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Design and Characterisation of Sustained Release Microcapsules of Salbutamol Sulphate

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ABSTRACT: Sustained release Microcapsules of Salbutamol Sulphate were prepared using cellulose acetate phthalate, Cellulose acetate and Glyceryl monostearate polymers in different drug polymer ratio and were evaluated for drug content, Particle size determination and in vitro release behavior as per United states Pharmacopoeia in simulated gastric fluid (pH 1.2 ± 0.1) up to 0-2 hrs and in simulated intestinal fluid (pH 7.5 ± 0.1) up to 2-12 hrs. Three formulations of 1:1, 1:2 and 1:3 in drug polymer ratio for cellulose acetate phthalate and cellulose acetate were prepared by solvent evaporation technique and three formulations of glyceryl monostearate were prepared by melt dispersion technique. All the formulations shown uniformity in drug content, sieve analysis results indicated that major fraction of microcapsules lies in the range of 425 to 600µm in all formulations and in vitro dissolution studies pointed that only CAP 1 and GMS 1 formulations failed to sustain the drug release up to 12 hrs. The drug release mechanism from all the prepared microcapsules was found to be diffusion controlled and they followed first order release kinetics. Finally it was concluded that Solbutamol sulphate can be effectively microencapsulated using Cellulose acetate phthalate (CAP) and cellulose acetate by solvent evaporation technique and glyceryl monostearate by melt dispersion technique..

Keywords: Microcapsules, Sustained release, Cellulose acetate phthalate, Cellulose acetate, Glyceryl Monostearate, Salbutamol sulphate.

INTRODUCTION: Asthma is an extremely common disorder which affects many people. Asthma is viewed as an inflammatory illness that has bronchial hyper-reactivity and bronchospasm[1]. Continuous therapy is required for the treatment of asthma. Salbutamol sulphate is used as a bronchodilator in the management of reversible airways obstruction in case of asthma and in some patients with chronic obstructive pulmonary disease.[2, 3.] Salbutamol sulphate is a good agent for the preparation of a sustained action dosage form as it is having an half life of 4-6 hrs[4] . Microencapsulation is one of the techniques used for the preparation of a sustained release dosage form.[5, 6]

In the present study nine formulations were prepared by using salbutamol sulphate and polymers (Cellulose acetate phthalate, Ethyl cellulose, Glyceryl monostearate). The concentration of salbutamol sulphate was kept constant in all the preparations and polymer concentrations were varied to know the effect on release pattern. All the prepared formulations were subjected to various evaluation tests (Content uniformity, Particle size distribution and Invitro dissolution) to know the better combination of the drug, polymer and polymer concentration

MATERIALS AND METHODS

Materials

Salbutamol Sulphate was a gift sample from M/s Cipla Ltd. Mumbai. Cellulose acetate Phthalate, Ethyl cellulose and Glyceryl monostearate were gifted by M/s Rolex. All other chemicals were of analytical/Pharmacopoeial grade from commercial suppliers and were used as received without further purifications. Paddle stirrer (Remi), Dissolution apparatus (Campbell electronics Mumbai), and UV-visible spectrophotometer (Systronics) were the equipments used in the study.

Methods

a).Standard curve for Salbutamol sulphate

For preparation of standard curve drug equivalent to 20mg was weighed accurately and was dissolved in 100 ml of simulated gastric fluid/simulated intestinal fluid. This solution resulted into drug concentration of 200µgm/ml.Then volumes of 0.5ml,1ml,1.5ml,2.0ml,2.5ml,3.0ml,3.5ml,4.0ml,4.5ml and 5.0ml were withdrawn and diluted to 10ml with respective G.I fluids to obtain drug concentration in range of 10 to 100 µg/ml. The absorbances of these solutions were recorded at 276 nm taking respective G.I fluids as blank using UV visible spectrophotometer.

b) Preparation of microcapsules of cellulose acetate phthalate and cellulose acetate by solvent evaporation method

For preparation of microcapsules of cellulose acetate phthalate and cellulose_acetate, Solvent evaporation technique was used. Acetone was used as polymer solvent; light mineral oil as the liquid manufacturing vehicle and n-hexane as the decanter of paraffin oil. To prepare microcapsules the various core to coat ratios as 1:1, 1:2 and 1:3 were taken. Here polymer concentration was varied keeping drug concentration and polymer solvent volume constant.

