.		8 p.m.	
		Absolute	% Predicted	Absolute	% Predicted	Absolute	% Predicted
1st	P	310 ± 30	56.43 ± 8.03	360 ± 40	58.60 ± 7.27	370 ± 40	59.67 ± 7.39
	S	480 ± 40	77.61 ± 7.11	490 ± 40	78.42 ± 5.98	500 ± 30	81.69 ± 6.03
2nd	P	370 ± 50	60.78 ± 8.15	380 ± 50	62.40 ± 8.93	400 ± 50	65.12 ± 8.98
	S	500 ± 20	80.86 ± 4.86	500 ± 20	80.03 ± 3.70	510 ± 15	83.30 ± 3.75
3rd	P	410 ± 40	66.74 ± 8.09	430 ± 50	69.46 ± 8.71	440 ± 40	72.15 ± 6.68
	S	510 ± 20	82.49 ± 4.90	510 ± 15	83.31 ± 3.75	520 ± 20	84.13 ± 4.91
4th	P	450 ± 50	73.25 ± 9.08	470 ± 40	75.95 ± 7.63	490 ± 20	80.26 ± 4.92
	S	520 ± 20	84.13 ± 4.91	520 ± 20	83.31 ± 3.75	520 ± 20	84.13 ± 4.91
5th	P	470 ± 60	75.93 ±10.84	480 ± 50	78.66 ± 9.13	500 ± 30	81.08 ± 4.42
	S	520 ± 20	84.13 ± 4.91	520 ± 20	83.31 ± 3.75	520 ± 20	84.13 ± 4.91
6th	P	470 ± 60	75.93 ±10.84	480 ± 50	78.66 ± 9.13	500 ± 30	81.08 ± 4.42
	S	520 ± 20	84.13 ± 4.91	520 ± 20	83.31 ± 3.75	520 ± 20	84.13 ± 4.91
7th	P	470 ± 60	75.93 ±10.84	480 ± 50	78.66 ± 9.13	500 ± 30	81.98 ± 4.42
	S	520 ± 20	84.13 ± 4.91	520 ± 20	83.31 ± 3.75	520 ± 20	84.13 ± 4.91

PEFR Pre-drug = 350 ± 50 Litre/Minute
PEFR Predicted = 620 ± 10 Litre/Minute
P : Plain drug
S : Sustained formulation

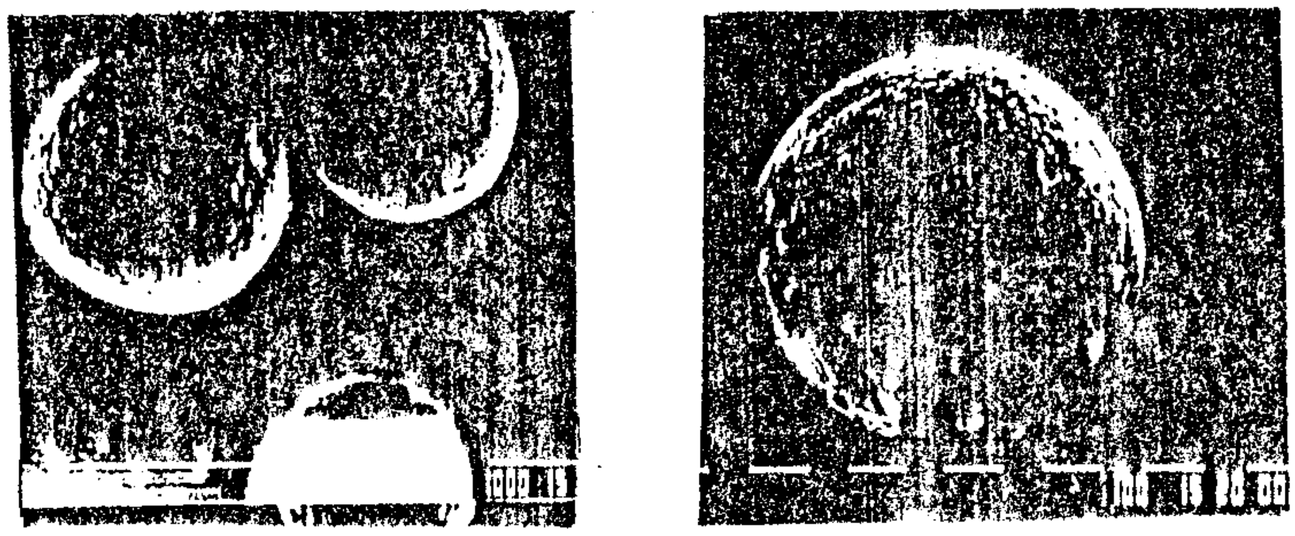

Figure (1) : Electron Scanning Photo-micrographs of Salbutamol Microcapsules Prepared by Using Cellulose Acetate Butyrate As The Coating Material and Drug Loaded onto Resin As The Core.

