Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2012, 4(6):3195-3200

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Design and development of chronopharmaceutical drug delivery of simvastatin

M. Sukanya* and V. Sai Kishore

Bapatla College of Pharmacy, Bapatla, Andhra Pradesh, India

ABSTRACT

The aim of the present investigation is to develop a pulsatile drug delivery system basedon an insoluble capsule body filled with simvastatin microspheres and sealed with HPMCK4M plug. Simvastatin is a water insoluble drug and its absorption is dissolution rate limited. Hence simvastatin microspheres were prepared by quasi emulsion solvent diffusion method of the spherical crystallization technique. Optimized microsphere formulations were selected by percentage drugcontent, invitrostudies. The plugs of varying thickness and hardness were prepared by direct compression which was then placed in the capsule opening. The drug delivery system was designed to deliver the drug at such a time when it was needed (nocturnal time). Dissolution studies of pulsatile capsule device in media with different pH (1.2, 7.4 and6.8) showed that drug release in colon could be modulated by optimizing the concentration of polymers in the plug and also the position of plug. The study showed that, lag time prior to drug release was highly affected by the plug position. The dissolution data revealed that the plug position and the composition of plug were very important to achieve a optimum formulation.The drug release from all the pulsing caps followed Zero order kinetics andmechanisam of drug release was governed by peppas - korsmeyermodel.Drug –polymer interaction studies indicated no interaction or complexation in between the drug and the polymer.

Keywords: simvastatin, quasiemulsion solvent diffusion,spherical crystallization,complexation, microspheres.

INTRODUCTION

In chronopharmacotherapy drug administration is synchronized with biological rhythms to produce maximal therapeutic effect and minimum harm for the patient. By basing drug delivery on circadian patterns of diseases drug effect can be optimized and side effects can be reduced[1]. If symptoms occur at daytime a conventional dosage form can be administered just prior the symptoms are worsening. If symptoms of a disease became worse during the night or in the early morning the timing of drug administration and nature of the drug delivery system need careful consideration.

Pulsatile drug delivery system is the one type of drug delivery system, where the delivery device is capable of releasing drug after predetermined time-delay (i.e. lag time) known as pulsatile drug delivery system[2].Pulsatile drug delivery systems have a peculiar mechanism of delivering the drug rapidly and completely after a "lag time," i.e., a period of "no drug release." These systems are beneficial for drugs having high first-pass effect drugs administered for diseases that follow chronopharmacological behaviour; drugs having specific absorption site in GIT, targeting to colon; and cases where night time dosing is required.

A circadian rhythm occurs during hepatic cholesterol synthesis. Studies with relationship of concentrations of mevalonic acid in plasma and circadian rhythm to cholesterol synthesis rates in man had suggested that the peak mevalonic acid concentrations were observed when the patients were at rest, at least 5 hr after the last meal[3].Statins are usually taken in one daily dose in the evening, presumably to coincide with cholesterol synthesis, which is thought to peak in the early morning hours [4-6]. Therefore the objective of the present work is to formulate a pulsatile drug delivery of simvastatinwhich can be taken before bed time (9 pm) and capable of releasing drug after predetermine time delay(5hours) and can characterized by proportioning drug concentration in the early morning hours when free cholesterol levels are more prevalent. The lag time was controlled by polymer plug which will be taken at bed time with a programmed start of drug release early in morning hours.

EXPERIMENTAL SECTION

Simvastatin was obtained as a gift sample from Dr. Reddy's Laboratories, Hyderabad, India. PEG-4000, Ethyl Cellulose, Aerosol, n-Dibutyl Phthalate, Dichloromethane, Alcohol, Acetone, HPMC K4M were obtained from SD fine chemicals.All chemicals and reagents were of analytical grade.

Preparation of Cross-Linked Gelatin Capsules:
The '0' sized hard gelatin capsules; about 100 in number were taken. The bodies of the capsules were then placed on a wire mesh. 25ml of 15% v/v formaldehyde was taken into a desiccators and potassium permanganate was added to it to generate formalin vapours. The reaction was carried out for 12 hours. After which the bodies were removed and dried at 50^0C for 30 minutes to ensure completion of reaction between gelatin and formaldehyde vapour. The bodies were dried at room temperature to facilitate removal of residual formaldehyde [7].

