Available online at www.pelagiaresearchlibrary.com

Pelagia Research Library

Der Pharmacia Sinica, 2014, 5(5):36-41

Der Pharmacia Sinica
ISSN: 0976-8688
CODEN (USA): PSHIBD

Development of chronomodulated drug delivery system of Pravastatin sodium for the treatment of hypercholesterolemia

Akila Ramanathan and Sreeja Sreekumar G.*

College of Pharmacy, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore, India

---

ABSTRACT

An attempt has been tried to develop a chronomodulated drug delivery of pravastatin sodium, which can be taken at bed time (10 pm) and capable of releasing the drug between night and early morning hours after predetermine time delay (4 h), when free cholesterol levels are more prevalent, can prevent various heart diseases like atherosclerosis, stroke, angina and myocardial infraction. The rationale of this study is to design and characterize an oral pulsatile drug delivery system containing pravastatin sodium, to modulate drug level in synchrony with the circadian rhythm of hypercholesterolemia. Various formulations have been made by varying the composition of pravastatin sodium with MCC, HPMC and the percentage release of the drug was analysed in each formulations. Drug-excipient possible interaction has been studied by FT-IR spectroscopic studies. The formulated tablets were evaluated by stability, friability, drug content uniformity tests.

Keywords: Pulsatile drug delivery, Hypercholesterolemia, Pravastatin sodium, Microcrystalline cellulose, Hydroxy propyl methyl cellulose

---

INTRODUCTION

Cholesterol is a substance that is produced in the body from foods that come from animals [1]. Though, body requires cholesterol for various processes such as building of cell membranes, making hormones, and for producing compounds that increase digestion of fat, high levels of cholesterol increases risk of developing heart disease. Hypercholesterolemia is a disease condition characterized by very high levels of cholesterol in the blood. Therefore, a suitable drug delivery system for the supply of drug in proper intervals of time and according to the cholesterol-level is very important.

Drug delivery system means to achieve an optimum response from any dosage form and a drug should be delivered to its site of action at a rate and concentration that both minimize its side effects and maximize its therapeutic effects. Among the various drug delivery systems employed, Pulsatile drug delivery system is being preferred often as it offers various advantages such as (i) release the active ingredient at a time other than immediately release after oral administration (ii) dosage forms can control where the drug is released etc [2-10] . In pulsatile drug delivery systems, the drug is released rapidly within a short period of time, after a specified lag time. This system has capable of providing one or more rapid release pulses at predetermined lag times, which results better absorption of active solute, and it provides more effective plasma concentration-time profile. These delivery systems are reservoir devices covered with a barrier coating and can dissolve, erode or rupture during/after a certain period of time. Then the drug is released rapidly from the inner reservoir core. Pulsatile drug release profile is widely used in cases, where the drug is released completely after a defined lag time, drugs which develop biological tolerance, drugs with an extensive first pass metabolism, drugs targeted to a specific site in the intestinal tract and for the adaptation of drug needs to circadian rhythms of body functions or diseases. The lag time was controlled by the hydration/expansion of the swelling layer and allowing a fast drug release for complete rupturing of the polymer coating. Based on the methodologies of time-lag drug release techniques, pulsatile drug delivery systems are again

categoried as (i) time controlled pulsatile drug delivery system (ii) Stimuli induced pulsatile drug delivery system (iii) Externally regulated pulsatile drug delivery system. Pulsatile drug delivery systems with externally regulated drug delivery systems are cumbersome as the drug delivery has to be controlled by any biological factor like temperature, or any other chemical stimuli. Similarly, pulsatile drug delivery systems using external stimuli such as ultra sound or magnetism etc are also not preferred due to the complicacy of the method. Therefore, time controlled pulsatile drug delivery system or chrono-modulated drug delivery systems are being recommended for the most of the oral drug delivery systems. Moreover, this method is safer as it is linked with circadian rhythm. This study focused on the development of press-coated pulsatile release tablets to treat hypercholesterolemia. The press–coated tablet investigated in current study consist of rapid release core tablet of pravastatin sodium which is press–coated with Hydroxy Propyl Methyl Cellulose which is swellable polymer and Microcrystalline Cellulose, a rupturable polymer for burst release. The purpose of study was to design the simple, single pulse technique and to investigate the effect of amount of swellable and rupturable polymer mix together in outer coating on drug release.

