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FORMULATION AND EVALUATION OF VERAPAMIL LOADED HOLLOW MICROSPHERES

Saniya Jawed [*1], Amit Sorathiya [2] and A. K. Srivastava [2]

PES College of Pharmacy [1], 50 Feet Road, Hanumanthnagar, BSK 1st Stage, Bengaluru - 560050, Karnataka, India.
Department of Pharmaceutics [2], Indian Institute of Technology, (Banaras Hindu University) Varanasi - 221005, Uttar Pradesh, India.

Keywords:

Hollow micro spheres, Verapamil Hydrochloride, Ethyl cellulose, Eudragit RS 100

Correspondence to Author:
Mrs. Saniya Jawed

Assistant Professor,
PES College of Pharmacy,
50 Feet Road, Hanumanthnagar,
BSK 1st Stage, Bengaluru - 560050,
Karnataka, India.

E-mail: saniya103@gmail.com

ABSTRACT: Verapamil Hydrochloride is phenyl alkyl amine derivative, Calcium channel blocker: Class IV, antiarrhythmic drug having short half-life of 2.8 – 7.4 hours so requires frequent dosing of 40 -120 mg thrice for treatment of arrhythmia and 80 -120mg thrice a day for treatment of angina and hypertension. It degrades at neutral and alkaline pH. So, study was taken up to Formulate, Optimize and Evaluate the Hollow microspheres of Verapamil Hydrochloride to prevent degradation and to reduce frequency of dose by having sustained release effect. Hollow microsphere or micro-balloons were prepared by non – aqueous solvent evaporation method using Ethyl cellulose and Eudragit RS 100 and optimized by changing drug: polymer ratio, and polymer combination. Thirteen batches containing only Ethyl Cellulose, only Eudragit RS 100 and both Ethyl Cellulose and Eudragit RS 100 were prepared and evaluated. Drug to Polymer ratio of 1:2 was found to be optimized. Micro-balloons were stable, white colored, spherical, free flowing in nature and showed controlled release up to 12 hours. The drug release from the micro-balloons followed Higuchi model indicating diffusion controlled non-Fickian drug release. Optimized formulation batch showed percentage yield 82.99%, percentage buoyancy 86.05 ± 0.93%, particle size 305.17 ± 3.43µm and percentage drug entrapment efficiency 83.45 ± 0.21%.

INTRODUCTION: In country like India because of ever increasing population, the demand for health care services is also increasing. With changing lifestyles and so-called 'fast culture' good health is almost deprived part. With the up gradation of lifestyle, the concept and severity of illness, diseases and disorders are also changing. The major challenged faced by health care professionals in this view is that of gradation of the available drug delivery systems.

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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 [1]. There are followings potential limitations associated with conventional per oral dosage forms [2], they are as follows;

a) The concentration of drug in plasma and hence at the site of action, fluctuates with dosing intervals even at the steady state concentration. Therefore it is very difficult to maintain

constant therapeutic concentration of drug at the site of action.

b) The fluctuations of steady state concentration of drug in plasma can cause either fewer doses or over dose of medication.

c) For drugs with short biological half-lives, frequent dosing would be required to maintain steady state plasma / blood concentration.

These limitations subject the need for design of new drug delivery systems, which will reduce or eliminate the fluctuating plasma / blood concentration. Controlled release drug delivery systems are developed to address many of the difficulties associated with traditional methods of administration. Controlled release drug delivery employs devices - such as polymer-based disks, rods, pellets, or micro particles - that encapsulate drug and release it at controlled rates for relatively long periods of time. Such systems offer several potential advantages over traditional methods of administration. Microspheres can encapsulate many types of drugs including small molecules, proteins, and nucleic acids and are easily administered through a syringe needle. Microspheres are small spherical particles; with diameters in the micrometer range (typically 1μm to 1000μm) [3] 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 [4]. 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.