Preparation of Hydrogel Plug:
Plug for sealing the capsule body was prepared by compressing equal amount of HPMC K4M and lactose using 7mm punches and dies on rotary tablet press keeping varying thickness and hardness values of tablet plug. This plug was then fitted into the body of hard gelatin capsule (containing microspheres equivalent to 40 mg of simvastatin) which was cross linked by exposing the capsule bodies to formaldehyde vapour in dessicator for 12 hour[8,9].

Preparation of microspheres:
The microspheres were prepared using the quasiemulsion solvent diffusion method of the spherical crystallization technique[10].Simvastatin (1.0 g) was dissolved with PEG4000(5 g) and Ethyl cellulose (0.5-2.0 g) in a mixed organic solution containing ethanol (7.5 ml), acetone (10 ml) and dichloromethane (10 ml). Then Aerosil (2.0g) was suspended uniformly in the drug–polymer solution under vigorous agitation, and n-dibutyl phthalate (30% w/w,for the polymers) was added as a plasticizer. The resultant drug–polymer–Aerosil suspension was poured into the distilled water (150 ml) containing 0.08% of Sodium lauryl sulphate (i.e. poor solvent) under a moderate agitation (600 rpm) and thermally controlled at 0–40^oC. Then the suspension was finely dispersed into quasi-emulsion droplets immediately under agitation, and the drug and polymerswere coprecipitated in the emulsion droplets. After agitating the system for 10 min, 200 ml of poor solvent was added slowly to the agitated system to promote the diffusion of the good solvent from emulsion droplets into poor solvent resulting in enhancement of the solidification of quasi-emulsion droplets. Agitation was extended for another 30 min until the translucent quasi-emulsion droplets turned into opaque microspheres. The solidified microspheres were recovered by filtration and washed with water, and the resultant products were dried in an oven at 50^oC for 6 h.

Designing of Pulsincap:
The Pulsincap was similar in appearance to a hard gelatin capsules, but the main body was water insoluble. Microspheres equivalent to 40mg of Simvastatin were accurately weighed and filled into the formaldehyde treated bodies by hand filling. The capsules containing the microspheres were then plugged with prepared hydrogel plug [11].

EVALUATION:
Physicochemical Characterization of Hydrogel Plug
Hydrogel Plugs were studied for hardness, friability, weight variation, lag time and Swelling Index.

Determination of Swelling Index of Hydrogel Plug:
Hydrogel plugs were taken in two different weights like 90mg, 100mg and kept immersed in three different pH conditions. Plugs were taken out carefully at 2, 4,6,8,10,12 hours and their weights were determined accurately[12].

$$\% \text{ Swelling} = \frac{\text{wet weight} - \text{dry weight}}{\text{wet weight}} \times 100$$

Drug content uniformity:
Then encapsulated microspheres equivalent to 40mg of simvastatin were taken and grounded. This was dissolved and filtered and estimated spectrophotometrically at 238nm[13].

***In vitro* release profile of pulsatile capsule:**
Dissolution studies were carried out by using USP XXIII dissolution test apparatus (paddle method). Capsule was tied to paddle with a cotton thread so that the capsule should be immersed completely in dissolution media but not float. In order to simulate the pH changes along the GI tract, three dissolution media with pH 1.2, 7.4 and 6.8 were sequentially used referred to as sequential pH change method. When performing experiments, the pH 1.2 medium was first used for 2 hrs (since the average gastric emptying time is 2 hrs), then removed and the fresh pH 7.4 phosphate buffer saline (PBS) was added. After 3 hrs (average small intestinal transit time is 3 hrs), the medium was removed and colonic fluid pH 6.8 buffer was added for subsequent hours[14]. Nine hundred millilitres of the dissolution medium was used at each time. Rotation speed was 100 rpm and temperature was maintained at 37 ± 0.5^{o}C. Five millilitres of dissolution media was withdrawn at predetermined time intervals and fresh dissolution media was replaced. The withdrawn samples wereanalysed at 238 nm, by UV absorption spectroscopy and the cumulative percentage release was calculated over the sampling times.