MATERIALS AND METHODS

Materials

All the chemicals and reagents were of analytical grade. Pravastatin sodium procured from Biocon Pvt. Ltd., Bengaluru, India, Micro crystalline Cellulose (MCC) was obtained from Loba Chemicals,Mumbai. Hydroxypropyl methyl cellulose (HPMC 100KM) was purchased from Ozone International, Mumbai, talc was purchased from M/s. Himedia Pvt. Ltd. Mumbai. Polyvinylpyrollidine, Iso-propyl alcohol and lactose were obtained from SD Fine Chemicals Mumbai.

Methods

Formulation of core tablets

The core tablets of pravastatin sodium (80mg/tab) prepared by direct compression method[11]. Polyvinyl pyrrolidone, talc, sodium starch glycolate and lactose were used as other ingredients. All the ingredients and with pure drug were mixed for 20 minutes , passed through a sieve and compressed by direct compression method on a rotator tablet machine. Formulations of various core tablets are shown in table 1.

Formulation of press coated pulsatile release tablets

The HPMC 100KM and MCC were weighed accurately as required for a particular batch of tablets as per formula given in table 1. 7.5 % PVP solution (hydro alcoholic mixture of iso-propyl alcohol and water in the ratio of 70:30) was used to wet mass the HPMC 100KM and MCC. Then the wet mass was passed through a sieve of 710µm aperture size. It was dried for 2 h at 45^0C in a hot air oven. Then the dried mass was screened through a sieve number of 500 µm aperture size. After that, half quantity of polymer granules were placed inside the die to make a powder bed. Then the core tablet was placed at the centre of polymer bed and remaining half of the polymer granules was filled into die. It was compressed at a constant compression force with a rotary compression machine to form a tablet [12].

Different formulations (F1-F9) were made by varying the proportion of HPMC100KM and MCC with a total weight of 200mg. The formulations are given in table 2.

Evaluation Studies

The pulsatile tablets of pravastatin sodium from each formulation were subjected to hardness, thickness, friability and drug uniformity tests [13].

Hardness test

The hardness of formulated pravastatin sodium pulsatile time release tablets were measured by Pfizer hardness tester.

Thickness

The thickness of individual tablet was measured with the help of micrometer, which provides information about variation between tablets].

Friability test

Friability test was conducted to measure the strength of tablet. It is frequently measured using Roche friabilator. The friability test was calculated by using the following expression $F = 100 \times (1\text{-}w/w_0)$ where, w = weight of tablets after friability, w_0 = weight of tablets before friability (Table 3).

Drug content uniformity test

The tablets from each formulation were powdered individually and a quantity equivalent to 80mg of pravastatin sodium was accurately weighed and dissolved in a suitable volume of 7.4 pH phosphate buffer. After making suitable dilutions the final solution was analyzed spectrophotometrically at 238 nm (Table.3)[14].

Rupture test to determine lag time

The time at which the outer coating layer starts to rupture is defined as the lag time. It was determined visually by using the USP dissolution apparatus II (900ml of 0.1N Hcl for initial 2h and then media was changed to phosphate buffer pH 6.8, 37± 0.5◦C and 50 rpm (Table.3) [15]. .

***In Vitro* Dissolution Studies**

The *in vitro* drug release from press coated tablets of pravastatin sodium observed by using USP paddle apparatus at 50 rpm and the temperature 37±0.5^{0}C. Acidic buffer pH 1.4 and phosphate buffer pH 7.4 were used as the as the dissolution medium. Tablets were subjected to dissolution medium at pH 1.4 for first 2 h and media was changed to phosphate buffer 7.4 up to 7 h. The samples were withdrawn at a regular interval. It was analyzed by UV spectrophotometer (Shimadzu UV/Vis 160) at 238nm to find out the presence of the drug. Cumulative percentage drug release was calculated using an equation from the standard curve. The results are given in Figure 1 and 2.

Drug- excipient Interaction

The IR spectrum of the coated tablets was recorded and compared with that of pravastatin sodium to confirm the chemical integrity of the drug in the coated tablets. The powdered mixture was taken in a diffuse reflectance sampler and the spectra recorded by scanning in the wavelength of 400 to 4000cm-1in a FTIR spectrophotometer-430 (Jasco, Japan) (Figure 3 and 4) [16] .

