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FORMULATION AND EVALUATION OF SUSTAINED RELEASE MICROSPHERES OF ROSIN CONTAINING ATORVASTATIN CALCIUM

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Abstract:

Atorvastatin Calcium was microencapsulated using rosin by o/w emulsion solvent evaporation technique. The effect of three formulation variables including the drug:polymer ratio, emulsifier (polyvinyl alcohol) concentration and organic solvent (dichloromethane) volume were examined. The prepared batches were characterized for microspheres particle size distribution, encapsulation efficiency and in vitro release behavior. The study reveals that drug:polymer ratio had a considerable effect on the entrapment efficiency, however particle size distribution of microspheres was more dependent on the volume of dichloromethane and polyvinyl alcohol concentration rather than on the drug: polymer ratio. Drug, polymer concentrations were varied to obtain optimum release profile for sustaining the action of the drug.

Keywords: *Atorvastatin Calcium. Rosin. Microspheres. Sustained release*

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INTRODUCTION:

Conventional oral drug administration does not usually provide rate-controlled release or target specificity. In many cases, conventional drug delivery provides sharp increase in drug concentration often achieving toxic level and following a relatively short period at the therapeutic level of the drug concentration eventually drops off until re-administration. In order to obtain maximum therapeutic efficacy, it becomes necessary to deliver an agent to the target tissue in the optimal amount for the required period of time, thereby causing little toxicity and minimal side effects [1,2]. Desired drug release can be provided by rate-controlling membranes or by implanted biodegradable polymers containing dispersed medication. Microparticulate drug delivery systems are considered and accepted as a reliable one to deliver the drug to the target site with specificity, to maintain the desired concentration at the site of interest without untoward effects [2]. Microencapsulation is a useful method which prolongs the duration of drug effect significantly and improves patient compliance. Eventually the total dose and few adverse reactions may be reduced since a steady plasma concentration is maintained [3]. In recent years much research in drug delivery has been focused on degradable polymer microspheres. Administration of medication via such systems is advantageous because microspheres can be ingested or injected, can be tailored for desired release profiles and in some cases it can provide organ-targeted release [4-7]. The meaning of microencapsulation is converting liquids to solids, altering colloidal and surface properties, providing environmental protection and controlling the release characteristics by using the coating materials.Emulsion solvent [5], phase-separation method10 and spray drying method [8] are commonly used for the preparation of microspheres. The success of any microencapsulation method depends on many factors such as the drug solubility, partition co-efficiency, polymer composition, molecular weight etc. Among the various microencapsulation methods, emulsion solvent evaporation technique is often widely used to prepare microcapsules of water insoluble drugs (within the water insoluble polymer). Microspheres are formed by the evaporation of an organic solvent from dispersed oil droplets containing both polymer anddrug[4,7,9,10,11]. Atorvastatin calcium is a HMG-CoA reductase inhibitor used in the treatment of hyperlipidemia. It has an oral bioavailability of less than 12% after a 40mg oral dose. It also undergoes high first pass metabolism. It is highly soluble in acidic pH and absorbed more in the upper part of the GIT. The major hurdle of atorvastatin is rate limited bioavailability. The main objective of the present work is to formulate microspheres of atorvastatin. The microspheres of atorvastatin may improve solubility and higher dissolution rate by decreasing particle size and increasing surface area. They may increase the patient compliance by significantly enhancement in oral bioavailability of the drug.

MATERIALS AND METHODS:

Materials

Atorvastatin calcium candida health pharmaceutical; Eudragit S100 Evonik Industries. Polyvinyl alcohol (PVA - MW 1, 30,000) from SD fine chemicals, Rosin from Yucca Enterprises, Dombivilli, and Thane, India were used in the study. Dichloromethane, Potassium dihydrogen phosphate, Sodium hydroxide and Camphor were procured from S.D. Fine Chemicals, Mumbai, India.