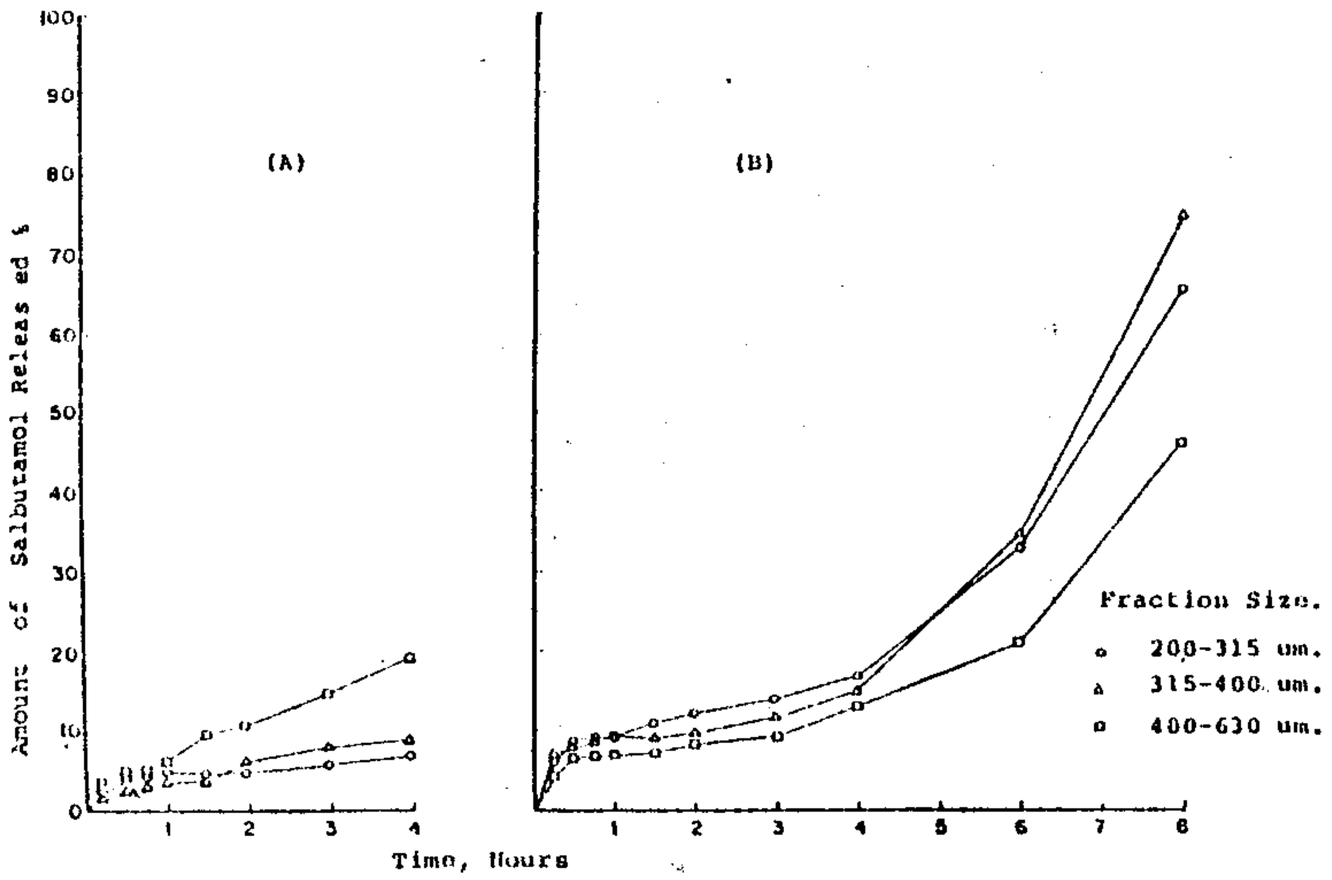

Figure (2) : In-Vitro Release of Salbutamol from its Microcapsules Prepared by Using PEG-Treated Cellulose Acetate Butyrate As The Coating Material and Drug Loaded onto Amb. IRP-69; H^+-Form, As The Core at 1:1 Core:Coat Ratio
Key : (A) in Simulated Gastric Fluid (B) in Simulated Intestinal Fluid