There are Various Types of Microspheres: [5]

a) Floating Microspheres: These microspheres are for making gastro-retentive formulation as their density is less than that of gastric fluid. This increases gastric retention time and fluctuation in plasma drug concentration is also decreased.

b) Radioactive Microsphere: Radioactive Microspheres are used in the same way as nonradioactive microsphere. Delivery of high concentration of drug to the target site does not damage normal surrounding tissue.

c) Hollow Microsphere: Hollow Microspheres are also called micro-balloon with drug filled up in their outer polymer shells.

d) Magnetic Microsphere: In this drug is magnetically targeted to desired organ rather than drug circulating in full body.

e) Muco-adhesive Microspheres: These micro-spheres adhere to mucus layer and release at controlled rate through this bioavailability of normally poorly absorbed drug is improved.

MATERIALS AND METHODS:

Materials and Equipment: Verapamil Hydro-chloride and Eudragit RS 100 and Ethyl Cellulose was kindly given by Department of Pharmaceutics IIT (BHU) Varanasi, Ethanol, dichloromethane, liquid paraffin light, Petroleum ether (S.D. Fine Chemicals). FT-IR spectro-photometer (SHIMAD-ZU, 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).

Preformulation 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 spectro-photometrically at 232nm for Verapamil Hydrochloride. Solubility study was done by shake flask 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.

Preparation of Microspheres: 50 ml of liquid paraffin was taken in a 250 ml beaker and 1% of span 60 were added. It was then stirred for 15 minutes. This was used as external phase. The accurately weighed amount of polymers was dissolved in 10ml alcohol and 10 ml DCM. Accurately weighed drug was dispersed in the polymer solution and stirred on Mechanical stirrer. 100 mg of magnesium stearate was added to this drug polymer solution as droplet stabilizer. To this internal phase was added drop by drop to the external phase with constant stirring by three blade mechanical stirrer at 1200rpm [6]. 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 RS-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

Evaluation of Microspheres: All the prepared Micro-balloons were evaluated for following parameters.

Micrometric Properties: [7, 8]

Angle of Repose: Angle of repose of different formulations was measured according to fixed funnel method. Completely dried Microspheres were weighed and passed through the funnel, which was kept at a height 'h' from the horizontal surface. The passed microspheres formed a pile of the height 'h' above the horizontal surface and the diameter of the pile was measured and the angle of repose was determined for all the formulation 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.

TABLE 2: SPECIFICATIONS OF FLOW PROPERTY ACCORDING TO ANGLE OF REPOSE

Angle of repose	Flow property
< 25	Excellent
25 - 30	Good
30 - 40	Fair to passable
> 40	Very poor

Bulk Density and Tapped Density: The loose bulk density (LBD) and tapped bulk density (TBD) of microspheres were determined. The prepared microspheres was poured into a calibrated measuring cylinder (10ml) then noted initial volume. Then the cylinder was allowed to fall under its own weight onto the hard surface from the height of 2.5cm at 2 seconds intervals. The tapping was the continued no further change in volume was noted. LBD and TBD were calculated using following equation:

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

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

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

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

TABLE 3: SPECIFICATIONS OF COMPRESSIBILITY INDEX

Carr's index	Flow property
5 - 15	Excellent
12 - 16	Good
18 - 21	Fair to passable
23 - 25	Poor
33 - 38	Very poor
> 40	Very very poor

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

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

Lower Hausner's ratio (< 1.25) indicates better flow properties than higher ones (> 1.25).

Particle Size Determination: [9] It was determined using optical microscope, eyepiece micrometer and stage micrometer. First the stage micro meter and eyepiece micrometer were set in the compound microscope. Then the shorter ruling of eyepiece micrometer was superimposed with larger ruling of stage micrometer and the calculation factor was obtained by dividing the divisions of eye piece micrometer by divisions of stage micrometer. The prepared microspheres were then spread on a glass slide and the diameter of 50 particles was determined and multiplied with factor to get the original dimensions this was done in triplicate.

Percentage Yield: [10] The prepared microspheres were dried properly and weighed accurately. This weight was divided by the total weight of drug and nonvolatile excipients.