Method

Microspheres of Atorvastatin calcium were prepared based on o/w emulsion solvent evaporation technique by using rosin as a polymer. Different batches of microspheres were prepared by dissolving the polymer and the drug in dichloromethane and then adding this oil phase in the aqueous phase (100 ml) containing various percentages of PVA as the emulsifying agent; the mixture was emulsified by constant stirring at 400 rpm for 4 h by using a propeller stirrer (Remi, India). The dispersed drug and polymer solution was immediately transformed into fine droplets, which subsequently solidified into rigid microspheres due to the solvent evaporation. The particles were collected by filtration, washed and dried in vacuum desiccators and characterized

Table 1: Composition of Atorvastatin calcium loaded microspheres

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7
Atorvastatin calcium	200	400	600	200	200	200	200
Rosin	200	200	200	400	600	400	600
PVA	0.25%	0.25%	0.25%	0.25%	0.25%	0.25%	0.25%
Dichloromethane	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml
Water	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml
Camphor	---	---	---	---	---	200	200

Drug-Excipients Compatibility Studies

Differential Scanning Calorimetery (DSC)

The DSC measurements were performed on a differential scanning calorimeter with a thermal analyzer. All accurately weighed samples were placed in sealed aluminum pans, before heating under nitrogen flow (20ml/min) at a scanning rate of 10 °C min−1 from 25 to 250 °C. An empty aluminum pan was used as reference.

Drug polymer Interaction (FTIR) study

Fourier-transform infrared (FT-IR) spectra were obtained by using shimadzu FTIR- 8400 Spectrophotometer. The samples were previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:5 (Sample/KBr) ratio, respectively. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press.

Percentage Yield

The yield of microspheres was determined by comparing the whole weight of microspheres formed against the combined weight of the copolymer and drug.

$$\text{Percentage yield} = \frac{\text{Mass of microspheres obtained}}{\text{Total weight of drug and polymer used}} \times 100$$

Particle size and size distribution

The microspheres were suspended in liquid paraffin and examined using an optical microscope. Laser diffraction technique (Malvern Instruments Ltd. Malvern, UK) was used to study the size distribution of the microspheres. The dispersant used was cyclohexane and the average particle size was calculated and expressed in microns.

Drug Entrapment efficiency

The drug entrapment efficiency (DEE) was calculated by the following formula

$$\textbf{DEE} = (\textbf{Pc} / \textbf{Tc}) \times \textbf{100}$$

Here, Pc is practical content,

Tc is the theoretical content.

X-ray Diffraction Studies (XRD)

X-ray diffraction analysis was performed using Bruker axs diffractometer D 8Advanced model (high beam monochromatic) using Cu radiation which was generated at 40 Kv and 40 mA at 1.540600A. The rate of the scanning was 0.30°C /min.

Drug Content Determination

ATR spherical agglomerates equivalent to 40 mg of ATR were accurately weighed, crushed and transferred to a 10 mL volumetric flask. To this, 50 mL of methanol was added and sample was sonicated for 20 min so as todissolve the drug and the polymer. The volume was made up to 100 mL withmethanol and filtered through a 0.45 µm filters. The filtrate was diluted withmethanol and analyzed at 246.5 nm by uv-spectrophotometer.

Solubility Study

The apparent solubility of Spherical crystals of Atorvastatin calcium determined In water.Each Spherical crystals in excess of drug equivalent to (40 mg) was added to 10 ml of solvent in glass vials with rubber closers. Then the vials were kept on a shaker incubator maintained at 37 ± 0.5 °C for 24 h. After shaking, the vials were kept in an incubator at 37 ± 0.5 °C for equilibrium for 10h. The solution was then filtered through 0.45 µm Millipore, filtered and the filtrate was assayed spectrophotometrically at 246.5 nm.

