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Design and Evaluation of Microcapsules of Sibutramine Hydrochloride Monohydrate

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In this paper, sibutramine hydrochloride monohydrate was formulated in the form of microcapsules *in lieu* of conventional tablet dosage form available to achieve its slower release rate and reduce the possible side effects of dry mouth, anorexia, insomnia, constipation and headache using ionotropic gel entrapment method with different ratio of biodegradable polymethacrylate polymers Eudragit RS-100 and RL-100. There was significant increase in half-life from 1.1-5.0 h. with entrapment up to 88 %. The physicochemical studies like bulk density, tapped density, carr's index confirmed free flowing natures of the granules. FTIR studies showed no interaction between drugs and polymer. SEM studies confirmed smooth topography of microcapsules. The *in vitro* dissolution studies showed maximum release of 82 % for best formulated batch B2 (1:2 drug polymer ratio) out of 5 batches B1, B2, B3, B4 and B5. The release was controlled upto 11 h. The release pattern was diffusion rate controlled and followed Higuchi pattern.

Key Words: Sibutramine hydrochloride monohydrate, Microcapsule, Eudragit RS-100 and RL-100, FTIR, SEM, Release profile.

INTRODUCTION

Sibutramine is an orally administered agent for treatment of obesity. It is centrally acting stimulant chemically related to amphetamines[1-4]. It reaches the peak plasma level after 1 h and has a half life[4] of 1.1 h. It is a neurotransmitter reuptake inhibitor acts by inhibiting the reuptake of serotonin, nor epinephrine and dopamine. It has considerable side effects like dry mouth, nausea, upset stomach, dizziness, drowsiness and increase in blood pressure including cardiac arrhythmia, mental/mood change, seizure, *etc*. An attempt is hereby made to develop the drug in controlled release delivery system *in lieu* of existing tablet formulation to achieve slower release rate and reduce the percentage of dose related side effects.

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EXPERIMENTAL

Sibutramine hydrochloride monohydrate was obtained as a gift sample from Nosch Labs., Hyderabad. Eudragit RS-100 and RL 100 were obtained from Degussa India Pvt. Ltd. Mumbai. All other reagents *i.e*., sodium alginate, calcium chloride were of analytical grade.

Methods: Microcapsules were prepared in five batches, B1, B2, B3, B4 and B5 using different proportions of Eudragit RS-100 and Eudragit RL-100 (80:20) namely 1.0:1.5, 1.0:2.0, 1.0:2.5, 1.0:3.0, 1.0:3.5, sodium alginate 2 % w/v, calcium chloride 4 % w/v adopting ionotropic gelation technique[1-3] with speed controlled stirrer (Remi, Mumbai). At first 2 % w/v sodium alginate was dissolved in water to make a gel. Drug and polymer separately dissolved in acetone with continuous stirring at 500 rpm using a speed controlled stirrer (Remi, Mumbai). Now this solution was poured drop wise using needle in sodium alginate gel with continuous stirring at 500-700 rpm using the above stirrer. Resultant mixture was added to 4 % calcium chloride solution and stir at 500-700 rpm for 2 h to form microcapsules. The resultants microcapsules were filtered, dried at 60 ºC. Final weight was taken and different physical characteristics of the microcapsules were studied. Solvent evaporation method normally involves water insoluble polymer as carriers which require large quantity of organic solvents for their solubilization. As a result this process becomes vulnerable to safety hazards, toxicity and increases cost of production making the technique uneconomical and ecologically unsafe. So ionotropic gelation technique was used for making microcapsules.

Evaluation of microcapsules

Drug entrapment study: 25 mg microcapsules were taken diluted to 10 mL with methanol. It was agitated in a sonicator for 12 h and after suitable filtration and dilution of aliquot, the absorbance was taken in UV-vis spectrophotometer (Shimadzu Pharma space UV 1700) at 220 λ_{max} and percentage entrapment was calculated adopting following formula:

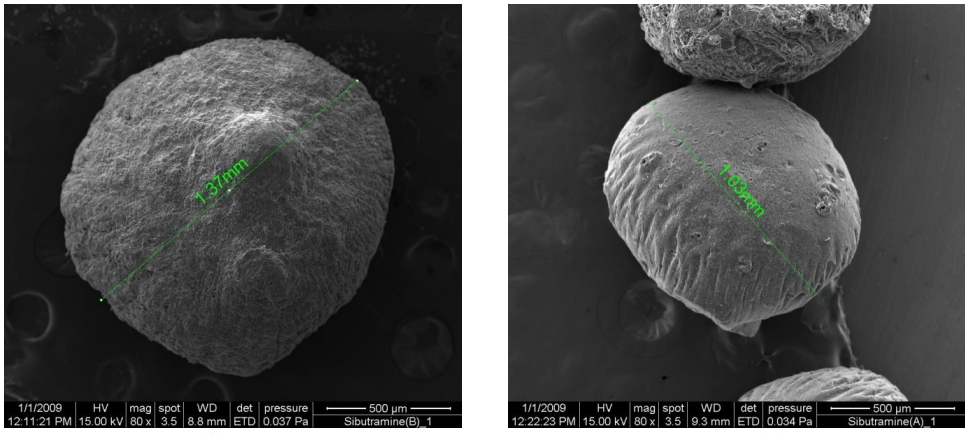
$$\text{Percentage of entrapment} = \frac{\text{Practical loaded drug}}{\text{Theoretical loaded drug}} \times 100$$

Size analysis: Microcapsules were separated into different size fractions by sieving for 0.5 h using a nest of BIS standard sieves (12-200 mesh) in sieve shaker. Results are given in Table-1.