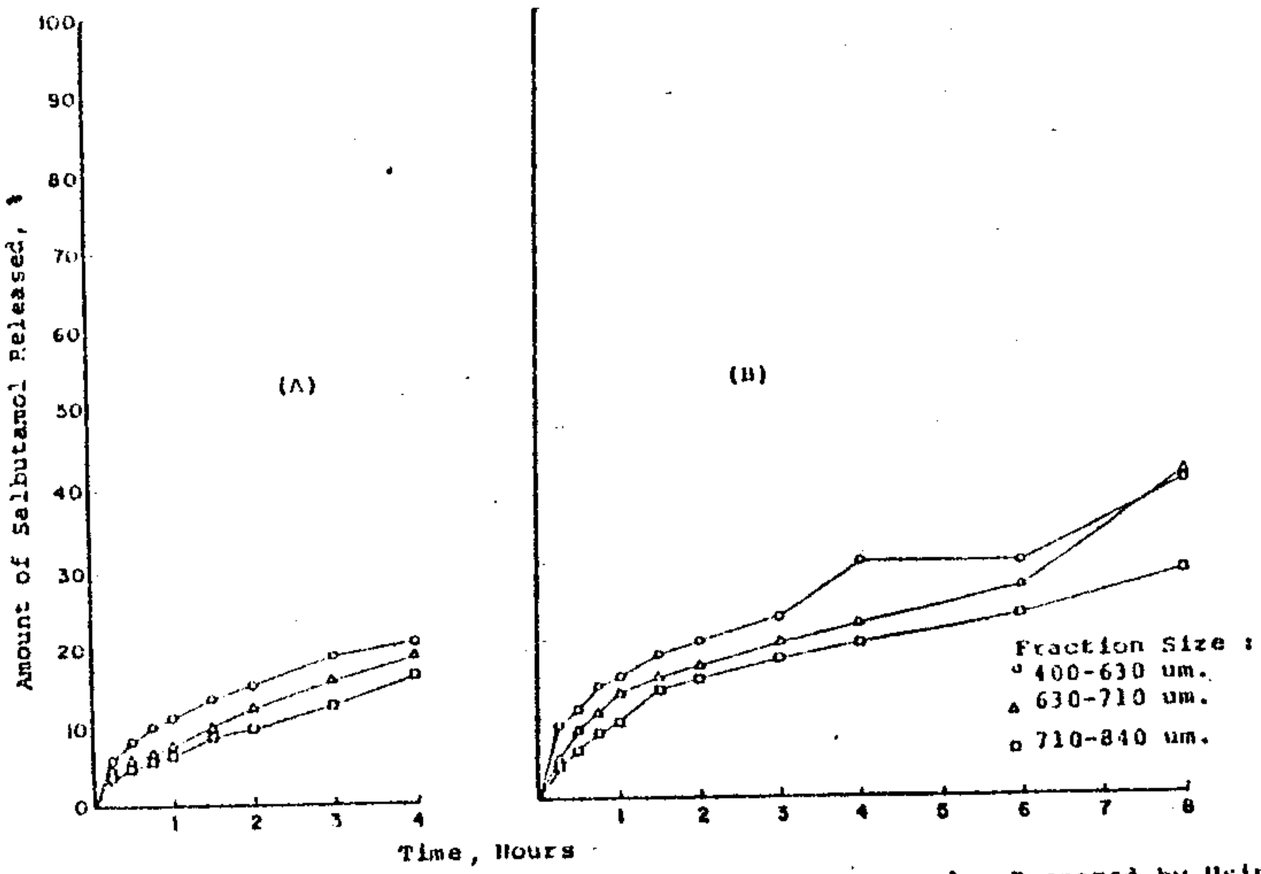

Figure (3) : In-Vitro Release of Salbutamol from its Microcapsules Prepared by Using PEG-Treated Cellulose Acetate Butyrate As The Coating Material and Drug Loaded onto Amb. IRP-69; H^+-Form, As The Core at 2:1 Core:Coat Ratio.
Key : (A) in Simulated Gastric Fluid (B) in Simulated Intestinal Fluid.