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

Entrapment Efficiency: [11-13] 100mg of dried microspheres were crushed properly and dispersed in 50ml distilled water. The content was stirred for 2 hrs and filtered through Whitman filter paper of pore size 0.45. It was then suitably diluted and analyzed spectrophotometricaly. The amount of drug was calculated from the standard calibration curve.

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

***In vitro* Buoyancy Studies:** [14 - 16] 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.

***In vitro* Drug Release Studies:** [17-19] 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 100mg of drug and introduced into the 900ml of dissolution medium (SGF; Acidic Buffer pH 1.2) maintained at 37 ± 0.5 °C 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 analysed spectrophotometrically. The dissolution studies were carried out in triplicate and then mean values were plotted as percentage cumulative drug release against time.

Kinetic Analysis of Drug Release Data:

Zero Order Kinetics:

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions are obtained) can be represented by the following equation:

$$f_t = k_o t$$

Where, f_t represents the fraction of drug dissolved in time t and k_o he apparent dissolution constant or zero order release constant [20].

First Order Kinetics: The pharmaceutical dosage forms following this dissolution profile, such as those containing water-soluble drugs in porous matrices [21], release the drug remaining in its interior, in such way, that the amounts of drug released by unit of time diminish.

$$\log Q_t = \log Q_0 + \frac{(k_1 t)}{2.303}$$

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: Higuchi was the first to derive an equation to describe the release of a drug from an insoluble matrix as the square root of a time-dependent process based on Fickian diffusion.

$$Q_t = [2DS\varepsilon (A - 0.5S\varepsilon)]^{0.5} * t^{0.5}$$

Simplifying,

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

Where, Q_t is the amount of drug released in time t, D is the diffusion coefficient, S is the solubility of drug in the dissolution medium, ε is the porosity, A is the drug content per cubic centimeter of matrix tablet, and k_H is the release rate constant for the Higuchi model. Plot linearity (% CPR vs square root of time) indicates that the release process is diffusion controlled and is applicable for matrix and transdermal formulation [22].

Korsmeyer - Peppas Model: In 1983 Korsmeyer *et al.,* developed a simple, semi-empiric model, when diffusion is the main drug release mechanism, relating exponentially the drug release to the elapsed time t.

$$Q_t = k.t^n \text{ or}$$

$$\log Q_t = \log k + n \log t$$

Where, Qt is the percent drug release at time 't', k is a constant incorporating structural and geometric characteristics of the drug dosage form, n is the release exponent, indicative of the drug release mechanism, and the function t is the fractional release of drug.

The value of n (release exponent) in Korsmeyer - Peppas equation is used to indicate different release mechanisms. A value of n = 0.5 indicates Fickian (case I) release; > 0.5 but < 0.89 for non-Fickian (anomalous) release; n = 1 indicates case-II transport (zero order release) and >1 indicates super case II type of release. Case II generally refers to the erosion of the polymeric chain and anomalous transport (Non-Fickian) refers to a combination of both diffusion and erosion controlled drug release [23].

Only the linear portion of graph was used to calculate the value of time exponent 'n'. The plot made: log cumulative % drug release vs log time (Korsmeyer-Peppas model).

Intercept of n Value:

TABLE 4: DIFFUSION MECHANISM IN ACCORDANCE WITH DIFFUSION EXPONENT (n)

Diffusion exponent (n)	Overall solute diffusion mechanism
0.4	Fickian diffusion
0.45 < n < 0.89	Anomalous (Non-Fickian) diffusion
0.89	Case-II transport
n > 0.89	Super case-II transport

Scanning Electron Microscopy: Morphologically characteristics were observed by SEM. The microspheres were spread on a circular aluminium stub pre-coated with silver glue, gold coating had done and then placed in the observation area of the instrument. It was then observed under the scanning electron microscope in varying magnify-cations and micrographs were recorded. Samples were analysed in SEM at low vacuum. The pressure was maintained in 5.99 to 6.022 torr. The detector used was secondary electron detector [24].