TABLE-1
WEIGHT (%)

Sieve No.	Batch-B1	Batch-B2	Batch-B3	Batch-B4	Batch-B5
10	5.30 ± 0.19	6.60 ± 0.14	4.10 ± 0.13	6.20 ± 0.14	4.20 ± 0.13
15	16.40 ± 0.11	17.40 ± 0.11	15.40 ± 0.11	16.70 ± 0.12	15.30 ± 0.11
20	45.70 ± 0.12	51.20 ± 0.11	46.10 ± 0.12	48.30 ± 0.11	46.00 ± 0.17
25	21.50 ± 0.14	17.00 ± 0.14	22.20 ± 0.15	19.50 ± 0.16	22.20 ± 0.14
30	11.10 ± 0.19	7.80 ± 0.19	12.20 ± 0.19	9.30 ± 0.17	12.30 ± 0.12

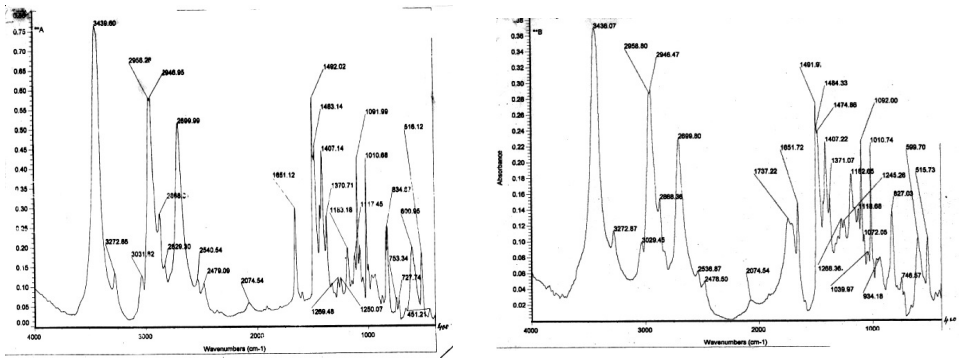
SEM: SEM study was carried out to see the surface topography of the microcapsule after gold coating (Quanta200 mk-2, make FEl, Netherlands) at Bose Institute, Kolkata (Figs. 1A and 1B)[5,6].



(A) (B)

Fig. 1. (A) Sibutramine microcapsule before dissolution (B) Sibutramine microcapsule after dissolution

FTIR study: FTIR of sibutramine blank and drug with polymer was carried out in KBr pellets using Perkin-Elmer model 883 spectroscope in range 4000-400 cm^{-1} at Indian Institute of Chemical Biology, Kolkata (Figs. 2A and 2B)[7,8].



(A) (B)

Fig. 2. (A) Blank drug (B) Drug with polymer

Physicochemical properties of microcapsules: Bulk density, tapped density, Carr's index and angle of repose were carried out on the prepared microcapsules to show the flow properties of the formulation (Table-2). Bulk and tapped density were measured by using 10 mL graduated cylinder. The sample poured in cylinder was tapped mechanically for 100 times, then tapped volume was noted down and

bulk and tapped density were calculated. Each experiment for physicochemical properties was performed in triplicate manner and average value reported.

TABLE-2
PHYSICOCHEMICAL PROPERTIES OF MICROCAPSULES

Batch No.	Entrapment (%)	Bulk density	Tapped density	Carr's index	Angle of repose (º)
B1	87.5 ± 1.160	1.10 ± 0.007	1.120 ± 0.009	2.30 ± 0.697	35 ± 0.681
B2	88.3 ± 0.660	1.11 ± 0.005	1.130 ± 0.007	2.31 ± 0.576	36 ± 0.605
B3	87.7 ± 1.160	1.10 ± 0.006	1.120 ± 0.014	2.30 ± 0.610	32 ± 0.616
B4	88.0 ± 0.660	1.09 ± 0.019	1.125 ± 0.015	2.15 ± 0.605	33 ± 0.625
B5	88.2 ± 1.165	1.10 ± 0.015	1.110 ± 0.160	2.20 ± 0.626	34 ± 0.629

***In vitro* drug release profile of microcapsules:** The release of sibutramine hydrochloride monohydrate from the microcapsules to the surrounding sink solution was carried out at pH 7.2 phosphate buffer media[9] as per USP dissolution apparatus. The concentration of sibutramine hydrochloride monohydrate was determined spectrophotometrically at λ_{max} 220 in five batches namely B1, B2, B3, B4 and B5 containing drug: polymer 1.0:1.5, 1.0:2.0, 1.0:2.5, 1.0:3.0, 1.0:3.5 (Eudragit RS: RL 80:20) and the cumulative amount of drug released against time was calculated (Fig. 3). The dissolution study was conducted on microcapsules in various particle size ranges and the microcapsules in the range of 80 mesh (max) was taken up for further study. The size distribution depicted in Bar chart (Fig. 4). Out of the five batches batch no B2 showed maximum release upto 11 h with increase in $t_{1/2}$ from 1.1-5.0 h.