In-vitro release studies

In-vitro dissolution studies were carried out with spherical agglomerates. Each test was carried out in United States Pharmacopoeia dissolution apparatus II

(Paddle) consisted of 900 ml , 0.1 N HCl maintained at 37.0 ± 0.5°C and stirring at 75 rpm. An accurately weighed quantity of each sample equivalent to 40 mg of Atorvastatin Calcium was subjected to the test. Samples 5 ml were withdrawn at predetermined time interval (5, 10, 15, 20 & 30 minutes) and immediately replace with the equal volumes of dissolution medium.. Diluted samples were analyzed at 246.5 nm by uv-spectrophotometer.

Flow Property

Flowability of ATR and its spherical agglomerates were determined in terms of the following parameters,Bulk density,Tapped density, Hausner ratio,Carr's index and Angle of repose.

RESULTS AND DISCUSSION:

Differential Scanning Calorimetery (DSC)

The pure drug Atorvastatin calcium shown as an endothermic peak at 189.14oC. The peak neither is nor shifted in the case of DSC of the Atorvastatin calcium microspheres formulation containing Atorvastatin calcium. The DSC of physical mixture of the Losartan Potassium showed an endothermic peak at 189.14oC. The DSC spectra as shown in Fig 1 & 2.

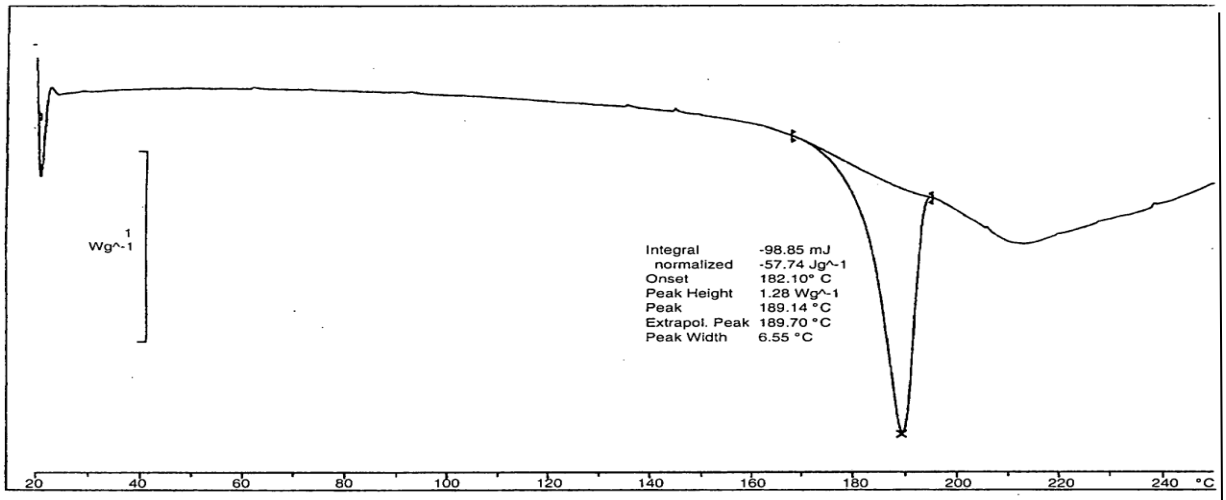

Fig. 1: DSC of Atorvastatin calcium

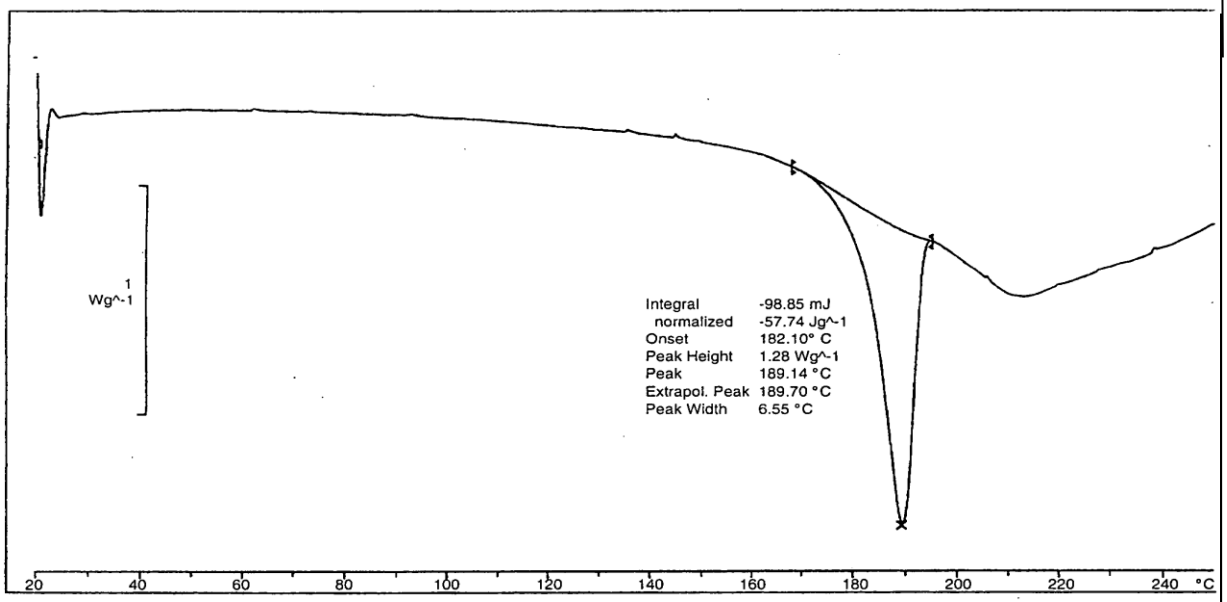

Fig. 2: DSC of Atorvastatin calcium with Physical mixture

Drug polymer Interaction (FTIR) study

From the spectra Atorvastatin calcium and physical mixture of Atorvastatin calcium, it was observed that all characteristic peaks of Losartan potassium were present in the combination spectrum, thus indicating compatibility of the Losartan potassium and polymer.