Stability studies:
Stability studies as per ICH guidelines were carried out for optimized formulation. The stability studies were carried out at 25 ± 2^{0} C / 60 ± 5% RH and 40 ± 2^{0} C / 75 ± 5% RH for 3 months[15].

RESULTS AND DISCUSSION

The colon is a site where both local and systemic delivery of drugs can take place. Treatment could be made more effective if it were possible for drugs to be targeted directly on the colon. Colon-specific systems could also be used in diseases that have diurnal rhythms. In the present study, attempt was made to target the drug to the colon, and intentionally delaying the drug absorption from therapeutic point of view in the treatment of hyperlipidemia, where peak symptoms are observed in the early morning.

Pulsincap dosage form was a capsule which consists of a water insoluble body and a water soluble cap. The drug formulation (microspheres) was sealed within the capsule body by means of a hydrogel plug. When the pulsing capwasswallowed, the water soluble cap dissolves in the gastric juice and the exposed hydrogel plug begins to swell. At predetermined time after ingestion, the swollen plug was ejected out and the encapsulated drug formulation was then released into the colon, where it is dissolved and then absorbed into blood stream. In the present study, capsule bodies which were hardened with formaldehyde treatment for 12hrs were used for the preparation ofpulsincaps. It was sealed with unhardened cap of the capsule. The microspheres prepared using the quasiemulsion solvent diffusion method of the spherical crystallization technique was sealed within the capsule body by means of a hydrogel plug.

When the resultant mixed solution of good solvent and bridging liquid containing drug and additives was poured into the poor solvent under stirring, finely dispersed droplets were formed immediately, and semi-transparent emulsions were observed visually. With the diffusion of the good solvent out of the droplets into the poor solvent, the drug and the polymers were coprecipitated in the droplets. The dichloromethane comixed into the good solvent, bridged the drug, Aerosil and ethyl cellulose in the droplets, and the droplets solidified gradually into the microspheres. It was found that the preparation of microspheres were controlled by three processes, such as forming emulsion droplets, consolidation and solidification; the sizes of the resultant microspheres were dependent on the sizes of the emulsion droplets formed at the initial stage; and prolonging the induction period of the coacervation of the droplets was required for forming uniform microspheres. In this case, a partial amount of the poor solvent (i.e.

150 ml) was used to decrease the diffusion rate of the good solvent from the emulsion droplets into the droplets, semi-transparent droplets transformed into coacervated droplets due to the coprecipitation of the drug and the polymers occurring in the droplets. After such processing for 10 min, 200 ml poor solvent was poured slowly into the system to promote the diffusion speed of the good solvent and a little of bridging liquid from the droplets to enhance the consolidation of droplets. The introduction of the plasticizer to the droplets and the control of the system at a certain temperature were propitious to deform plastically, and to easily form a spherical shape by agitation. The preparation condition with lower temperature and small amount of plasticizer caused the coacervated droplets to be consolidated in an irregular shape rather than in a spherical form. In this study, 30% of n-dibutylpthalate was used as the plasticizer, and the system was controlled at about 35^0C. It was found that the spherical shape and size of the microspheres were determined during the forming coacervated droplets period while, in the solidification period, the shape and sizes of the microspheres were not affected by agitation speed and agitation time even if the temperature of the system was increased. In the consolidation period, the agitation time was continued for 30 min, and the temperature of the system was decreased with ice to improve the solidification if necessary.

