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FORMULATION AND *IN VITRO* EVALUATION OF ETHYL CELLULOSE FLOATING MICROSPHERES

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ABSTRACT

The present study aim towards formulation and *in vitro* evaluation of floating microspheres by oral drug delivery system. The main objective of study is to develop sustained release floating microsphres of diltiazem hydrochloride by using non-aqueous emulsification solvent evaporation method. The experimental work was done as per preformulation study of diltiazem hydrochloride i.e.calibration curve of drug in 0.1 N HCl and IR analysis of drug and polymer like ethyl cellulose 10 cps. Evaluation study of floating microsphere are characterized by micromeretics properties such as particle size, percentage yield, taped density, flow property, percentage floating, percentage drug entrapment, dissolution study and advanced study that is of drug and polymer, SEM of floating microsphere.

Key words: GRDD's, ODDS, Sustained release floating microspheres, *in vitro* study, Ethyl cellulose 10 cps, Dilitiazem hydrochloride.

INTRODUCTION

In the last few decades, many different types of controlled release or sustained release formulation have been developed to improve clinical efficacy of drug and patients compliance. These formulations are designed to deliver the drug at sustained and predetermined rate; thus, maintaining their therapeutic effect and concentration in systemic circulation for prolonged period of time. However, particular formulation may exhibit different drug release profile under different physical status owing to name of excipients and method of manufacturing. Diltiazem HCl is an orally active calcium channel-blocking agent effective in angina and in the management of hypertension. Diltiazem HCl has a relatively short biological half-life of 3-4 hrs. Because of this and rather high frequency of

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administration, it is necessary to develop sustained release preparation. Sustained release diltiazem tablets have been successfully introduced in European and US market. The present study aims towards the microencapsulations of diltiazem HCl with ethyl cellulose 10cps and evaluatation for drug content, % floating, dissolution, bulk density, etc. and the results are reported here.

EXPERIMENTAL

Materials and methods

Material

Diltiazem HCl (IP) supplied by Modi-Mundipharma, Modipuram (GJ), Ethyl cellulose 10cps or Surelease supplied by Fine Chem. Labs, Mumbai, and liquid paraffin (AR), acetone (AR), isopropyl alcohol (AR), petroleum ether (AR), supplied by Merck Ltd., Mumbai were used in present investigation.

Method: The microspheres were prepared by non-aqueous emulsification solvent evaporation method. Briefly, drug and polymer i.e. diltiazem HCl and ethyl cellulose 10cps were mixed in acetone at various ratios by using blending solvent i.e. isopropyl alcohol. The slurry was introduced into 200 mL of liquid paraffin while being stirred at 1200 rpm by mechanical stirrer for 2 hr to allow the solvent to evaporate completely and the microspheres were collected by filtration. The microspheres were washed repeatedly with petroleum ether 40–60^{o}C until free from oil. The collected microspheres were dried for 1 hr at room temperature and subsequently stored in a desiccator over fused calcium chloride.

Preparation of calibration curve of diltiazem HCl in 0.1N HCl (1.2 pH)

Accurately weighed diltiazem HCl (100 mg) was dissolved in 100 mL of pH 1.2 simulated gastric fluid. Dilutions were made in the range of 2- 12 µg/mL. The absorbance values at 203.2 nm corresponding to each concentration were then statistically evaluated and plotted taking absorbance on Y-axis and concentration on the X-axis.

Micromeritics studies of floating microspheres

Particle size determination: Using an optical microscope under regular polarized light, the mean particle size was calculated by measuring 200-300 particles with the help of Ocular micrometer.

Carr's compressibility index: % Compressibility index was calculated by using the formula –

$$(C.I.) = \{(\rho_t - \rho o) / \rho t\} \times 100 \quad \ldots(1)$$

Where, ρ_t = Tapped density and ρ_o = Bulk density.

Hausner ratio = $\rho t / \rho o$

Angle of repose (θ) was calculated as $\tan \theta = 2H / D$**.**

Percentage yield of microsphere

The measured weight of prepared microspheres was divided by the total amount of all the non-volatile components used for the preparation of the microspheres, which gives the total percentage yield of floating microspheres.