Differential Scanning Calorimetry: Thermo analytical method, Differential Scanning Calorimetry (DSC) is a very useful tool in the characterization. The thermal analysis of Verapamil Hydrochloride, Ethyl cellulose, Eudragit RS-100 was performed using Differential Scanning calorimeter (DSC) (Mettler-Toledo DSC Model 822e). The apparatus is equipped with a ceramic sensor FRS5 (heat-flux sensor with 56 thermo-couplea Au-Au/Pd). The DSC was previously calibrated using indium and zinc standards for temperature and power calibration. The auto sampler available on Mettler-Toledo DSC Model 822e was used to automate the experimental procedure. The measuring range was extended to -65 °C by a cooling Intra cooler system (RP = 100 MT; PowerPoint 2000 LDT). Sample (approx. 5 to 10mg) was heated from 20 to 290 °C at the rate of 20°C/min. Thermogram are acquired under nitrogen flow of 5ml/min. Cooling rate selected was 10 °C/min. Three DSC runs were carried out to determine various glass transitions (Tg) as well as the melting behaviour of the samples at a higher temperature [25].

X-Ray Diffraction Analysis: 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. Powder diffractometer operating on Bragg-Berntano geometry was fitted with a curved crystal graphite monochromator in the diffraction beam from range of 10-90 ° (2θ) and with a step size of 0.020. The powder was packed into the rotating sample holder. The scanning rate was set at 10°/minute [26].

Stability Studies: From the prepared floating microspheres which showed appropriate balance between the buoyancy and the percentage release was selected for stability studies. A stability study of optimized batch of Floating Microsphere was performed under accelerated stability conditions (40 ± 2 °C / 75 ± 5% RH) for 3 months according to ICH guidelines for stability testing of new products. The samples were withdrawn at different interval (0, 1 and 3 months) and evaluated in terms of buoyancy and the percentage release [27].

RESULTS AND DISCUSSIONS: The Particle Size for ethyl cellulose formulations was found in the range of 275.85 ± 1.05µm to 564.71 ± 2.14µm Eudragit formulations was found in the range 192.61 ± 2.1µm to 405.41 ± 4.1µm and for the blend of ethyl cellulose and Eudragit RL 100 formulations was found in the range of 215.54 ± 2.63µm to 535.84 ± 4.71µm.

The Percentage Yield for ethyl cellulose formulations was found in the range of 76.13% to 87.04%, for Eudragit formulations was found in the range of 66.98% to 77.64% and for the blend of ethyl cellulose and Eudragit RS 100 formulations was found in the range of 72.11% to 82.99%.

The Entrapment Efficiency increased from 69.21 ± 0.45 to 84.91 ± 0.91 for ethyl cellulose, 58.71 ± 0.31% to 72.17 ± 0.91% for Eudragit and 65.21 ± 0.93% to 84.04 ± 0.19% for blend of Ethyl cellulose and Eudragit RS 100.

All the batches of microspheres showed very good percent buoyancy in the range of 64.31 ± 0.26% to 86.05 ± 0.93%.

TABLE 5: EFFECT OF DRUG: POLYMER RATIO ON PARTICLE SIZE, % ENTRAPMENT EFFICIENCY, % YIELD AND % BUOYANCY

Batch code	Drug : polymer Ratio	Particle Size (µm ± SD)	%Entrapment Efficiency	% Yield	% Buoyancy
A1	1:1	275.85±1.05	69.21 ± 0.45	77.56	75.12 ± 0.25
A2	1:2	401.42± 1.62	82.68± 0.82	82.98	81.07 ± 0.13
A3	1:3	564.71 ± 2.14	84.91 ± 0.91	85.17	82.92 ± 0.18
B1	1:1	192.61±2.1	58.71 ± 0.31	68.32	64.31 ± 0.26
B2	1:2	265.86 ±3.4	68.54 ± 0.17	74.61	67.05 ± 0.31
B3	1:3	405.41 ±4.1	72.17 ±0.91	77.65	67.81 ± 0.19
F1	1:1	215.54 ± 2.63	65.21 ± 0.93	72.48	77.15 ± 0.34
F2	1:2	303.54 ± 3.37	76.32 ± 0.54	83.11	78.27 ± 0.21
F3	1:3	535.84 ± 4.71	78.42 ± 0.82	86.54	79.54 ± 0.48
F2	1:1	303.54 ± 3.31	76.32 ± 0.54	83.11	78.27 ± 0.21
F4	1:2	274.61 ±1.58	71.05 ± 0.51	76.22	75.81 ± 0.41
F5	2:1	305.17 ±3.43	83.45 ± 0.21	84.61	86.05 ± 0.93
F6	1:3	268.94 ±2.82	67.98 ± 0.71	76.53	71.98 ± 0.16