In this preparation process, another key point for reliable processing was to prevent the cohesion of droplets during the consolidation period of the droplets. Besides the solvent system, the formulation of the microspheres was an important factor. To enhance the drug release and absorption in the intestinal tract, a solid dispersion structure in microspheres was fabricated with PEG-4000, that can dissolve in intestinal juice at pH 7.0.Ethyl cellulose was chosen as retarding agents and formulated in the microspheres to control the release rate of the drug. All of these polymers revealed a high viscosity during the formation of coacervation droplets, and resulted in the droplets often agglomerating into an irregular mass and adhering to the propeller or the vessel wall. To overcome these problems, Aerosil particles having high porosity and specific surface area were introduced into the formulations of the microspheres to avoid the coalescence of the droplets and to act as a drug dispersion agent closely packed in the microspheres. It was also found that introducing proper amounts of additives into the distilled water was a favorable method to prevent coalescence of the droplets. In this study, the distilled water containing sodium lauryl sulphate (0.08% (w/v)) was selected as a poor solvent and ideal microspheres of simvastatin were prepared successfully.

When n-dibutylpthalate was introduced to the drug– polymer solution as a plasticizer, the surface of the resultant microspheres became much smoother. It was assumed that plastic deformation of the microspheres had happened during consolidation.

The polymer plugs were formed by direct compression method with a single punch press with varying compression pressures. A tight fit between the plug and the impermeable capsule was very important in order to prevent water penetration to the capsule content and drug release prior to complete erosion of the plug material. In order to identify proper plug materials, they were tested for swelling index using disintegration apparatus.

The weight of plug optimized by various pH conditions like phosphate buffer pH 1.2, 6.8, 7.4 pH condition and the 100 mg of plug was not more change in different pH condition. So the 100 mg was optimized for Hydrogel plug in Pulsincap formulation.

From the *in-vitro* release studies of device, it was observed that with all formulation, there was absolutely no drug release in simulated gastric fluid (acidic pH 1.2) for 2 hours and in simulated intestinal fluid (pH 7.4 phosphate buffer). Burst effect was found in colonic medium (pH 6.8 phosphate buffer). *In vitro* release profiles in colonic medium were found to have very good sustaining efficacy.

The drug release from all the pulsing caps F1, F2, F3 and F4 prepared by using different quantity of ethyl cellulose polymer followed Zero order kinetics (r = 0.9939-0.9987). When percent drug released were plotted against time, linearity was observed for all the pulsincaps as shown in the figure1. The plots of log fraction drug released versus log time of all the pulsincaps were found to be linear, which indicated that mechanisam of drug release was governed by peppas - korsmeyermodel.It was found that diffusional exponent (n) values of all the pulsincaps were ranging from 1.0804-1.2656 indicating that the drug release mechanism followed super case –II transport diffusion. Drug –polymer interaction studies indicated no interaction or complexation in between the drug and the polymer.

FIGURE 1: In vitro dissolution profile of simvastatin formulated with ethyl cellulose in different ratios