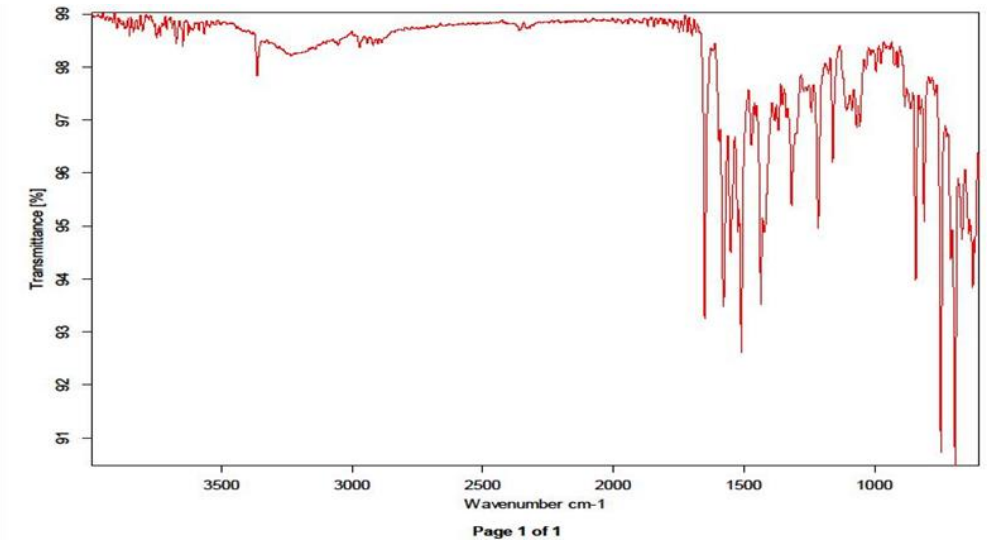

Fig No.3: F IR of Atorvastatin calcium

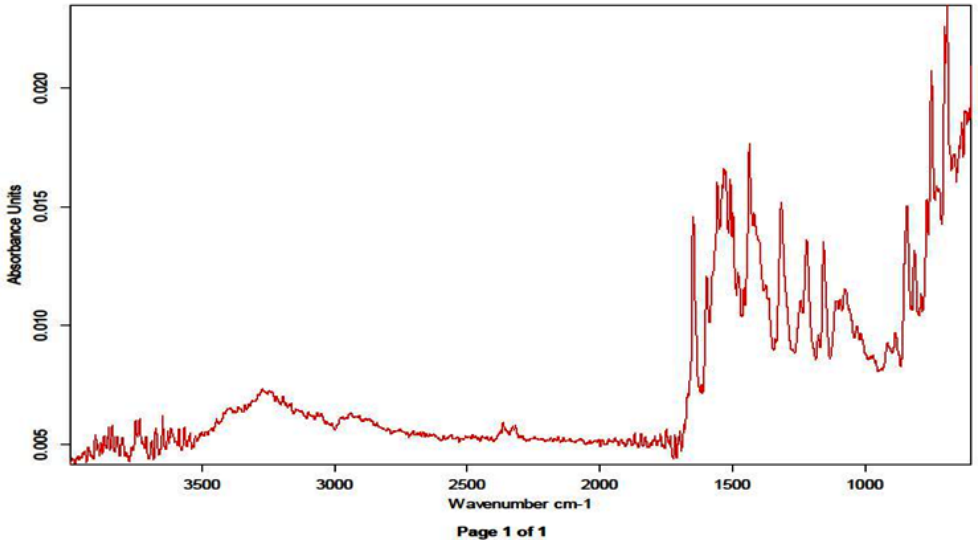

Fig No.4: FTIR of Atorvastatin calcium Physical Mixture.

Table 2 Characteristics of Atorvastatin calcium microspheres

Formulation code	Percentage Yield	Particle size(µm) Mean±SD	% Drug Content	Entrapment efficiency (%)
F1	45.0	112±0.02	48.32	78.41±0.01
F2	50.0	118±0.04	52.32	80.30±0.01
F3	64.1	140±0.06	65.12	83.31±0.01
F4	80.0	167±0.02	81.23	85.21±0.01
F5	90.83	171±0.01	92.36	94.12±0.01
F6	85.0	172±0.03	86.00	91.14±0.01
F7	91.5	174±0.07	92.36	93.16±0.01

SEM studies

The microspheres are almost spherical with smooth surface.

