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Floating controlled drug delivery system of verapamil loaded Microballoons

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Abstract
The purpose of this study was to develop a sustained release floating drug delivery system (hollow microsphere or microballoons) of Verapamil hydrochloride using Ethyl cellulose and Eudragit RL 100. Microballoons were prepared by non – aqueous solvent evaporation method and optimized by changing drug: polymer ratio, and polymer combination. Thirteen batches containing only Ethyl Cellulose, only Eudragit RL 100 and both Ethyl Cellulose and Eudragit RL 100 were prepared and evaluated. Drug to Polymer ratio of 1:2 was found to be optimized.
Microballoons were stable, white colored, spherical, free flowing in nature and showed controlled release up to 12 hours. The drug release from the microballoons followed Higuchi model indicating diffusion controlled non-Fickian drug release. Optimized formulation batch showed percentage yield 80.99%, percentage buoyancy 84.05±0.93%, particle size 301.17±3.43µm and percentage drug entrapment efficiency 81.45 ± 0.21%.

Keywords: Micro balloons, verapamil hydrochloride, ethyl cellulose, eudragit RL100

1. Introduction
The ultimate goal of any drug delivery system is effective disease/disorder management, minimum side effects and greater patience compliance in the cost effective manner. The drug therapeutic indices could be maximized while indices of adverse reactions or side effects could be minimized by regulating the drug release in body in a well-defined controlled manner. This would eliminate the hazard and uncontrolled blood plasma profiles of drug usually associated with conventional dosage forms.
Verapamil Hydrochloride is a calcium channel blocker widely used in the treatment of hypertension arrhythmias and angina pectoris. It is well absorbed following oral administration. It's solubility in stomach pH is higher than intestinal pH. The peak plasma concentration is reached after 1-2h. The sustained release formulations may have slightly low bioavailability and peak plasma concentration occurs between 4-6h. The absorption of sustained release formulation may be affected by presence of food. It undergoes presystemic metabolism which is stereospecific and distributes widely and rapidly in body.
Microspheres can encapsulate many types of drugs including small molecules, proteins, and nucleic acids and are easily administered through a syringe needle. They are small spherical particles, with diameters in the micrometer range (typically 1 µm to 1000 µm) Microspheres are sometimes referred to as micro particles. They are generally biocompatible, can provide high bioavailability, and are capable of sustained release for long periods of time. The microsphere fabrication method is a governing factor in the encapsulation and release of therapeutics. In addition, a complicated array of factors including the type of polymer, the polymer molecular weight, the copolymer composition, the nature of any excipients added to the microsphere formulation (e.g., for stabilization of the therapeutics), and the microsphere size can have a strong impact on the delivery rates. A variety of excipients may be added to microsphere formulations to stabilize the drug during fabrication and/or release and may impact drug release through several different mechanisms. Microsphere drug delivery systems have been fabricated by a variety of techniques including combinations of phase separation or precipitation, emulsion/solvent evaporation, and/or spraying methods.

2. Materials and method
2.1 Materials
Verapamil Hydrochloride and Eudragit RL100 was kindly given by Department of Pharmaceutics IIT (BHU) Varanasi, Ethyl Cellulose (Central Drug House Pvt. Ltd.) Ethanol,

dichloromethane, liquid paraffin light, Petroleum ether (S.D. Fine Chemicals).

2.2 Equipment
FT-IR spectrophotometer (SHIMADZU, Model 8400S, Tokyo, Japan), UV/Visible spectrophotometer (SHIMANDZU (1700), Double beam, Japan), Scanning Electron Microscope (ZEISS EVO 18, SEM, China), Differential scanning calorimetry (Mettler Toledo, USA), X Ray diffraction (Rigaku Japan).

2.3 Pre-formulation Studies
The calibration curves of Verapamil Hydrochloride were prepared in distilled water/phosphate buffer pH 7.4/acidic buffer pH 1.2. Then absorbance of the solutions was measured spectrophotometrically at 232nm for Verapamil Hydrochloride. Solubility study was done by shake flak method Distilled Water, Simulated Gastric Fluid or Hydrochloric Acid Buffer (SGF; pH 1.2) Simulated Intestinal Fluid (SIF; pH 6.8) Phosphate Buffer (PB; pH 7.4). Drug-Drug and Drug Polymer Compatibility study was done by FTIR Spectroscopy.