Depending upon the ratio polymer, cellulose acetate phthalate and cellulose acetate were weighed and dissolved in 30 ml of acetone. Then accurately weighed quantity of drug was uniformly dispersed in polymer solution and stirred for 20 mins.The dispersion was then poured into 100 ml of light mineral oil containing 1.3% tween 80 and stirred for 5 hrs at 1100 rpm at room temperature. During 5 hrs stirring period acetone used as polymer solvent was removed completely by evaporation. The light mineral oil was decanted and the collected microcapsules were washed twice with 100 ml of n-hexane at room temperature, after which the microcapsules were separated by filtration and dried [7].

c)Preparation of microcapsules of Glyceryl mono stearate by melt dispersion technique.

In this method accurately weighed quantity of glyceryl monostearate according to drug polymer ratio of 1:1,1:2 and 1:3 was taken and melted, to this melted polymer added the required quantity of salbutamol sulphate and mixed well in molten condition. The resulting drug polymer mixture was poured in cold benzene (maintained at 5ºC) with a stirring at 300rpm.Microencapsulation occurred instantaneously, the product thus formed was collected by filtration and washed with distilled water and dried at room temperature for 12 hrs. [8]

d) Drug content estimation

Drug content of Salbutamol Sulphate in the microcapsules was performed for three randomly picked up samples from each formulations. For each 100 mg of sample was pulverized added to 100 ml of simulated gastric fluid (pH 1.2) and kept for 5 hrs to allow the complete drug extraction from microcapsules. After 5 hrs this solution was filtered and 5 ml of this solution was then withdrawn and diluted suitably and absorbance of same was measured at 276 nm taking respective dissolution fluid as blank [7, 10].

e) Sieve analysis

The known amount of microcapsules was placed on the top sieve and the set was vibrated in a mechanical device for a predetermined period. The results are obtained by weighing the amount of material retained on each sieve. Different sizes in a batch of dried microcapsules were separated by using sieve no. 16, 25 and 36 [7, 9].

f) In vitro drug release studies of microcapsules

In vitro drug release of prepared microcapsules were carried out using USP dissolution test apparatus type 1 (rotating basket method) in simulated gastric fluid (pH 1.2 ± 0.1) up to 0-2 hrs and in simulated intestinal fluid (pH 7.5 ± 0.1) up to 2-12 hrs.The rotation speed of 50 rpm at temperature 37±1ºC and dissolution medium of 900 ml was maintained through out the experiment. A quantity of microcapsules equivalent to 8 mg of drug were tied in a muslin bag and kept in the basket. For 0-2 hrs drug release was studied in simulated gastric fluid (pH 1.2 ± 0.1) and then from 2-12 hrs in simulated intestinal fluid (pH 7.5 ± 0.1). 5 ml of dissolution fluid were withdrawn at regular time interval and was replaced with fresh quantity of dissolution fluid. The samples were filtered, diluted and analyzed by UV-Visible Spectrophotometer at 276 nm for all formulations. The dissolution was carried out for triplicate and mean values were calculated. Dissolution studies of marketed product were carried in same way [7, 10].

RESULTS

1. Standard curve for Salbutamol sulphate

Table No.1 shows the mean absorbance of triplicate readings of salbutamol sulphate standard solution containing 10-100 µg/ml of drug in simulated gastric fluid (pH 1.2± 0.1) and simulated intestinal fluid (pH 7.5 ± 0.1). Standard curve is shown in fig.1.

2. Drug content estimation

The drug content estimation in the microcapsules were carried out for three randomly picked up samples and then mean drug content in respective formulations are shown in Table no. 3 with values of S.D., indicating uniformity of drug content in the formulations.

3. Sieve Analysis

The sieve analysis results of all formulations of microcapsules are shown in Table No. 4. The sieve fraction of 25/36 was found to be major fraction in all the microcapsules having size range of 425-600 µm.