Stability studies

The stability study of the optimized batches in which the tablets were monitored upto 3 months as per ICH guidelines at room temperature and relative humidity (25◦C±2◦C, RH75 ±5%). The tablets were analysed for appearance, weight, thickness, hardness, drug content, drug release. (Table.4)[17].

RESULTS AND DISCUSSION

The pulsatile system described herein consist of two different components, the central rapid release core tablet made up of drug and other excipients and external barrier layer consisting of HPMC 100KM and Microcrystalline cellulose MC. External layer consist of polymer materials and are intended to regulate function of the system and modify the release of drug. The above system was prepared by a press–coating technique which has been applied for many drugs to develop the site- and/or time-controlled release preparation.This technique has many advantages such as short processing time and limited steps, and low labour and energy requirements.

Based on the concept of chronotherapy or chronopharmacology, recent pharmaceutical investigations have focused on developing a site or time-controlled drug delivery system for the treatment of various diseases. [18] Drugs used for the ideal treatment of diseases should be administered only at the required time to maintain a therapeutic blood level. This reveals that the drug release behaviour should be controlled by time rather than by rate. In order to achieve the development of chronopharmaceutical dosage forms, the site and/ or time controlled release preparation with a designated initial lag time phase without drug release followed by a rapid release phase should be investigated. Hypercholesterolemia is a condition, in which the cholesterol level in our body is elevated and is a major risk factor for various heart diseases. The peak time of cholesterol synthesis is between night and early morning hours. The present work aimed to formulate pulsatile tablets of pravastatin sodium taken at bed time and releasing the drug between 2am to 6pm after a lag time of 4 h to control cholesterol. The evaluation studies on press coated tablets of formulation F1-F9 were found within the limits. The invitro dissolution studies revealed that there was no drug release for the initial 2h pH1.4) followed by the controlled release at pH7.4 depending upon the quantity of polymer. HPMC forms a gel but it does not hydrate quickly and included to prolong the lag time. MCC is a good disintegrant and acts by wicking mechanism. The drug release from the core tablet after the rupture of outer polymer mix. This could be due to pressure built up and attributed to the influx of dissolution medium by the wicking effect of MCC and suggests that MCC might be acting as pore forming agent rather than disintegrant. Based on the results obtained F6 was considered as the optimum pulsatile formulation.

The IR spectra of pure drug of pravastatin Sodium and the coated tablets of pravastatin Sodium are shown in (Figure 3 and Figure 4). This drug-excipient interaction study by FTIR ruled out the possibility of chemical interaction between the pravastatin Sodium and the added excipients as the characteristic peaks observed for both drug and excipients remain unchanged and the spectra data was superimposed. There was no significant difference

in the stability study of the pravastatin sodium tablets before or after 3 months of storage either in the physical properties of the drug or in its dissolution profile.

Table 1: Formulation of Pravastatin sodium core tablets

Drug and excipients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Pravastatin sodium	80	80	80	80	80	80	80	80	80
Sodium starch glycolate	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8
Talc	1.92	1.92	1.92	1.92	1.92	1.92	1.92	1.92	1.92
PVP	2.88	2.88	2.88	2.88	2.88	2.88	2.88	2.88	2.88
Lactose	30.4	30.4	30.4	30.4	30.4	30.4	30.4	30.4	30.4

Table 2: Formulation of Pravastatin sodium press coated tablets

Excipients	F1	F2	F3	F4	F5	F6	F7	F8	F9
HPMC	60	80	160	140	120	40	200	_	100
MCC	140	120	40	60	80	160	_	200	100
Hydro alcoholic 7.5% solution of PVP	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Table 3. Hardness, thickness, friability, weight variation and drug content test of press-coated tablets corresponding to F1-F9 formulations

S. No.	Formulation	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Drug content (%)
1	F1	7.06	3.21	0.52	96.98
2	F2	6.8	3.28	0.77	97.01
3	F3	6.9	3.41	0.82	95.98
4	F4	7.0	3.22	0.81	97.21
5	F5	7.0	3.62	0.72	95.01
6	F6	7.03	3,42	0.60	97.98
7	F7	6.91	3.28	0.52	98.13
8	F8	6.31	3.31	0.72	96.98
9	F9	7.01	3.44	0.62	97.91