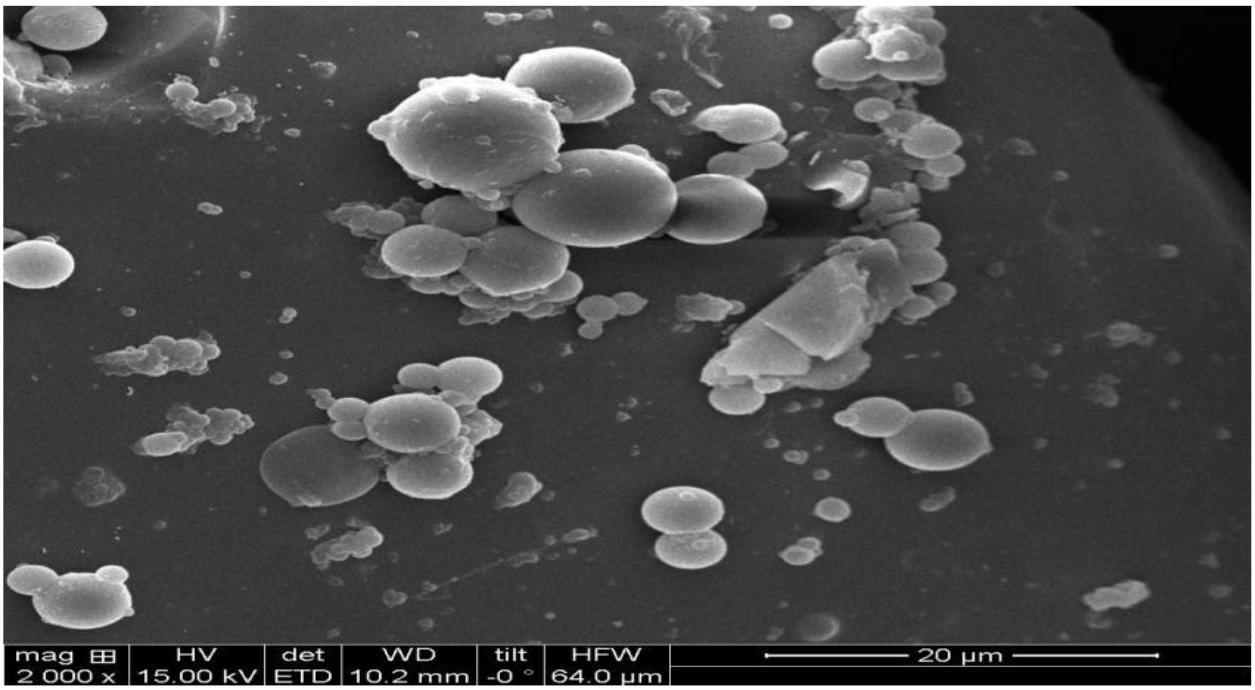

Fig 1: SEM photographs of Atorvastatin calcium microspheres

Table 3: In-vitro release studies

Time (hrs.)	Percent drug release at time (hr)						
	F1	F2	F3	F4	F5	F6	F7
1	50.20±0.9	49.2±0.6	44.31±0.3	46.21±0.9	43.21±0.6	42.13±0.3	43.12±0.2
3	55.10±0.3	54.21±0.2	53.20±0.9	52.41±0.4	51.23±0.5	49.21±0.5	48.32±0.2
6	60.01±0.34	59.01±0.1	57.23±0.3	56.14±0.3	55.32±0.4	54.25±0.5	53.23±0.1
9	68.87±0.32	63.02±0.69	61.35±0.2	60.54±0.1	59.24±0.2	58.36±0.5	56.32±0.2
12	75.58±0.7	67.58±0.6	63.21±0.7	62.30±0.5	61.25±0.2	6887±0.6	59.23±0.2
15	79.58±0.7	72.71±0.1	71.03±0.9	70.21±0.2	69.58±.0.5	73.21±0.4	66.54±0.6
18	88.4±0.4	77.15±0.52	76.8±0.1	75.21±0.3	74.21±	78.89±0.4	72.36±0.2
21	98.52±0.2	84.14±0.3	85.74±0.3	84.33±0.4	83.25±0.5	88.54±0.4	86.56±0.5
24	---	91.23±0.2	92.69±0.5	91.36±0.3	89.72±0.3	98.31±0.4	93.36±0.3

In order to improve the release rate of drug from microspheres, 2.0 % w/v of camphor was included in the formulations. The composition of the formulation is shown in Table 1. Camphor was dissolved in the polymer solution, its forms uniform distribution in the polymer solution. Upon microencapsulation the particles will be getting encapsulated by polymer along with camphor. On drying due to volatile nature camphor may get evaporated and forms pores on the surface of the microspheres, through which drug could easily diffuse to the aqueous phase or dissolution medium. Microspheres were prepared by the emulsion solvent evaporation method and evaluated. *In vitro* release studies for the prepared microspheres were carried out .The release results are shown in table 3. Formulation F6 showed better release rate than F7. The reason for this retarded drug release may be due to the hydrophobic nature of the polymer, which prevents the penetration of the dissolution medium into the microspheres leading to slower dissolution and diffusion of the drug molecules from the microspheres.