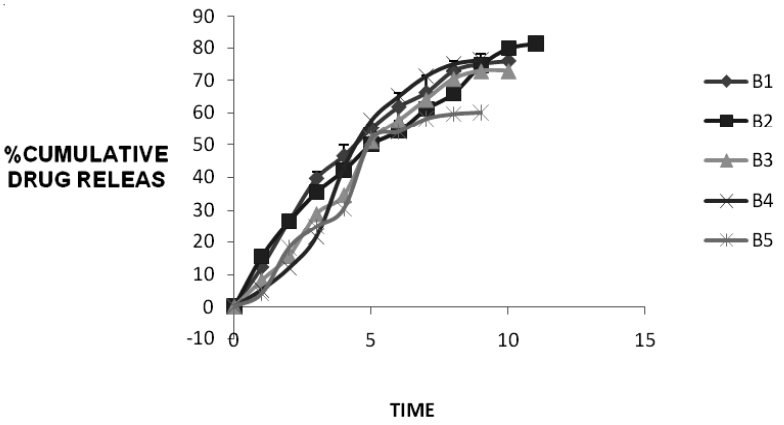


Fig. 3. *In vitro* drug release profile of sibutramine microcapsule

Kinetic assessment of release data: The data obtained from the *in vitro* dissolution studies in different ratio of drug: polymer in batches B1, B2, B3, B4 and B5 were analyzed in terms of different kinetic models[10,11] and regression coefficients were compared. The study confirmed that the release was diffusion rate controlled and followed Higuchi pattern (Table-3).

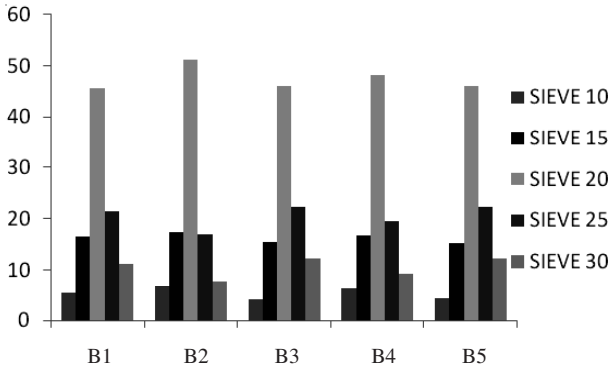


Fig. 4. Sieve analysis

TABLE-3
KINETIC ASSESSMENT OF RELEASE DRUG

Batch No.	Zero order	First order	Higuchi model	Koresmeyer Pappa's
B1	0.9142	0.7778	0.9749	0.9708
B2	0.9811	0.8630	0.9961	0.9935
B3	0.9443	0.8146	0.9798	0.9736
B4	0.9441	0.8143	0.9797	0.9735
B5	0.9811	0.8627	0.9958	0.9932

RESULTS AND DISCUSSION

FTIR results show that there is no interaction between the Eudragit co-acrylic polymers and the drug as no new peaks have been observed. The topographical studies are seen from SEM photographs. The porous nature of surface of the microcapsules show that the drug release is diffusion rate controlled through this micro pores. Studies were also conducted to see affect of topographical change of the microcapsules before and after dissolution studies. The drug entrapment was found to vary from 87.5 ± 1.16 to 88.3 ± 0.66 % from batch B1 to B5 which is quite significant and would not be a constraint for adopting this technology for industrial scale up. The sieve analysis studies showed the maximum percentage of micro capsule is in the range of 51.20 ± 0.11 % in 20 mesh sieve size for batch B2. It is expected that the plurality of the size of microcapsule will give a uniform drug release over a prolonged period to sustain therapeutic activity. Similarly bulk density, tapped density, Carr's index and angle of repose were found to be 1.11, 1.13 and 2.31 g/mL, 36º, respectively for the best optimized batch B2, which show that the result are quite significant for transfer of microcapsule into a bigger capsule (size 0) for therapeutic compliance. Finally the kinetic studies were conducted and the release were fitted into different models for best optimized batch B2 and showed pseudo first order release pattern ($r^2 = 0.985$) with extension of $t_{1/2}$ from 1.1 to 5.0 h. It was diffusion rate controlled and also followed the Higuchi pattern.

On the basis of the above studies, the antiobesity drug sibutramine could be successfully formulated in micro-capsulated form to prolong it therapeutic activity and improve patient compliance.

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