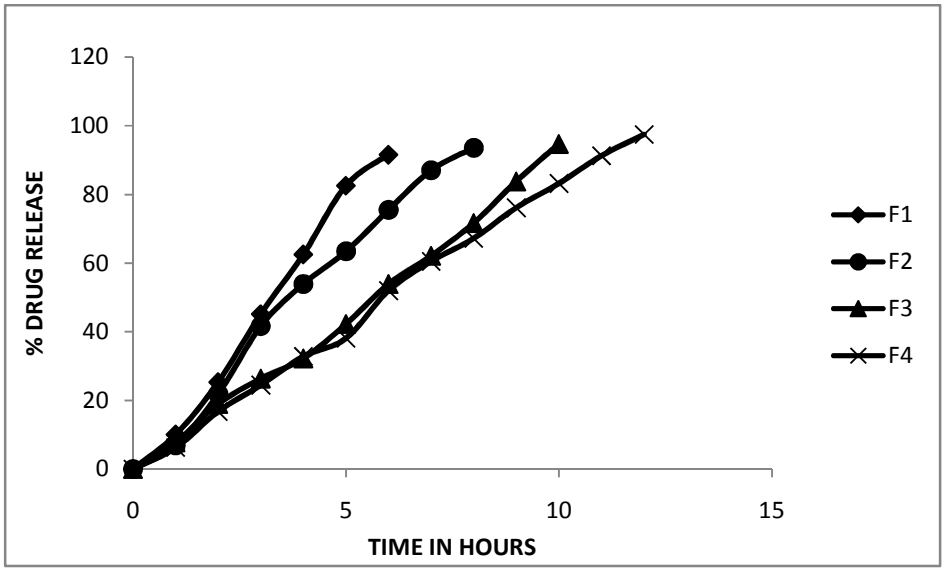

TABLE1: Evaluation parameters for hydrogel plug

HYDROGEL PLUG CODE	WEIGHT (mg)	THICKNESS (MM)	HARDNESS (kg/cm2)	LAG TIME (hours)
PF1	90	2.76	1.7	3.5
PF2	90	2.84	1.9	4
PF3	100	3.24	2.3	4.5
PF4	100	3.54	2.4	5

TABLE 2: Invitro disssolution kinetics parameters of simvastatin formulated with ethyl cellulose in different ratios

FORMULATIONS	CORRELATION COEEFICIENT				DISSOLUTION RATE CONSTANT VALUE(k)mg/hr	DIFFUSION EXPONENT VALUE(n)
	ZERO ORDER	FIRST ORDER	HIGUCHI	PEPPAS		
F1	0.9939	0.9284	0.9114	0.9974	15.4704	1.2656
F2	0.9940	0.9400	0.9329	0.9851	12.3390	1.2358
F3	0.9973	0.8751	0.9127	0.9975	9.0825	1.0505
F4	0.9987	0.8805	0.9257	0.9968	8.2990	1.0804

CONCLUSION

In conclusion, results suggested that lag time is dependent on the nature of the materials employed in plug preparation and found that position of the plug in the capsule body significantly affects lag time. It is evident that an increase in the filler concentration in the plug results in a decrease in lag time. Finally, it is possible to release a drug over a predetermined period of time with specific release rates by manipulating the polymers used to prepare plugs. The obtained results showed the capability of the system in delaying drug release for a programmable period of time and the possibility of exploiting such delay to attain colon targeting.

REFERENCES

[1] XM Peter; XiaohuaLiua; JP Glenda; KM Laurie, *Biomaterials*., **2007**, *28*(*28*), 4124–4131.
[2] AVGothoskar;AMJoshi;NH Joshi, *Drug Delivery Technology*., **2004**,4(5),1-11.
[3] SP Thomas;JM Donald; Clinton Brown; Owen Garrigant; Rachael Kolb;HeddaBatwin, *Proc. NatL Acad. Sci.*, **1982**,79(5),3037-3041.
[4] WLGoff;MGuerin;JChapman;EBruckert, Sang *ThrombVaiss.,* **2001**,13(1),461– 467.

[5] EA Stein;MHDavidson;ASDobs;HSchrott;CADujovne;HBays;SRWeiss;MRMelino; Mitchel ME; Mitchel YB, *Am J Cardiol*., **1998**,82(2),311- 316.
[6] MD Richard; J Havel, *Am J Med*., **1989**,87(4), 1– 59.
[7] Sindhu Abraham; S Bharath; BV Basavaraj; V D Madhava, *The pharma review*., **2007**, 142-144.
[8] IKrogel;R Bodmeir, *Pharm Res*., **1998**,15,474-81.
[9] IKrogel;R Bodmeir, *Pharm Res*., **1999**,19,1424-9 .
[10] Fude Cui; Mingshi Yang; Yanyan Jiang; DongmeiCun; Wenhui Lin; Yuling Fan; Yoshiaki Kawashima, *Journal of Controlled Release.* , **2003**,91, 375–384.
[11] AMeena; B Kumar, *IJPWR*.,**2011**,2(2),1-16.
[12] RTAvinash ; GG Surendra , *Pharmaceutical Development and Technology*, **2009**, 14(4),
[13] 380-387.
[14] Rongfeng Hu; Jiabi Zhu; Guang Chen; Yuliang Sun; Kangkang Mei; Shi Li, *AJPS*.,**2006**,1,47-52.
[15] AmitBhat; KPR Chowdary; RH Shobharani., *IJPSR*., **2011**, 2(4), 1023-1030.
[16] KMManjanna; B Shivakumar; TM Pramodkumar, *IJPR*.,**2009**,3(1),940-952.