% Floating of microspheres

$$\% \text{ Floating microsphere} = \frac{\text{Weight of floating microspheres after time (t)}}{\text{Initial weight of floating microspheres}} \times 100 \quad \ldots(2)$$

$$\% \text{ Floating microsphere} = Q_f / (Q_f + Q_s) \times 100 \quad \ldots(3)$$

Where, Q_f and Q_s are weights of the floating and the settled microspheres, respectively.

Percentage of drug entrapment in microspheres

Weight (50 mg) of floating microspheres were mechanically busted. These powders were dissolved in 50 mL 0.1N HCl and filtered through filter paper. Then 5 mL of this solution was diluted up to 50 mL by blank and the absorbance was noted at 203.2 nm against 0.1N HCl as a blank.

Dissolution study

The dissolution study was done by using standard six stations USP paddle method (Shimadzu). Firstly 900 mL of 0.1 N HCl (pH 1.2) medium was taken; the temperature of the medium was set at $37^0 \pm 2^0$ C and rotational speed of paddle was set at 50 rpm. The 5 mL of sample was withdrawn at predetermined time interval of 1 hour for 12 hours and same volume of fresh medium was replaced. The withdrawn sample was diluted by 0.1N HCl and analyzed by UV-1700 spectrophotometer at the respective λ_{max} values for diltiazem HCl (203.2 nm). The content of drug was calculated using the equation generated from standard curve.

Morphological study using SEM

SEM study was done by using FEI-Philips XL-30 Analytical Electron Microscope (IICT, Hydrabad).

RESULTS AND DISCUSSION

Calibration curve for diltiazem HCl in 0.1 N HCl

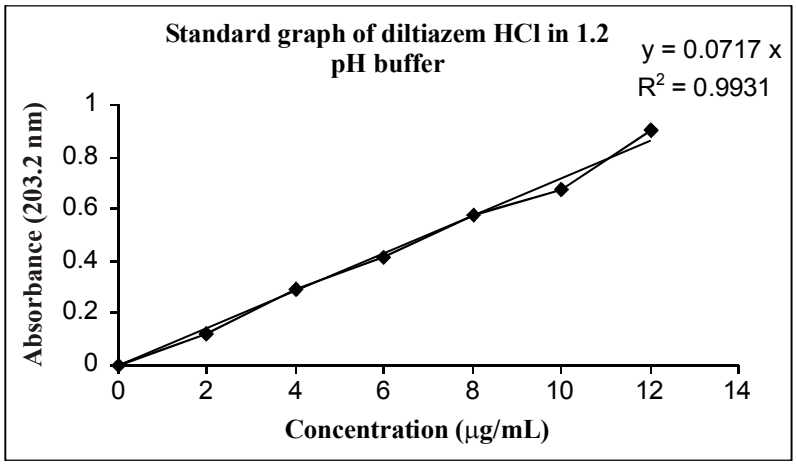


Fig. 1: Calibration curve for diltiazem HCl

Table 1: Calibration curve of diltiazem HCl

S. No	Concentration (μg/mL)	Mean absorbance at 203.2 nm
1	2	0.123
2	4	0.296
3	6	0.411
4	8	0.580
5	10	0.676
6	12	0.900

Micromeritics studies of floating microspheres

The optimized batch has the average particle size in the range of 219.0 ± 13.7 μm.

Tapped density 0.802 g/cm^3 and bulk density is 0.795 g/cm^3. whereas Carr's index is 12.6% and Hausner ratio within 0.180 and angle of repose was found to be 40^o 18', which is an appreciable limit for microspheres to show flow property while formulating in the dosage form.