Micromeritic analysis of the microspheres play an important role in the various pharmaceutical processing such as mixing, filling, compression and packaging of pharmaceutical dosage form. Different micromeritic parameters (such as angle of repose, bulk density, Carr's index and Hausner's ratio) of all batches of hollow microspheres have been shown in the **Table 6**. The percent compressibility of the microspheres was found to be less than 16.28%, Hausner's ratio was found to be within 1.15 and Angle of repose within 25.46, 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/cm^3 which is essential for floating property in the gastric fluid.

TABLE 6: MICROMERITIC PROPERTIES OF THE MICROSPHERES

Batch code	Bulk Density	Tapped Density	Percent Compressibility	Housner's Ratio	Angle of Repose
A1	0.4523	0.5137	13.14	1.05	25.21
A2	0.4851	0.5872	12.56	1.14	17.92
A3	0.5265	0.6129	15.24	1.07	15.98
B1	0.8124	0.8625	8.67	1.04	20.84
B2	0.8371	0.8601	12.12	1.03	21.27
B3	0.8424	0.8651	11.01	1.02	23.68
F1	0.6271	0.6681	13.91	1.10	13.97
F2	0.6342	0.6821	12.14	1.12	11.84
F3	0.6246	0.6714	13.01	1.09	10.12
F4	0.6724	0.6901	11.12	1.02	21.05
F5	0.6345	0.6398	14.02	1.03	12.58
F6	0.7125	0.7215	9.34	1.04	17.04
F7	0.6017	0.6814	15.64	1.13	18.99

The dissolution studies were carried out in triplicate and then mean values were plotted as percentage cumulative drug release against time. The drug release in Eudragit microspheres showed biphasic behaviour consisting of initial burst release followed by a slow release phase. But Eudragit optimized batch B2 gave 97.53% release in 10 hours. In microspheres, prepared by ethyl cellulose with optimized drug: polymer ratio 1:2 gave 77.98% release in 12 hours.

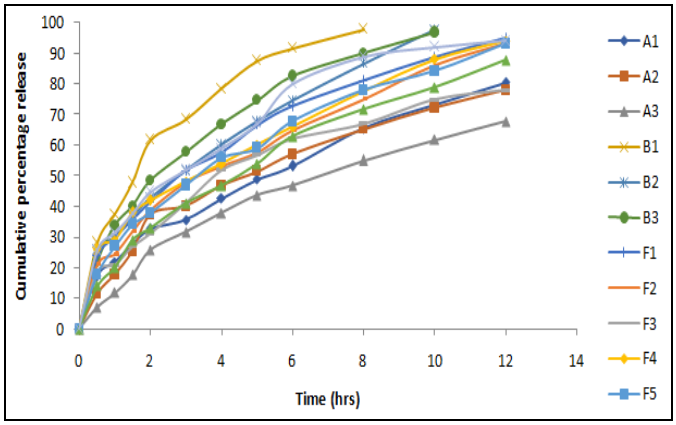

FIG 1: *IN VITRO* RELEASE DATA OF VERAPAMIL HCL IN ACIDIC BUFFER (pH 1.2)

Ethylcellulose released drug in very controlled manner. Best release result was given by blend of Eudragit RS 100 and Ethyl cellulose 94.96% release in 12 hours. Optimized with all responses F5 batch gave 93.52% release in 12 hours.