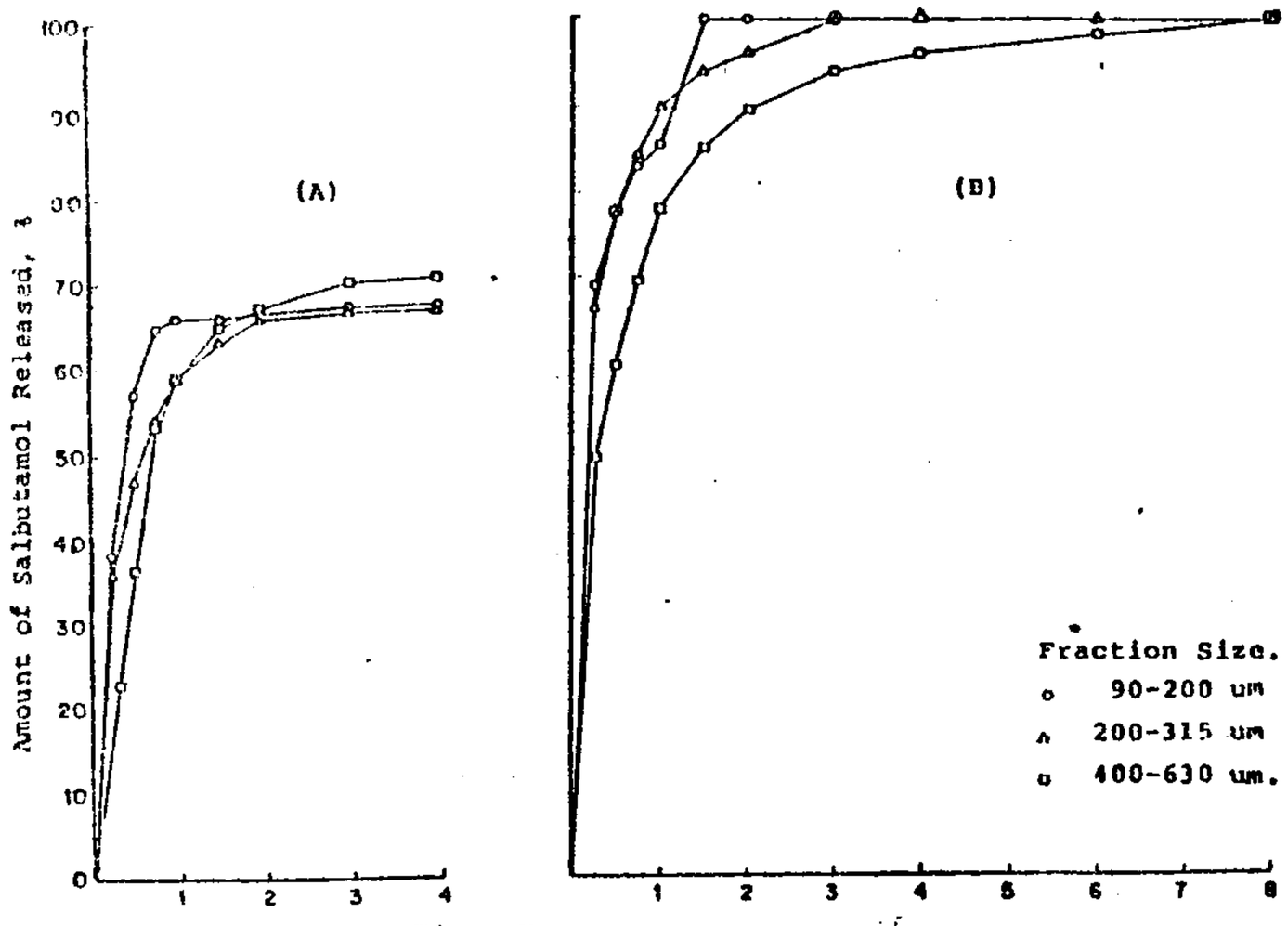

Figure (4) : In-Vitro Release of Salbutamol from its Microcapsules Prepared by Using PEG-Treated Cellulose Acetate Butyrate As The Coating Material and Drug Loaded onto Amb. IRP-69; Na^+-Form, As The Core at 1:1 Core:Coat Ratio.
Key : (A) in Simulated Gastric Fluid (B) in Simulated Intestinal Fluid.

