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Studies on Microencapsulation of Salbutamol Sulphate

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ABSTRACT

Discrete free flowing microcapsules of salbutamol sulphate having good spherical geometry and smooth surface were prepared by complex emulsion method using guar gum, sodium carboxymethylcelulose, chitosan, carbopol, gelatin and sodium alginate alone and in combination. Different sizes in a batch of dried microcapsules were separated by sieving. SEM revealed the morphology of microcapsules. *In vitro* drug release from all the formulations in SGF and SIF and mechanism of the drug release are identified. The drug release decreased with an increase in the concentration of polymers. The mechanism of drug release from all the formulation was found to be diffusion controlled first order kinetics. The short-term accelerated stability studies revealed that all the formulations were found to be stable. The data demonstrate that microcapsules of salbutamol sulphate can be prepared by complex emulsion method using guar gum with sodium alginate and chitosan with sodium alginate to sustain the drug release.

Keywords: Salbutamol sulphate, microcapsules, guar gum, chitosan, sodium alginate.

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INTRODUCTION

Salbutamol sulphate belongs to the class called selective β2 adrenergic stimulant. It is used in the management of asthma, chronic bronchitis and other bronchopulmonary disorders involving bronchospasm. It is an odourless [1] white powder with slightly bitter taste. It is soluble in water and slightly soluble in alcohol, chloroform and solvent ether. Salbutamol sulphate is rapidly absorbed after oral administration and peak plasma concentration is attained in 2.5 to 3 h. It has half life of 4 h [2]. Sustained release dosage form of salbutamol sulphate is useful in protecting patient for longer duration from bronchospasm, bronchopulmonary disorders involving bronchospasm. Its dose is 2-8mg three to four times a day. Hence to improve its therapeutic efficacy, patient compliance and to reduce frequent dosing, sustained release dosage forms are needed for salbutamol sulphate [3], the present study deals with formulation and evaluation of salbutamol sulphate microcapsules by complex emulsion method.

MATERIALS AND METHODS

Materials

Salbutamol sulphate was obtained as a gift sample from Neuland laboratories Ltd. Hyderabad. Guar gum procured from Indian gum industries ltd. Sodium alginate and sodium cmc from loba chemicals Mumbai and gelatin from CDH Mumbai. All other chemicals and solvents used were of analytical reagent grade.

Preparation of Microcapsules

(a) By using guar gum and sodium alginate

Preparation of microcapsules containing salbutamol sulphate as the core material and guar gum as polymer and sodium alginate as co-polymer was done by complex emulsion method. The required quantities of polymers as mentioned in the Table.1 were taken in a beaker, 10 ml of 1% w/v tween 80 was added and stirred to form viscous solution, then the drug was dispersed, this solution was added in dropwise by using a syringe no 21(0.80x25mm) to 300 ml of liquid paraffin rotating at a speed of 250 ±20 rpm by using over head remi stirrer. Then 100 ml of 10%w/v calcium chloride solution was added slowly and stirring was continued for 20 mins. The microcapsules obtained were filtered and washed twice with 100 ml of petroleum ether, later they were dried in hot air oven at 50^0 C for 5 h and stored in dessicator.

(b) By using sodium cmc and gelatin

Sodium cmc and gelatin were weighed as mentioned in Table.1 and soaked separately in a beaker containing 10 ml of 1%w/v tween 80, for 2 h, both polymer solutions were mixed and drug was dispersed with stirring .This solution was added in dropwise by using a syringe no 21 (0.80x25mm) to 300 ml of liquid paraffin, 200mg of dioctyl sodium sulfo succinate was added

and stirred at a speed of 250 ±20 rpm by using a over head remi stirrer for 15 mins. 0.5 ml of glutaraldeyde solution was added and stirred for 20 mins. Further 2 ml of benzyl chloride was added and stirred for 15 mins. Microcapsules were transeferd to 200 ml of 15% w/v sodium bisulphate solution and allowed to warm at 40^{o} C, for 10 mins, later they were filtered dried at room temperature and stored in a dessicator.

(c) By using chitosan

Chitosan was weighed as mentioned in Table.1 and soaked for overnight in 1% v/v glacial acetic acid solution, and then it was uniformly mixed by using stirrer along with co-polymers and drug. A beaker containing the above solution was added dropwise by using a syringe No 21(0.80x25mm) to 300 ml of liquid paraffin, 50 mg of dioctyl sodium sulfosuccinate was added and stirred at 250 ±20 rpm by using remi stirrer .Then to the above, 3 ml of 29%v/v glutaraldehyde saturated toluene solution was added and stirred for 30 mins. The microcapsules were filtered, washed twice with100 ml of petroleum ether, later they were dried at room temperature and stored in a dessicator.