Table 5: Flow Properties of Losartan Potassium Microspheres

Formulation code (Avg. ± S.D.)	Bulk density (Avg. ± S.D.)	Tapped density (Avg. ± S.D.)	Compressibility index (Avg. ± S.D.)	Haussner's ratio (Avg. ± S.D.)	Angle of repose (Avg. ± S.D.)
F1	0.426 ± 0.02	0.349 ± 0.01	3.702 ± 0.02	1.064 ± 0.01	22.170 ± 0.14
F2	0.232 ± 0.01	0.389 ± 0.03	4.349 ± 0.03	1.059 ± 0.01	21.120 ± 0.17
F3	0.310 ± 0.02	0.329 ± 0.01	3.601 ± 0.01	1.038 ± 0.02	18.170 ± 0.15
F4	0.416 ± 0.01	0.355 ± 0.02	3.875 ± 0.01	1.040 ± 0.01	20.140 ± 0.12
F5	0.326± 0.02	0.387 ± 0.02	3.659 ± 0.02	1.045 ± 0.01	22.070 ± 0.11
F6	0.327 ± 0.02	0.431 ± 0.01	3.071 ± 0.02	1.087 ± 0.01	21.210 ± 0.18
F7	0.340 ± 0.03	0.375 ± 0.04	4.129 ± 0.02	1.084 ± 0.02	22.490 ± 0.14

CONCLUSION:

This study shows that o/w emulsion solvent evaporation can be used as a simple method to prepare Aceclofenac sustained release microspheres by suing rosin as an encapsulating polymer. The drug entrapment efficiency of prepared microspheres were affected only by the drug:polymer ratio. The emulsifier concentration and organic phase volume influenced the particle size distribution of microspheres. Based on the above findings, it was observed that formulation F6 showed optimum release characteristics. The release rate of drug from the microspheres could be properly controlled for about 24h. Appropriate variation in the proportions of drug; polymer and stabilizer can lead to a product with the desired controlled release features

REFERENCES:

1. Jayakrishnan A, Latha MS. Biodegradable polymeric microspheres as drug carriers. In: Jain NK, Editor. Controlled and Novel drug delivery. New Delhi: CBS publishers. 1997. pp 236-255.
2. Vyas SP, Khar RK. Proteins and peptides delivery considerations. In: Vyas SP, Khar RK, Editor. Controlled drug delivery concepts and advances. 1st ed. New Delhi: CBS publisher and Distributor. 2002; pp 549.
3. Fu, X, Ping Q, Gao Y. Effects of formulation factors on encapsulation efficiency and release behavior *in vitro* of huperzine A-PLGA microspheres. J Microencap 2005; 22(7): 705-714.
4. Jalil R, Nixon JR. Biodegradable poly (lactic acid) and poly(lactide-co-glycocide) microcapsules: problems associated with preparative techniques and release properties. J Microencap 1990b; 7: 297–325.
5. Kawaguchi H. Functional polymer microspheres. Prog Polym Sci 2000; 25: 1171–1210.
6. Mueller RH, Jacobs C, Kayser O. Nanosuspensions as particulate drug formulations in therapy rationale for development and what we can expect for the future. Adv Drug Deliv Review 2001; 47: 3–19.
7. Edlund U, Albertsson AC. Degradable polymer microspheres for controlled drug delivery. Adv Polymeric Science 2002; 157: 67–112.
8 Bain DF, Munday DL, Smith A. Solvent influence on spray dried biodegradable microspheres. J Microencap 1999; 16: 453-474.
9. Oh JE, Nam YS, Lee KH, Park TG. Conjugation of drug poly(d,l-lactic-co-glycolic acid) for controlled release from biodegradable microspheres. J Con Release 1999; 57: 269- 280.
10.Pistel KF, Bittner B, Koll H, Winter G, Kissel T. Biodegradable recombinant human erythropoietin loaded microspheres prepared from linear and start-branched block copolymers: influence of encapsulation technique and polymer composition on particle characteristics. J Con Release 1999; 59: 309-325.
11. Bai XL, Yang YY, Chung TS, Ng S, Heller J. Effect of polymer compositions on the fabrication of poly(ortho-ester) microspheres for controlled release of protein. J Appl Poly Sci 2001; 80: 1630-1642.