2.4 Preparation of Microspheres
The constituents of each of the seven formulations are presented in table 1.

Table 1: Batch specifications of prepared hollow microspheres.

Batch code	Drug (mg)	Ethyl cellulose (mg)	Eudragit RL-100	Drug polymer Ratio	EC: EU Ratio
A1	300	300	0	1:1	1:0
A2	300	600	0	1:2	1:0
A3	300	900	0	1:3	1:0
B1	300	0	300	1:1	0:1
B2	300	0	600	1:2	0:1
B3	300	0	900	1:3	0:1
F1	300	150	150	1:1	1:1
F2	300	300	300	1:2	1:1
F3	300	450	450	1:3	1:1
F4	300	200	400	1:2	1:2
F5	300	400	200	1:2	2:1
F6	300	150	450	1:2	1:3
F7	300	450	150	1:2	3:1

*****Stirring speed = 1500 rpm, Liquid paraffin 100ml, Magnesium Stearate = 45 mg, Solvent (ethanol and DCM) = 20ml (1:1), Span 40 = 1%

2.5 Micro balloons evaluation
All the prepared Microballoons were evaluated for following parameters

2.5.1 Micrometric Properties
Angle of repose
Angle of repose of different formulations was measured according to fixed funnel method using the formula,

$$\text{Tan}\theta = {}^{h}/_{r}$$

$$\text{Angle of Repose}(\theta) = \tan^{-1}({}^{h}/_{r})$$

Where, h is the height of the pile and r is the radius.

Bulk density and Tapped Density
The loose bulk density (LBD) and tapped bulk density (TBD) of microspheres were determined using the formula

$$\text{LBD} = \frac{\text{weight of the powder}}{\text{Volume of the packing}}$$

$$\text{TBD} = \frac{\text{weight of the powder}}{\text{Tapped volume of the powder}}$$

Compressibility Index
The compressibility index (Carr's Index) of the all formulations were determined by using the below mentioned equation,

$$\text{Carr's Index}\ (\%) = \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \times 100$$

Hausner's Ratio
Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula,

$$\text{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Particle Size Determination
It was determined using optical microscope, eyepiece micrometer and stage micrometer.

2.5.2 Percentage Yield
The prepared microspheres were dried properly and weighed accurately. This weight was divided by the total weight of drug and nonvolatile excipients.

$$\%\text{Yield} = \frac{\text{Weight of microspheres}}{\text{Weight of polymer} + \text{Drug}} \times 100$$

2.5.3 Entrapment Efficiency
The amount of drug was calculated from the standard calibration curve.

$$\%\text{Entrapment efficiency} = \frac{\text{Amount of drug actually present}}{\text{Theoretical drug loaded expected}} \times 100$$

2.5.4 *In Vitro* Buoyancy Studies
300 mg of Microspheres were spread over the surface of the dissolution medium (simulated gastric fluid, SGF, pH 1.2 containing 0.02% w/v of Tween 20) that was agitated by a paddle rotation speed at 100 rpm. After agitation for a predetermined time interval, the microspheres that floated over the surface of the medium and those settled at the bottom of the flask were recovered separately. After drying, each fraction of the micro particles was weighed and their buoyancy was calculated by the following equation.

$$\text{Buoyancy}\ (\%) = \frac{Q_f}{Q_f + Q_s} \times 100$$

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

2.5.5 *In Vitro* Drug Release Studies
The *In-Vitro* drug release studies were carried out using USP type II (Electro Lab.) paddle type dissolution apparatus. Drug loaded microspheres were weighed equivalent to 100 mg of drug and introduced into the 900 ml of dissolution medium (SGF; Acidic Buffer pH 1.2) maintained at 37±0.5 ºC with paddle rotating at 100 RPM. 5 ml sample were withdrawn at pre-set time interval (0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12) up to 12 hours. Aliquots were withdrawn and the same volume of fresh

medium was refilled for the maintenance of sink condition. The samples were suitable diluted and analyzed spectrophotometrically. The dissolution studies were carried out in triplicate and then mean values were plotted as percentage cumulative drug release against time.

Data analysis of release study

The data of drug release from the tested micro balloons were subjected to theoretical analysis to determine the order of kinetic release according to the following equations:

Zero order kinetic $f_t = k_o t$

Where, f_t represent the fraction of drug dissolved in time t and k_o the apparent dissolution constant or zero order release constant

First order kinetic

$$logQ_t = logQ_0 + \frac{(k_1 t)}{2.303}$$

Where, Q_t = Amount of drug released in time t

Q_0 = Amount of drug initially

K_1 = first order rate constant Here the graphical representation of the log cumulative of % drug remaining vs. time will be linear.