Table 1: Formulae of different Microcapsules of Salbuatamol Sulphate

Formulation	Polymers	Co-Polymers	Polymer : Co-Polymer	Drug: Polymer
M1	Guar gum	Sodium Alginate	1 : 1	1 : 1
M2	Guar gum	Sodium Alginate	2 : 1	1 : 1
M3	Guar gum	Sodium Alginate	3 : 1	1 : 1
M4	Sodium CMC	Gelatin	1 : 1	1 : 1
M5	Sodium CMC	Gelatin	2 : 1	1 : 1
M6	Sodium CMC	Gelatin	3 : 1	1 : 1
M7	Chiosan	Sodium Alginate	3 : 1	1 : 1
M8	Carbapol	Sodium Alginate	2 : 1	1 : 2
M9	Gelatin	-	-	1 : 1
M10	Gelatin	-	-	1 : 2
M11	Gelatin	-	-	1 : 3

Drug content estimation [4-5]

Drug content of salbutamol sulphate in the microcapsules was performed for three randomely 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 5h to allow the complete drug extraction from microcapsules .After 5 h this solution was filtered and 5 ml of this solution was then withdrawn and diluted suitably and absorbance of the same was measured using uv-vis spectrophotometer(HITACHI U-2000) at 276 nm taking respective dissolution fluid as blank.

Sieve analysis [3, 5]

The known amount of microcapsules was placed on top sieve and the set was vibrated in a mechanical sieve shaker 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. Studies were carried out in duplicate. The average size of the microcapsules were calculated by using the equation

$$Dave = \frac{\sum xi.fi}{Fi}$$

Where xi is the mean size of the range and fi is the percent material retained on the smaller sieve in the size range.

***In vitro* release**

Dissolution studies were carried out in 900 ml of SGF (pH 1.2) using, USPXX1 basket apparatus (Electrolab). The sample of microcapsules equivalent to 50 mg of drug was taken in a basket. A speed of 75 rpm and a temperature of $37^{o}\pm1^{o}C$ were maintained throughout the experiment. A sample of 5 ml dissolution fluid were withdrawn at regular intervals of time and replaced with same volume of SGF. The samples were suitably diluted and analyzed for the drug by measuring their absorbance at 276nm against blank using UV Spectrophotometer. After 2h the entire SGF was replaced with SIF of pH 7.4 and dissolution was continued in the same manner up to 12h and studies were carried out in duplicate**.** The mean percentage of drug released at various time intervals was calculated.

SEM Analysis

The particle size, shape and surface morphology of microcapsules were examined by scanning electron microscopy; Microcapsules were fixed on aluminium studs and coated with gold using a sputter coater SC 502, under vacuum (0.1mmHg).The microcapsules were then analyzed by using SEM [6].

Accelerated Stability studies

The optimized formulation were packed in glass vials and stored at $40\pm2^{0}C/75$ ±5% RH for three months in stability chamber (Thermolab). The samples were withdrawn at every 10 day time intervals and analyzed for physical parameters and drug content.

RESULTS AND DISCUSSIN

The microcapsules of salbutamol sulphate were prepared by complex emulsion method using varying concentration of guar gum, sodium alginate, sodium carboxymethylcellulose, gelatin, chitosan and carbopol alone and in combination to know their effect on drug release. The resulting microcapsules were evaluated for drug content and the results are shown in Table 2. The drug content was uniform and reproducible in each batch of microcapsules with low SD values, thus ensuring good encapsulation efficiency. Dried microcapsules were separated by sieving and size analysis was carried out, the results are shown in Table 3, about 62.3% of microcapsules were in the size range of # 22-44 with an average size about 438.37μm. Scanning electron microscopy photograph of microcapsule is shown in fig.1. The microcapsules were

found to be discrete, spherical and free flowing. *In vitro* dissolution studies were performed using USP XXI basket apparatus at 75 rpm in SGF and SIF; the samples withdrawn were analyzed after suitable dilution at 276 nm spectrophotometricaly.

Table 2: Evaluation data of Salbutamol Sulphate Microcapsules

Formulations	Weight Taken in (mg)	Theoretical Drug Content (mg)	Practical Drug content (mg±SD)*	Encapsulation Efficiency (%)	Wt.of microcapsules Equivalent to 50mg of Drug (mg)	Batch Yield (%)
M1	100	50.31	48.38±0.027	96.16	31.00	99.37
M2	100	50.50	47.99±0.270	95.02	31.25	99.00
M3	100	50.27	48.37±0.027	96.22	31.01	99.45
M4	100	50.37	48.03±0.031	95.35	31.23	99.25
M5	100	50.46	47.01±0.026	93.16	31.90	99.08
M6	100	50.29	48.41±0.025	96.26	30.98	99.41
M7	100	50.16	47.85±0.037	95.39	31.34	99.66
M8	100	50.50	48.78±0.026	96.59	30.75	99.00
M9	100	51.10	49.12±0.039	92.03	30.53	97.83
M10	100	33.67	32.30±0.018	95.93	46.43	99.00
M11	100	25.33	24.50±0.013	96.70	61.22	98.60