The release kinetics study was done for batch F5 only which was optimized with respect to all the formulation factors. Highest r^2 value obtained in Higuchi model for all the batches so it is concluded that release kinetics followed Higuchi model (R^2 = 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 modelling 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. Also r^2 is higher for higuchi hence release was diffusion controlled.

TABLE 7: RELEASE KINETIC MODELS FOR VERAPAMIL HYDROCHLORIDE

Model	0 order model	1st order model	Higuchi model	Korsmeyer Peppas model	
Batch code	r^2	r^2	r^2	r^2	n
F5	0.9144	0.9718	0.9983	0.9973	0.51

The surface morphology, shape of batch F5 was studied by using scanning electron microscopy shown in **Fig. 2** and **3**. The images showed spherical structure of microspheres. 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. The DSC curve of the pure drug Verapamil Hydrochloride is indicative of its crystalline state. The DSC thermogram is characterized by an endothermic melting peak at 142 °C.

In the formulation, the characteristic peak of Verapamil Hydrochloride is not retained but a single endothermic peak at 112 °C and a glass transition at 38 °C shown in **Fig. 4**. It can be concluded that the drug changes from crystalline to amorphous form in the formulation, which is also responsible for the increase in the solubility of the drug.

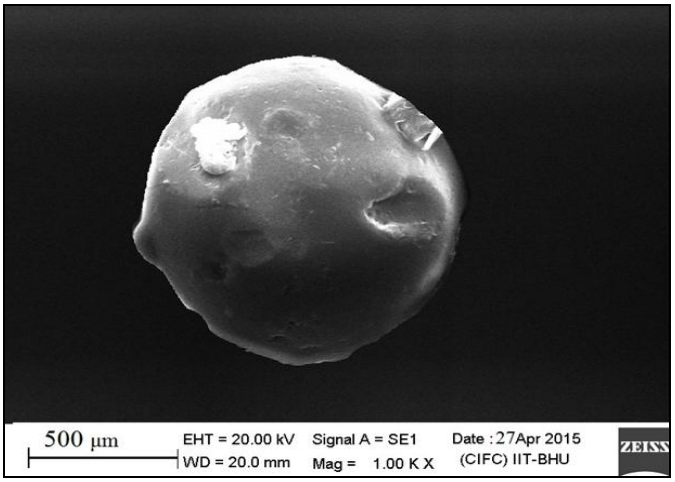

FIG. 2: SEM IMAGE OF SINGLE MICROSPHERE SHOWING SPHERICAL SHAPE

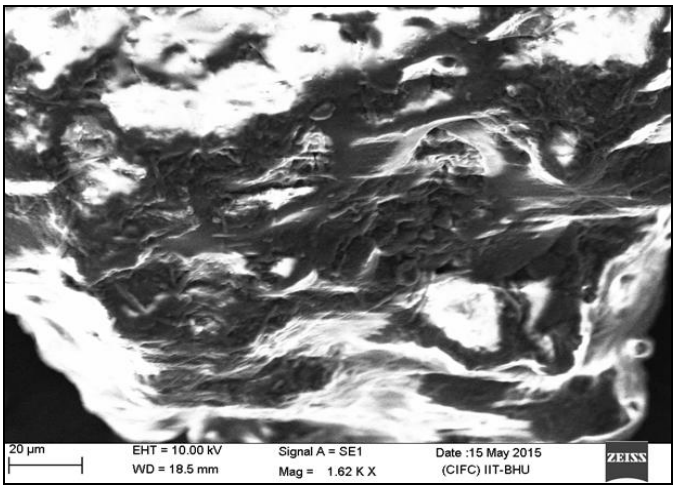

FIG. 3: SEM IMAGE OF MICROSPHERE SURFACE SHOWING LESS PORES AND CRYSTALLINE DRUG ADSORBED SURFACE

In X-RD studies some changes in peak position of verapamil HCl were observed in hollow microsphere (Batch F5). The prominent peaks from pure verapamil HCl at 2θ of 10.59°, 14.45°, 17.07°, 18.1°, 18.84°, 20.29°, 21.32°, 23.06°, 23.75°, and 26.29°, etc. were clearly seen at the same position in the hollow microsphere (Batch F5) but the peak intensities were decreased to some extent. From the stated observations, we can conclude that the crystalline nature of the drug was still maintained, but the small reduction of diffraction intensity of verapamil HCl in Eudragit, Ethyl cellulose hollow microsphere suggests that the quality of the crystals was reduced and/or presence of high-concentration polymer.