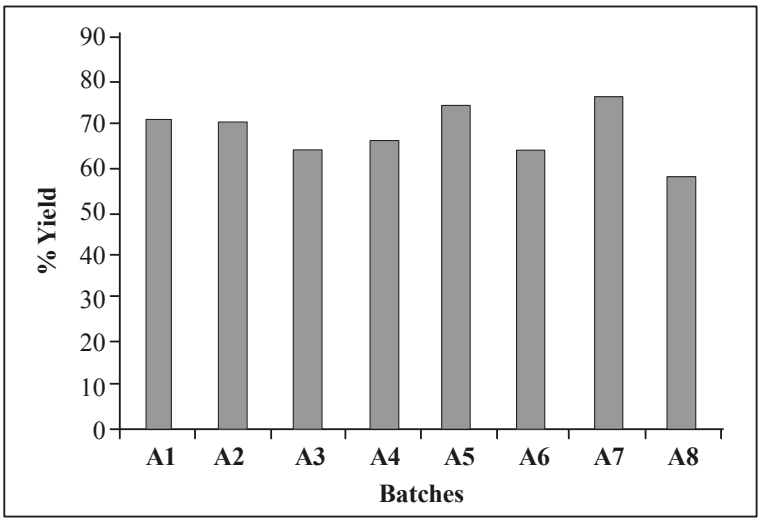


Fig. 2: Percentage yield of microspheres

Table 2: Percentage yield

Batch No.	Percentage yield
A1	70.86
A2	69.56
A3	64.45
A4	66.45
A5	74.42
A6	63.65
A7	76.29
A8	57.17

The maximum percentage yield was found in A7 optimized batch i.e. 76.29% among all the batches.

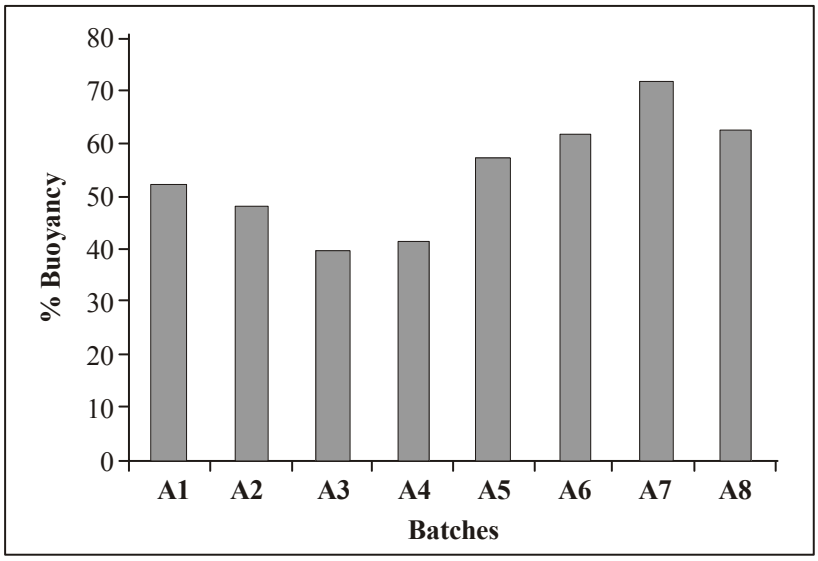


Fig. 3: % Buoyancy test

Table 3: % Buoyancy

Batch No.	Percentage buoyancy
A1	52.12
A2	48.34
A3	39.56
A4	41.65
A5	57.2 0
A6	61.48
A7	72.05
A8	62.18

The maximum percentage buoyancy was found in A7 optimized batch i.e. 72.05% among all the batches.