*All values are mean ± SD(n=3)

Table 3: Particle Size Analysis of Salbutamol Sulphate Microcapsules

Sieve no passed/retained	12/22	22/44	44/60	60/85	85/120
Size range(µm)	1680-710	710-355	355-250	250-180	180-150
Formulations %Retained					
M1	-	61.8	33.60	6.6	-
M2	-	66.2	29.0	4.8	-
M3	-	67.6	26.6	5.8	-
M4	-	55.08	40.32	4.6	-
M5	-	62.9	29.3	0.80	-
M6	-	55.0	40.4	4.6	-
M8	-	56.6	31.0	12.4	-
M9	-	61.0	27.4	11.6	-
M10	-	64.0	32.02	3.98	-
M11	-	73.6	22.4	4.00	-

In vitro release profiles of microcapsules of all the formulations are shown in fig.2. Formulation M6 and M9 released above 90% at 8^{th} h, Formulation M5, M8, M10 and M11 released below 90% at 9^{th} h, Formulation M3 and M4 released below 90% at 10^{th} h, Formulation M1, M2 and M7 released above 90% at 10^{th} h, The drug release decreased in all the formulation with an increase in the concentration of polymers. The formulation containing guar gum with sodium alginate and the formulation containing chitosan with sodium alginate released above 90% at the end of 10^{th} h. This indicates that microcapsules containing guar gum

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with sodium alginate and chitosan with sodium alginate can be used to sustain the drug release. The mechanism of drug release from all the formulation was found to be diffusion controlled first order kinetics. The short-term accelerated stability studies were performed and all the formulations were found to be stable.

Figure 1: SEMphotograph of microcapsule of salbutamol sulphate encapsulated with polymer and co-polymer

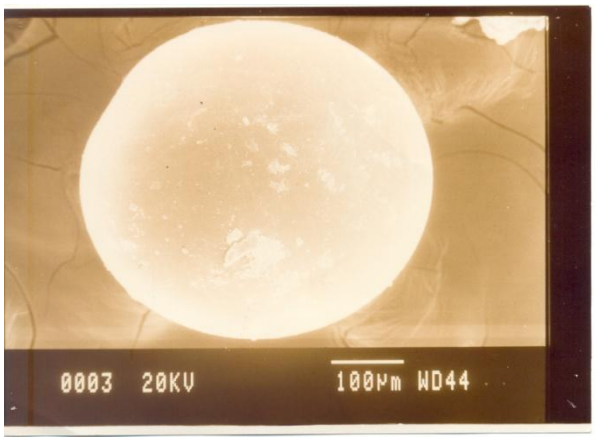
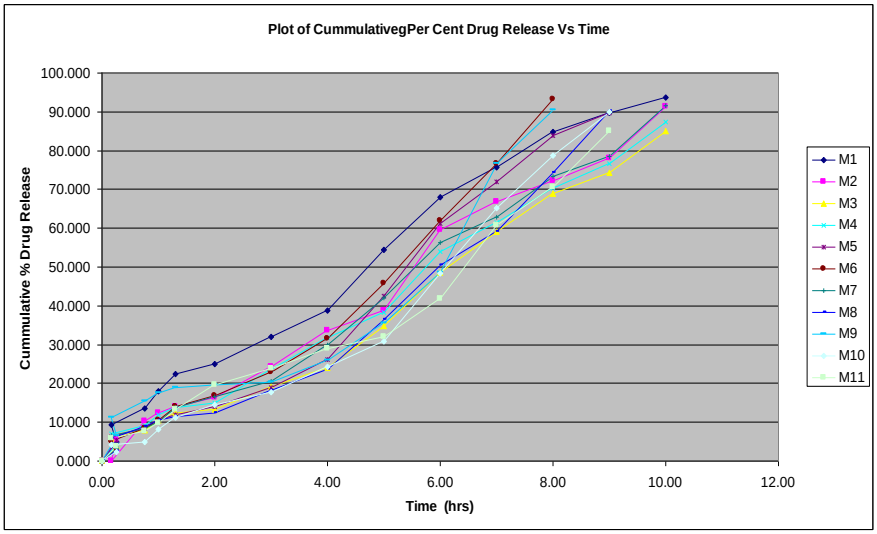


Figure 2: *In vitro* drug release of microcapsules



CONCLUSION

Finally it can be concluded that microcapsules of salbutamol sulphate can be prepared by complex emulsion method using guar gum with sodium alginate and chitosan with sodium alginate to sustain the drug release.

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