Higuchi Model $Q_t = k_H (t)^{0.5}$

Where, Q is the percentage of drug release at time t and k_H is the diffusion rate constant.

Korsmeyer-Peppas model $Q_t = k.t^n$

Where, Q_t is the percent drug release at time't', n is the release exponent.

2.5.6 Sem, Dsc, Xrd

Morphologically characteristics were observed by SEM. The thermal analysis of Verapamil Hydrochloride, Ethyl cellulose, Eudragit RS-100 was performed using Differential Scanning calorimeter (DSC). Powder X-Ray Diffraction (XRD) patterns of verapamil hydrochloride, ethyl cellulose, Eudragit RS-100 were collected in transmission using an Miniflex II Desktop X-ray diffractometer (Rigaku, Japan) with monochromatic CuKα$_1$ radiation (λ= 1.5406 ˚A) generated at 30 kV.

2.5.7 Stability studies

A stability study of optimized batch of Floating Microsphere was performed under accelerated stability conditions (40 ± 2 ºC/75 ± 5% RH) for 3 months according to ICH guidelines for stability testing of new products.

3. Results and discussions

The Particle Size for ethyl cellulose formulations was found in the range of 271.85±1.05µm to 568.71 ± 2.14µm Eudragit formulations was found in the range 196.61±2.1µm to 410.41 ±4.1µm and for the blend of ethyl cellulose and Eudragit RL 100 formulations was found in the range of 211.54 ± 2.63µm to 525.84 ± 4.61µm.

The Percentage Yield for ethyl cellulose formulations was found in the range of 74.53% to 86.14%, for Eudragit formulations was found in the range of 62.98% to 72.61% and for the blend of ethyl cellulose and Eudragit RL 100 formulations was found in the range of 70.11% to 82.99%.

The Entrapment Efficiency increased from 67.21 ± 0.45 to 82.91 ± 0.91 for ethyl cellulose, 54.71 ± 0.31% to 70.17 ±0.91% for Eudragit and 63.21 ± 0.93% to 82.04 ±0.19% for blend of Ethyl cellulose and Eudragit RL 100.

All the batches of microspheres showed very good percent buoyancy in the range of 64.31 ± 0.26% to 84.05 ± 0.93%. The percent compressibility of the microspheres was found to be less than 15.78%, Hausner's ratio was found to be within 1.05 and angle of repose within 25 for most of batches, which is an appreciable limit for microspheres to show good flow properties while formulating in dosage form. The density of all the batches was found to be less than 1g/cm3 which is essential for floating property in the gastric fluid.

3.1 *In-Vitro* Drug Release Studies

The *in Vitro* release pattern showed biphasic release pattern with initial burst effect followed by sustained release up to 12 hrs. Eudragit optimized batch B2 gave 96.83% cumulative release in 10 hours. Ethyl cellulose optimized batch A2 gave 75.88% cumulative release in 12 hours. Optimized blend of Eudragit RL 100 and Ethyl cellulose F5 gave cumulative release of 94.12% release in 12 hours. EU RLeugragit -100 gave burst release and Ethyl cellulose control the drug release thus releasing drug in optimum time 12 hours as microspheres became more permeable. Fig.1

The release kinetics study was done for batch F5 only which was optimized with respect to all the formulation factors. Highest r2 value obtained in Higuchi model for all the batches so it is concluded that release kinetics followed Higuchi model (R2 = 0.998) and most of the drug was released in 12 hours. The release of drug from the microspheres was due to diffusion of drug from polymer surface. Ethyl Cellulose is insoluble in water therefore there is less chance of drug release due to surface erosion of the microspheres. The Korsmeyer- Peppas modeling showed n >0.45. Hence, it can be interpreted that the drug release from the formulation followed non Fickian diffusion, and the drug is uniformly distributed within the polymer as in matrix system.