Figure 1: Dissolution profile of formulations F1- F9 at pH 1.4

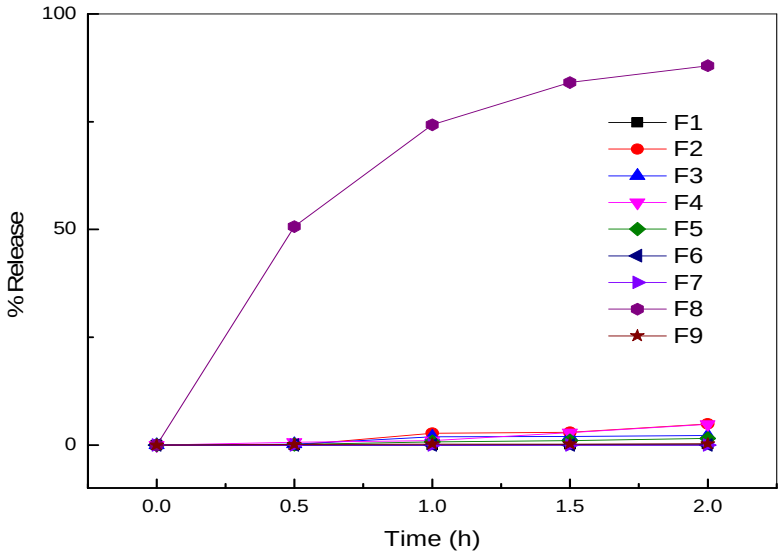


Figure 2: Dissolution profile of formulation F1- F9 at pH 7.4

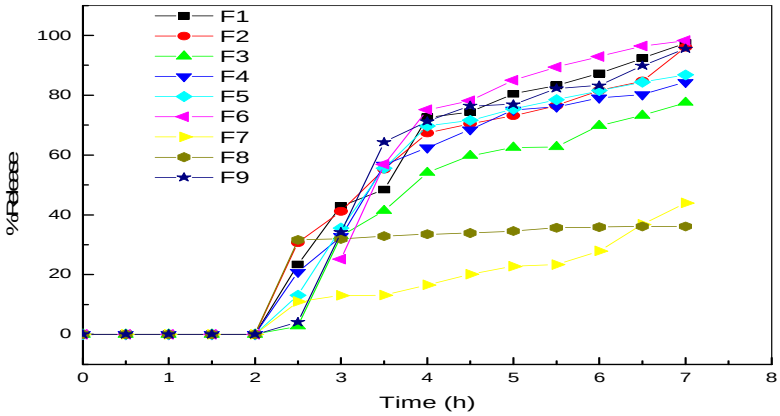


Figure 3: FT-IR spectrum of pure drug of pravastatin sodium

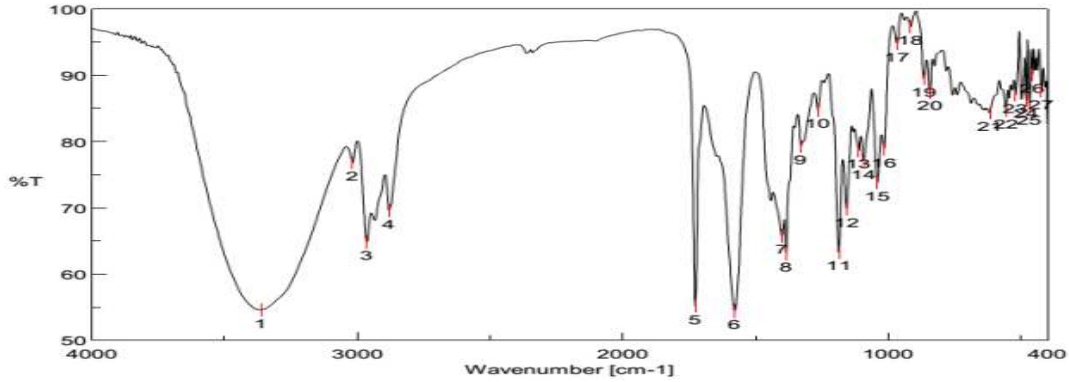
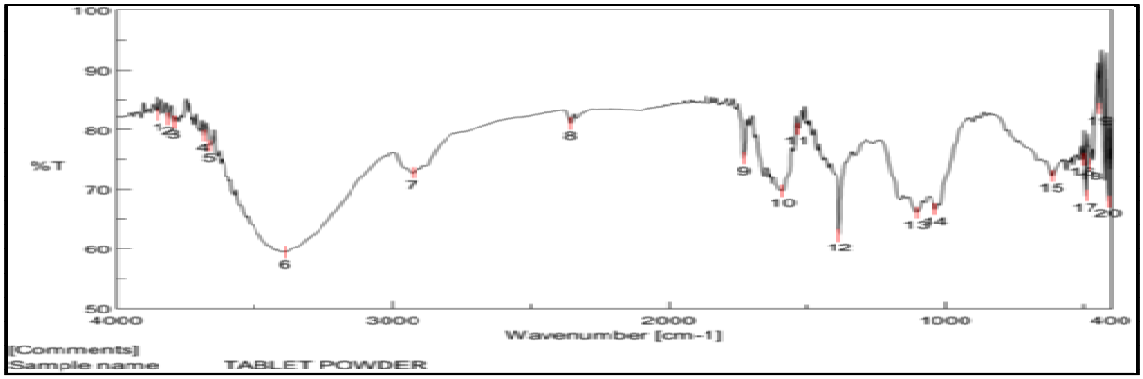