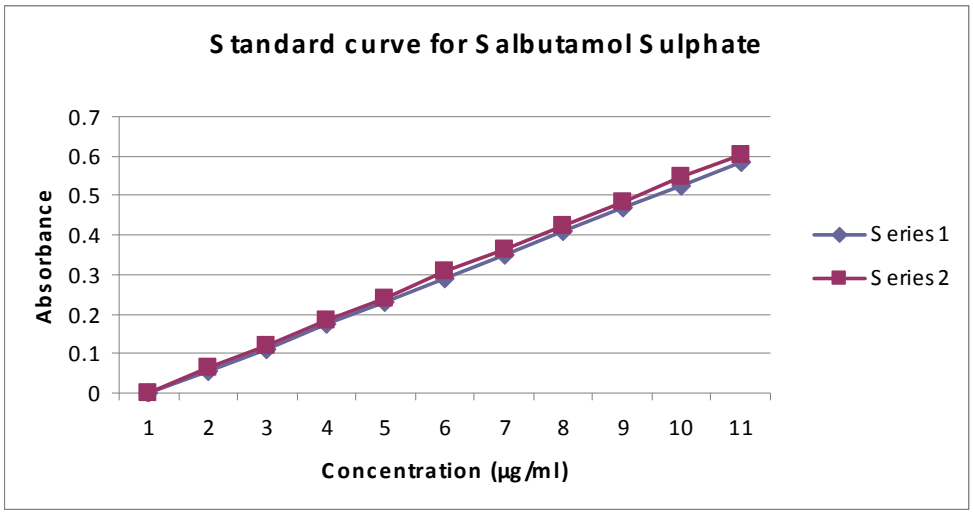
In vitro release studies

The invitro release rate studies for all the formulation were carried out in triplicate and the results shown in the Table No.5 are mean of the triplicate values with S.D. In vitro drug release profile of Salbutamol Sulphate and prepared microcapsules is shown in Fig.2. From the results it was clear that only CAP 1 (1:1) and GMS 1 (1:1) formulations failed to sustain the release up to 12 hrs. The release of the drug from other microcapsules exhibits a sustained release and was completed within 12 hrs. The plots of amount of drug released Vs time were found to be linear indicating that the drug release mechanism might be of diffusion type proposed by Higuchi.[11]

Table No.1. Mean absorbance readings of Salbutamol Sulphate

Sl.No.	Concentration (µg/ml)	Absorbance at 276 nm	
		Simulated gastric fluid (pH 1.2 ± 0.1)	simulated intestinal fluid (pH 7.5 ± 0.1)
1	10	0.055	0.065
2	20	0.110	0.121
3	30	0.175	0.183
4	40	0.230	0.240
5	50	0.290	0.308
6	60	0.350	0.362
7	70	0.410	0.424
8	80	0.470	0.483
9	90	0.525	0.548
10	100	0.586	0.604

Fig.1 Standard curve for Salbutamol Sulphate



Series 1: Simulated gastric fluid (pH 1.2 ± 0.1)
Series 2: Simulated intestinal fluid (pH 7.5 ± 0.1)

Table No.2 The composition of the different formulations

Formula	Ratio of core: coat	Percentage yield			Mean % yeild	S.D
		I	II	III		
CAP 1	1:1	79	80	81	80	0.8165
CAP 2	1:2	79	78.33	76.67	78	0.9793
CAP 3	1:3	75	72.5	74	73.83	1.027
CA 1	1:1	85	87.5	86	86.16	1.027
CA 2	1:2	83	83	82	82.67	0.4713
CA 3	1:3	80	81.25	83.25	81.5	1.338
GMS 1	1:1	97.5	96	95	96.16	1.0274
GMS 2	1:2	94	93	95	94	0.8165
GMS 3	1:3	90	91.25	88.75	90	1.0416

CAP: Cellulose acetate phthalate, CA: Cellulose acetate, GMS: Glyceryl Monostearate

Table No 3. . Mean Drug content and loading efficiency of different formulations

Formulations	Wt.Taken (mg)	Mean Drug Content (mg ± S.D.)	% Drug Content (Theoretical)	% Drug Content (Practical)	Loading Efficiency (%)
CAP 1	100	42.84 ± 0.2981	50	42.84	85.68
CAP 2	100	26.68± 0.1244	33.33	26.68	80.00
CAP 3	100	19.92 ± 0.222	25	19.92	79.68
CA 1	100	43.67± 0.4662	50	43.67	87.34
CA 2	100	28.41 ± 0.382	33.33	28.41	85.24
CA 3	100	20.96 ± 0.342	25	20.96	83.86
GMS 1	100	47.33 ± 0.4666	50	47.33	94
GMS 2	100	30.66 ± 0.4713	33.33	30.66	91.98
GMS 3	100	21.33± 0.4714	25	21.33	86.64