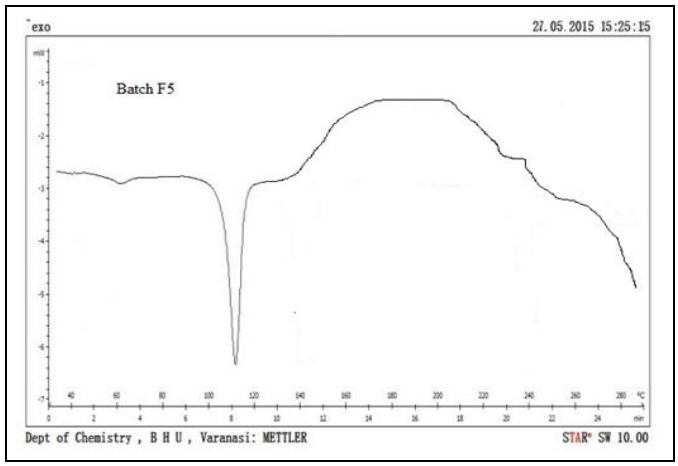

FIG. 4: DSC THERMOGRAM OF OPTIMIZED MICROSPHERES BATCH F5

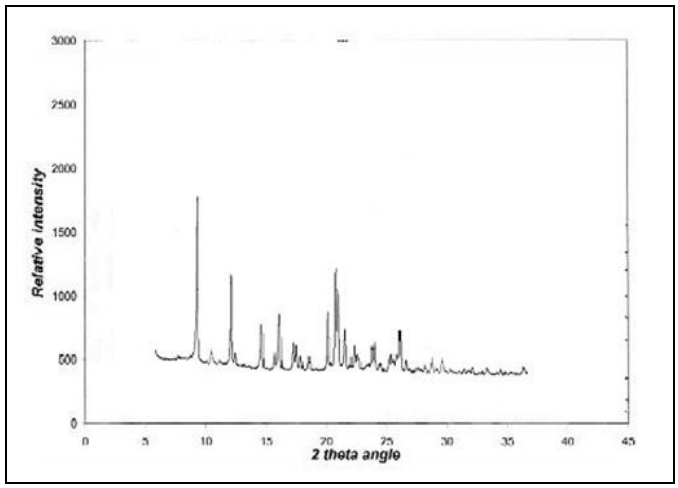

FIG. 5: X- RAY DIFFRACTOGRAPH OF BATCH F5

The stability was evaluated on the basis of percentage entrapment efficiency and cumulative percentage release in 15days interval up to 45 days. No significant change in percentage entrapment efficiency and cumulative percentage release was observed for all the storage time which indicated that batch F5 was stable.

TABLE 8: STABILITY STUDY OF OPTIMIZED BATCH F5

Parameters	0 days	15 days	30 days	45 days
Percentage Entrapment Efficiency	83.45 ± 0.21	82.33 ± 0.22	81.54 ± 0.24	80.68 ± 0.27
Cumulative Percentage Release	93.22	92.32	91.56	90.86

CONCLUSION: From the study, it was concluded that there is feasibility of formulating Verapamil hydrochloride loaded hollow microspheres of ethyl cellulose and Eudragit RS 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 82.99%, percentage buoyancy 86.05 ± 0.93%, particle size 305.17 ± 3.43µm and percentage drug entrapment efficiency 83.45 ± 0.21%.

Moreover, *in vivo* pharmacokinetic, bio-distribution and preclinical studies are required to be done. As a part of future work, the work will be continuing in future at lab scale with *in vivo* pharmacokinetic and bio distribution studies.

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