Figure 4: FT-IR spectrum of pravastatin pulsatile release tablets



CONCLUSION

The validity of the above work may be confirmed with the reproducible *in vitro* release and *in vivo* study in animal and human beings. The cardiovascular diseases are difficult to treat but the pulsatile drug delivery can be considered as one of the promising delivery system by controlling the cholesterol level.

Acknowledgements
The authors sincerely thank Prof.Dr.M.Gopal Rao, Head of the Pharmaceutics Department, College of Pharmacy, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore for providing necessary facilities to carry out this work.

REFERENCES

[1] Farooq S A, Saini V, Singh R, Kaur K, *Journal of chemical and pharmaceutical sciences*, **2013,** 6, 138-146.

[2] Arora S, Ali J, Ahuja A, Baboota S, Qureshi J, *Ind. J. Ph arm. Sci.*, **2006,** 68, 295-300.
[3] Bussemer T, Otto I, Bodmeier R, *Crit. Rev. Ther. Drug Carrier Syst.* **2001,** 18(5),433-58.
[4] Maroni A, Zema L, Cerea M, Sangalli M E, *Expert Opion. Drug Deliv*, **2005,** 2, 855-871.
[5] Ryuzo I, Yoshino H, Hirakawa Y, Noda K, *Chemical & pharmaceutical bulletin*, **1992,** 40, 3036-3041.
[6] Till B, Otto I, Bodmeier R, *Critical Reviews in Therapeutic Drug Carrier Systems*, **2001,** 18, 5-11.
[7] Amidon G L, Leesman G D." U.S. Patent 5,229,131, **1993**.
[8] Qiu Y, Park K, *Advanced drug* delivery reviews, **2001,** 53. 321-339.
[9] Bussemer T, Peppas N A, Bodmeier R, *European journal of pharmaceutics and biopharmaceutics* **2003,** 56, 261-270.
[10] Percel P, Vishnupad K S, Venkatesh G M, U.S. Patent 6,627,223, **2003.**
[11] Janugude B U, Patil S S, Patil SV, Lade P D, *Int. J. Chem. Res.*, **2009,** 1, 690-691.
[12] Latha K, Uhumwangho M U, Sunil S A, Srikanth M V, Ramana Murthy KV, *Trop. J. Pharm. Res.*, **2011,**10, 551-560
[13] Lachman L, Lieberman H A, Kanig J L, Theory and Practice of Industrial Pharmacy, Varghese publishing house, Bombay, Tenth edition, **1990,** 551-558
[14] Swartz M E, Krull I S, Handbook of Analytical Validation ,CRC Press, Boca Raton, London.
[15] Qureshi J, Md. Amir, Ahuja A, *Indian J. Pharm. Sci.*, **2008,** 3, 351-356
[16] Akila RM, Sharma B, *Der Pharmacia Sinica*, **2013**, 4, 67-71.
[17] Bajaj S, Singla D, Sakhuja N, *J. Applied Pharm. Sci.*, **2012,** 2, 129-138.
[18] Lin S Y, Li M J, Lin K, *AAPS Pharm SciTech*,**2004**, 5,1-5.