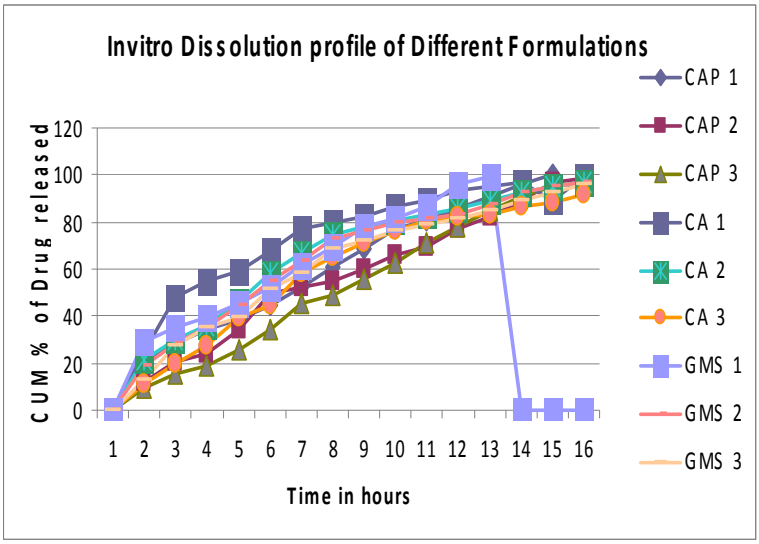
Table No. 4. Particle Size distribution

Sieve No. (Passed/retained)	Below 36	25/36	16/25	Above 16
Size range (µm)	425	425-600	600-1000	1000
Formulations (% retained)				
CAP1	10.26	60.45	19.88	9.4
CAP2	8.36	62.39	23.87	5.37
CAP3	3.48	64.84	26.57	5.10
CA 1	11.44	58.72	20.77	9.06
CA 2	4.80	60.27	28.88	6.06
CA 3	1.01	64.86	29.32	4.80
GMS 1	5.30	59.82	28.82	6.05
GMS 2	2.08	55.45	39.52	2.94
GMS 3	1.3	53.45	40.44	4.8

Table No.5. In Vitro dissolution of Salbutamol Sulphate microcapsules with all the polymers at different ratios

Time (Hours)	Cum. % Drug released ± S.D (CAP 1)	Cum. % Drug released ± S.D (CAP 2)	Cum. % Drug released ± S.D (CAP 3)	Cum. % Drug released ± S.D (CA 1)	Cum. % Drug released ± S.D (CA 2)	Cum. % Drug released ± S.D (CA3)	Cum. % Drug released ± S.D (GMS 1	Cum. % Drug released ± S.D (GMS2)	Cum. % Drug released ± S.D (GMS 3)
0.25	20.32±0.213	12.15±0.345	9.81±0.336	25.14±0.197	21.32±0.315	11.02±0.176	29.21±0.401	18.91±0.198	13.04±0.413
0.5	28.21±0.311	20.34±0.401	15.62±0.286	48.12±0.387	30.21±0.254	19.85±0.356	35.10±0.395	28.34±0.251	27.11±0.216
0.75	34.10±0.286	24.32±0.293	19.19±0.215	55.14±0.254	36.10±0.397	27.03±0.316	39.42±0.296	35.32±0.382	35.39±0.293
1	38.32±0.197	34.45±0.208	25.35±0.338	59.32±0.199	46.32±0.417	39.53±0.295	45.41±0.387	44.86±0.414	39.56±0.254
2	44.41±0.345	49.32±0.198	34.56±0.340	68.10±0.413	58.41±0.286	44.62±0.397	52.59±0.287	55.12±0.187	51.78±0.413
3	52.58±0.198	52.51±0.349	45.81±0.424	77.29±0.453	66.58±0.354	58.33±0.408	61.73±0.137	63.31±0.276	58.11±0.285
4	60.73±0.210	54.92±0.444	48.74±0.195	80.11±0.196	74.73±0.399	64.81±0.197	69.84±0.221	72.45±0.318	68.81±0.316
5	68.84±0.345	60.12±0.319	55.67±0.288	82.45±0.297	78.13±0.358	70.79±0.233	77.72±0.301	76.63±0.217	72.11±0.440
6	76.72±0.175	66.34±0.285	62.81±0.279	86.23±0.255	80.98±0.401	76.51±0.316	81.22±0.295	79.32±0.228	76.07±0.485
7	80.22±0.220	69.51±0.228	70.72±0.113	89.17±0.188	83.12±0.488	80.63±0.228	86.57±0.175	81.14±0.188	79.10±0.263
8	85.57±0.380	76.81±0.288	77.93±0.301	93.25±0.402	85.97±0.397	82.31±0.350	95.92±0.413	83.19±0.381	81.84±0.199
9	91.19±0.181	82.16±0.301	84.87±0.386	95.26±0.253	89.34±0.285	83.29±0.392	99.02±0.220	87.27±0.254	84.58±0.397
10	96.02±0.220	89.32±0.380	90.80±0.440	97.01±0.319	92.52±0.197	86.42±0.454	-	92.17±0.382	88.87±0.197
11	99.89±0.434	96.71±0.215	95.42±0.291	89.05±0.217	94.86±0.219	88.19±0.332	-	95.23±0.335	92.50±0.216
12	-	98.82±0.333	97.28±0.118	99.12±0.282	96.91±0.285	91.79±0.412	-	96.85±0.320	95.60±0.380