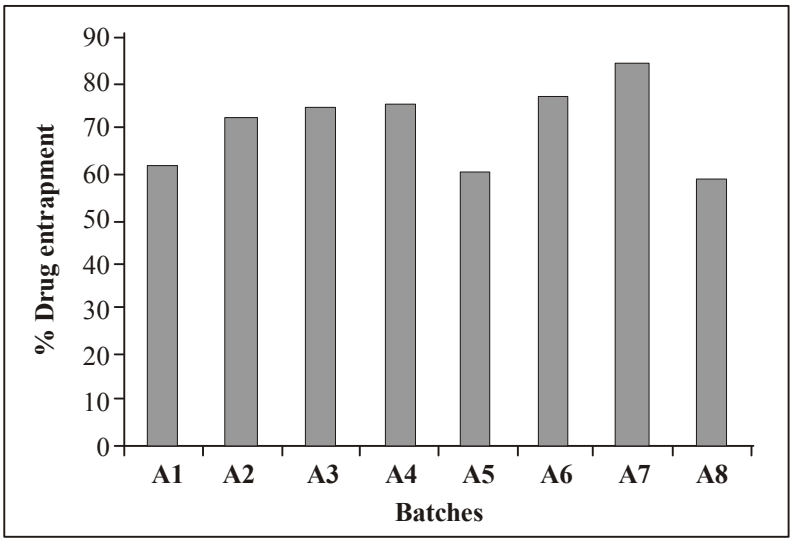


Fig. 4: -% Percentage of drug entrapment

Table 4: % of drug entrapped

Batch No.	Drug incorporation efficiency	
	Drug concentration (mg)	% Drug entrapment
A1	99.61	62.26
A2	116.6	72.87
A3	119.3	74.56
A4	121.0	75.26
A5	96.7	60.43
A6	123.3	77.03
A7	135.9	84.93
A8	94.52	59.07

The microspheres of A7 optimized batch showed an maximum entrapment i.e. 84.93%.