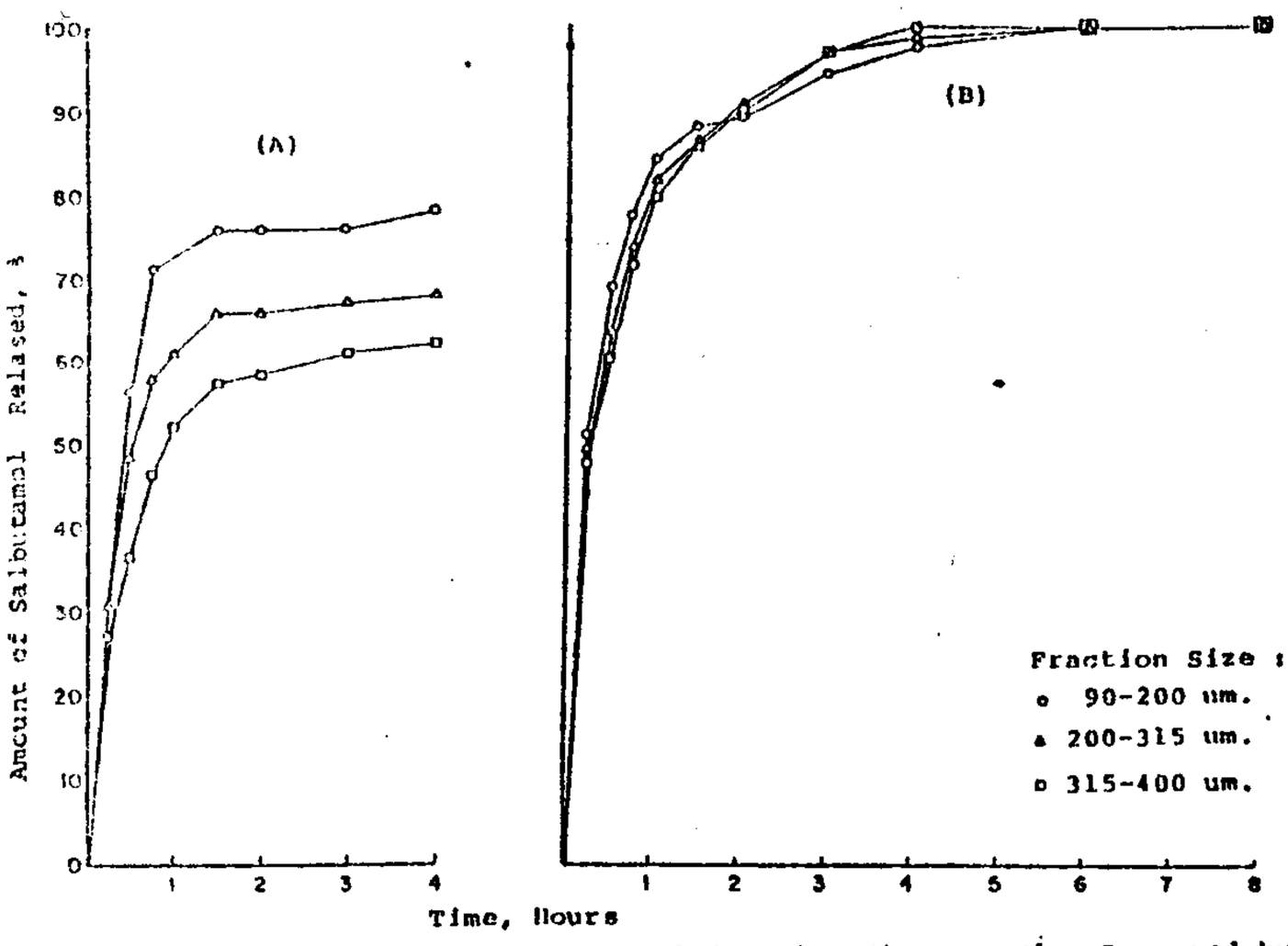

Figure (5) : In-Vitro Release of Salbutamol from its Microcapsules Prepared by Using PEG-Treated Cellulose Acetate Butyrate As The Coating Material and Drug Loaded onto Amb. IR-120; Na^+-Form, As The Core at 1:1 Core:Coat Ratio.
Key : (A) in Simulated Gastric Fluid (B) in Simulated Intestinal Fluid.

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تصميم صياغات ممتدة المفعول لعقار السلبيوتامول

١ ـ استخدام راتنجات التبادل الايونى

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فى محاولة لتصميم صياغات ممتدة المفعول لعقار السلبيوتامول المستخدم كموسع للشعب الهوائية تم تحميله على بعض راتنجات تبادل الايون الموجب من نوع امبولايت IRC-50 , CG-50 , MB-1 , IR-120, IRP-69

وتمت دراسة عدة عوامل متمثلة فى زمن التوازن وتأثير تركيز العقار ونوع ايون التبادل على قدرة الراتنج المستخدم فى التحميل . وبدراسة معدلات انطلاق العقار من هذه المحملات وجد انها اسرع من تلك المطلوبة لصياغات ممتدة المفعول لذا اجريت حوصلة بعض الراتنجات المحملة . وتم اختيار بعض الحويصلات المحضرة لصياغتها فى اشكال ممتدة المفعول وتقييمها علاجيا فى عدد من مرضى الربو الشعبى وقد وجد ان تعاطى هذه الاشكال بواقع جرعتين يوميا يعطى نفس التحسن وربما بصورة افضل مقارنة بجرعات من مسحوق العقار تعطى بواقع ثلاث مرات يوميا .

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