Fig.2: Comparison of In vitro dissolution profiles of different formulations



DISCUSSION

From the drug content estimation it was clear that all the formulations shown uniformity in drug content. By sieve analysis it was evident that the sieve fraction of 25/36 was found to be major fraction in all the microcapsules having size range of 425-600 µm.In vitro dissolution studies pointed that only CAP 1 and GMS 1 formulations failed to sustain the drug release up to 12 hrs.

CONCLUSION

The method of preparation of microcapsules of Salbutamol Sulphate was found to be simple and

reproducible. The sustained release of Salbutamol Sulphate from microcapsules will help to improve the therapeutic efficacy and patient compliance by reducing the dose and frequency of dosing of Salbutamol Sulphate.This study shows that Cellulose acetate could be used as carrier for Salbutamol Sulphate for retarding its release as compared to cellulose acetate phthalate and glyceryl monostearate.

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REFERENCES

(1). William E. Serafin, "Drugs used in the treatment of asthma". Chapter 28th In, Goodman's & Gilman's, The pharmacological basis of the therapeutics, ninth edition. McGraw Hill Companies, U.S.A 1996; 659-678

(2). K.D. Tripathi, "Drugs for Cough and Bronchial Asthma". 15th Chapter in, Essentials Of Medical Pharmacology, IVth edition Jaypee Brothers, Medical Publishers (P) Ltd. Delhi India, 222-238.

(3). Flores.G, Horwitz RI. Efficacy of β2-agonists in bronchiolitis a reappraisal and MetaAnalysis. Paediatrics 1997; 100; 233-9.

(4). Walker SR, et al. The clinical Pharmacology of oral and inhaled Salbutamol.Clin Pharmacol Ther.1972; 13; 861-7.

(5).Mathiowitz E.,Kreitz M.R microencapsulation. In encyclopedia of controlled drug Delivery; Mathiowitz E., Ed. John Wiley and sons inc; New York,U.S.A 1999 ;Vol 2,493-546.

(6). V.H Lee and J.R.Robinson in sustained and controlled release drug delivery Systems. Ed. Marcel Dekker, New York, 1978, 71.

(7) A. Amperiadou M. Georgarakis, 1995. "Controlled release of Salbutamol Sulphate Micro capsules prepared by Emulsion solvent evaporation technique and study on the release affected parameters". International Journal of Pharmaceutics, 60(1990); 83-88.

(8)

(8). N. B. Dharmadhikari &S. B. Joshi, 1994, "Micro encapsulation of Salbutamol Sulphate by Melt Dispersion technique". The Eastern Pharmacist, October, 1994; 129-131.

(9). Eugene L. Parrott, "Milling", Chapter 2 in: Theory and Practice of Industrial Pharmacy, Leon Lachman, Herbert A Lieberman and Joseph L. Kanig,Third edition, Varghese Publishing House, Bombay, India, 1991; 26-27.

(10).Indian Pharmacopoeia, Volume III, Ministry of Health and Family Welfare, Govt.of India, New Delhi, 5th Edn, 2007, 1689-1690.

(11). Higuchi T., Mechanism of sustained release action Medication, Theoretical Analysis of rate of Release of Solid Drugs Dispersed in Solid Matrices, J.Pharm.Sci, 1963, 52, 1145-1149.

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