Dissolution (*in vitro* drug release) studies

Cumulative release of all batches of floating microspheres

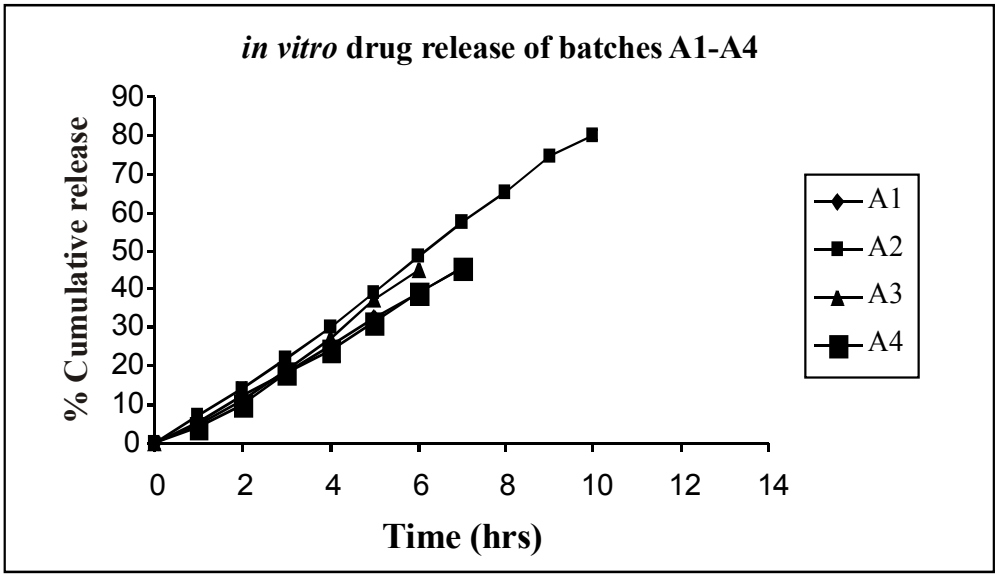


Fig.: 5 Drug release of batch A1-A4

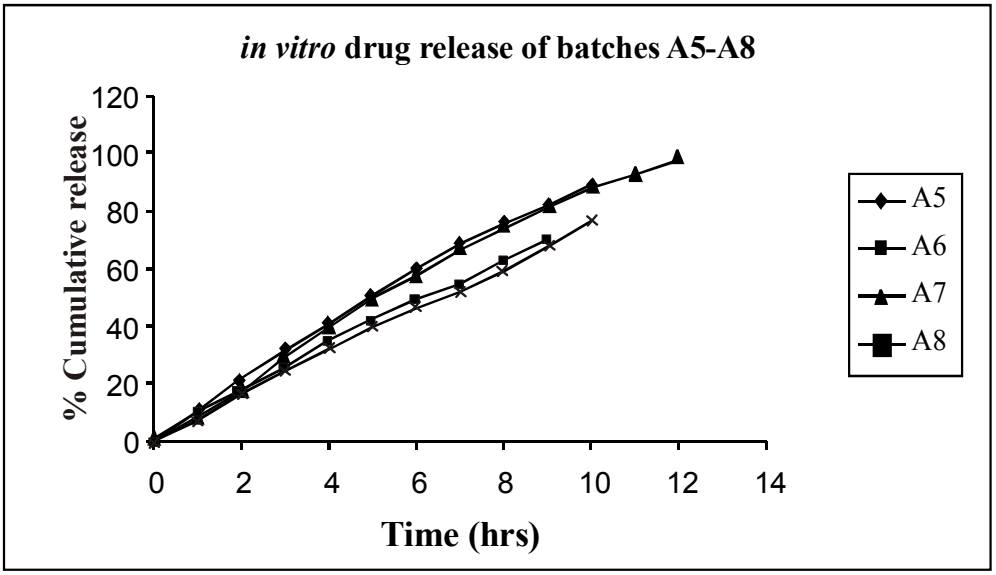
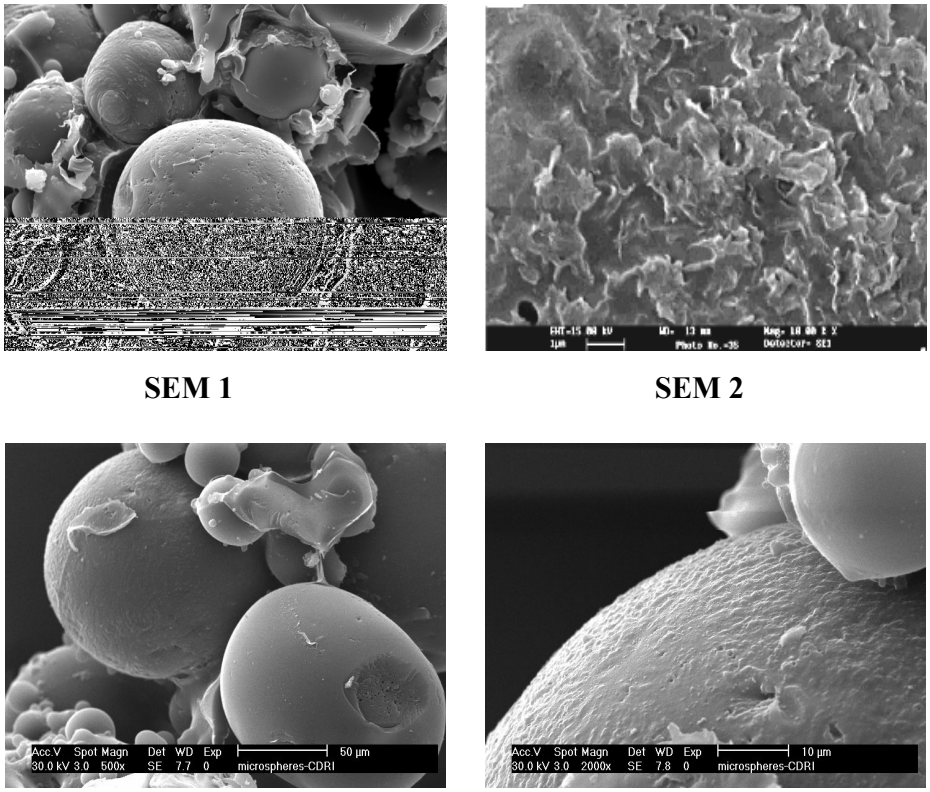


Fig. 6: Drug release of batch A5-A8

The maximum drug release was found in optimized A7 batch i.e.98.89%.

Morphological results with scanning electron microscopy (SEM)



SEM 1 **SEM 2**

SEM 3 **SEM 4**

Fig. 7: SEM Photomicrographs of floating microspheres

SEM 1: Shows smooth texture of floating microspheres.

SEM 2: Shows surface morphology of floating microspheres.

SEM 3: Shows dents on the surface.

SEM 4: Shows pore visibility of floating microspheres.

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