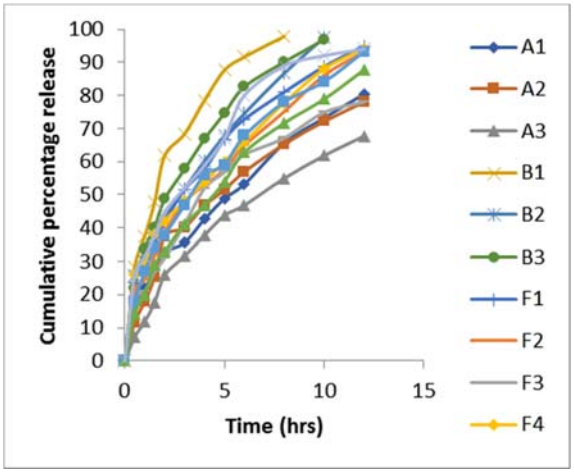

Fig 1: *In vitro* release data of Verapamil hydrochloride in Acidic buffer pH 1.2

3.2 Sem Dsc Xrd

The shape of microspheres was studied under optical microsphere. (Fig.2) It revealed the shape of microspheres was to be spherical. The SEM image of optimized batch F5 revealed that the particles are smooth, dense, less porous and spherical in shape. The magnified view of microsphere surface revealed that surface of the microspheres was covered with the free crystal drug, which in turns responsible for initial burst release of drug from the surface of the microspheres in the acidic buffer of pH 1.2(Fig 3)

The DSC and FTIR studies revealed that there was no interaction between drug and polymer.

The XRD spectrum showed that Verapamil hydrochloride changed from crystalline to slightly less crystalline state. It means the crystallinity of both drugs was reduced after its entrapment in floating hollow microspheres.

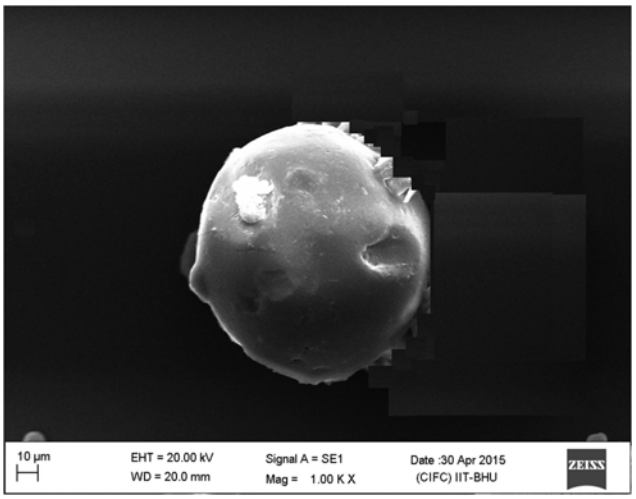

Fig 6.28: SEM image of single microsphere showing spherical shape

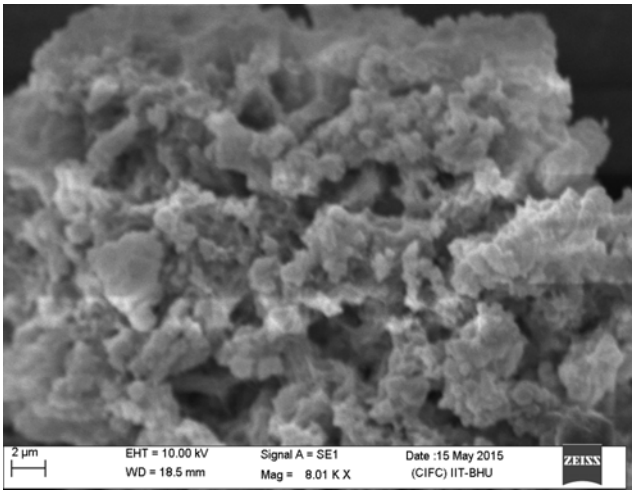

Fig 6.29: SEM image of microsphere surface showing less pores and crystalline drug adsorbed surface.

4. Conclusion

From the study, it was concluded that there is feasibility of formulating Verapamil hydrochloride loaded hollow microspheres of ethyl cellulose and Eudragit RL 100 by non–aqueous solvent evaporation method. Formulation factors like drug: polymer ratio and polymer combination proved to be important factors for the formation Verapamil hydrochloride loaded hollow microspheres. Verapamil hydrochloride loaded hollow microspheres were stable, white colored, spherical, free flowing in nature and showed controlled release up to 12 hours. The drug release from the hollow microspheres followed Higuchi model indicating diffusion controlled non Fickian drug release. Optimized formulation batch F5 showed percentage yield 80.99%, percentage buoyancy 84.05 ± 0.93%, particle size 301.17 ±3.43µm and percentage drug entrapment efficiency 81.45 ± 0.21%.

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