Available online at www.pelagiaresearchlibrary.com

Pelagia Research Library

Pelagia Research Library

Der Pharmacia Sinica, 2013, 4(5):67-71

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

Chronotherapeutic formulation of metformin hydrochloride

Akila R. M.* and Bharat Sharma

Department of Pharmaceutics, College of Pharmacy, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore, Tamilnadu, India

---

ABSTRACT

As a novel chronotherapeutic approach, in the present work a pulsatile drug delivery system for metformin hydrochloride was designed to control early morning hyperglycemia to synchronize the circadian rhythm of Diabetes Mellitus. The drug delivery system was prepared by using HPMC K100M as inner swellable and ethyl cellulose (18cps) as outer rupturable polymer. The core tablet was prepared by direct compression. The ethyl cellulose containing triethyl citrate as plasticizer was coated to core tablet by pan coating. The prepared film coated tablet was evaluated for in vitro drug dissolution study to get desirable immediate release of drug after lag time of 6 hours. Drug-excipients compatibility study by IR spectrophotometer showed that all the excipients were compatible with the drug. The stability study was carried out for the desired optimized formulation for a period of 3months and showed insignificant difference.

Keywords: Chronotheraputics, Circadian rhythm, Hyperglycemia, Pulsatile drug delivery, lag time.

INTRODUCTION

Due to the advancement of technology in the pharmaceutical field, drug delivery systems have drawn an increasing interest over the last few decades. Presently the emphasis of pharmaceutical, galenic research is turned towards the development of more efficacious drug delivery systems with already existing molecules rather than going for new drug discovery because of inherent hurdles posed in drug discovery and development process [1].Recently it has been highlighted that the time at which a medication is administered may play a pivotal role in determining the outcome and tolerability of a pharmacological therapy. The temporal rhythms of bodily functions have indeed been demonstrated to affect not only the incidence and severity of chronic pathologies, but also the pharmacokinetics as well as pharmacodynamics of most bioactive compounds in use [2, 3]. As a result, chronotropic or pulsatile drug delivery system has been emerged with the rationale behind is to release the drug at desired time as per pathophysiological need of disease, resulting in improved patient therapeutic efficacy and compliance. As the name suggests, the systems are meant for chronopharmacotherapy, treatment of those diseases that are caused due to circadian changes in body. These systems are developed when zero order release is not desired [4]. The need for a pulse of therapeutic concentration in a periodic manner acts as a push for the development of pulsatile drug delivery system. These systems have a peculiar mechanism of delivering drug rapidly and completely after a lag time i.e. a period of no drug release, characterized by a programmed drug release [5]. Pulsatile drug delivery systems are generally classified into time controlled and site specific delivery systems. The release from the first group is primarily controlled by the system, while the release from 2nd group is primarily controlled by the biological environment in the G.I.T such as pH or enzymes [6].

Before designing a chronotropic or pulsatile drug delivery system, understanding of a disease and role of circadian rhythm in its sleep- wake cycle in a day is necessary and is influenced by genetic make-up and body functions like metabolism, physiology, behaviour, sleep pattern and hormone production [7]. Diseases that are currently targetted by chronotropic systems are bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer,

diabetes, attention deficit syndrome, hypercholestemia and hypertension[8]. Among these diseases, Diabetes mellitus was considered for the study as it has been called the epidemic of 21st century. International Diabetes Federation data presents the current scale of the diabetes problem. Approximately 336million people affected with Diabetes mellitus worldwide. Expected to hit 438 million by 2030 [9]. At present over 30 million people are affected in India and is responsible for 4.6 million deaths each year or one death every 7 seconds due to diabetes related stroke, blindness, cardiac, kidney and nerve failure.

Fasting hyperglycemias is an important phenomenon observed in almost all individuals with diabetes [10]. In non-diabetic individuals, fasting plasma glucose concentration was within normal limits and higher in the afternoon than in the morning. In diabetic patients, fasting plasma glucose concentration was not only abnormally high but was significantly higher in the morning than in the afternoon. This shows the association between diabetes and morning hyperglycemias and this is also called as liver dump or dawn phenomenon and usually occurs between 4am and 8am.When hormone insulin is out of balance with other hormones (cortisol, glucagon and epinephrine), the liver will release too much glucose. Treatment for dawn phenomenon depends on type I and type II diabetes. For type I diabetics, insulin dosing has to be adjusted so that peak action occurs closer to the morning rise in blood glucose. For type II diabetics, metformin can be given to reduce the liver's glucose production. Metformin Hcl are administered once daily as extended SR forms may not be to counteract the early morning hyperglycemia due to dawn phenomenon [11].The time of administration of the drug play a key role in the treatment of diabetes for effective therapy. Hence in this research work pulsatile delivery system of metformin Hcl was developed at a predetermined lag time of 6h as a bed time dosing.

MATERIALS AND METHODS

Metformin Hcl was received as a gift sample from IPCA Laboratories, Mumbai, India. HPMC K100M obtained from Ozone International, Mumbai and Ethyl Cellulose (18cps) procured from SD Fine Chemicals, Mumbai.PVPK30 from Loba Chemicals, Mumbai. Triethyl citrate from HiMedia Laboratories, Mumbai. Talc and Magnesium Stearate from SD Fine Chemicals, Mumbai. All other chemicals used were of analytical reagent grade.

Formulation of pulsatile release tablet

Preparation of Immediate release core for burst release

Core tablets of metformin Hcl were prepared by direct compression method. All the ingredients were weighed accurately and blended homogeneously for 15 mins. Tablets were compressed in Minipress tablet compression machine using 8mm round concave punches. (Rimitek-minipress -11 MT), Karnavati Engineering Ltd, Ahmedabad, India [12]. The composition of core tablet is given in Table1.

Time-lagged coating of core tablets for pulsatile release tablets of metformin Hcl

Pulsatile release tablets can be achieved by coating swellable core with water insoluble film forming polymer ethyl cellulose which is more brittle with a lower strain and complete film rupture. The permeability of mechanical properties of ethyl cellulose could be affected by plasticizer. TEC is hydrophilic plasticizer. Hydrophilic plasticizer increases permeability of hydrophobic coat which is required for swelling core. Acetone was selected as a solvent for coating since both EC and plasticizer TEC are soluble in it. The composition of coating solution is given in Table 2.

The coating solution was prepared by hydrating EC in acetone by overnight storage. This hydrated solution was stirred for 15 min. Plasticizer (TEC) was added into the polymeric solution. The polymer solution was sprayed on to the core tablets in a conventional pan coating apparatus.The coating process was repeated till the desired level of coating was achieved. The coated tablets were further dried in the coating pan for 15 mins at 40°C [13].

***Invitro* drug release studies**

The *invitro* drug release from coated tablets was carried out in 900ml of standard buffer of pH 1.2 for the first 2 h, followed by pH 6.8 for the remaining time period up to9 h using USP paddle apparatus at 50 rpm and temperature at 37± 0.5°C. The samples were diluted to make up the volume of 10ml with pH 1.2 buffer for first 2 hours and then by pH 6.8 buffer and were replaced with the fresh dissolution medium equilibrated at the same temperature. The drug released at the different time intervals from the dosage form is measured by U.V. visible spectrophotometer, by measuring the absorbance for the samples solutions at 233 nm. The release studies for each formulation were conducted in triplicate, indicating the reproducibility of the results [14,15,16].

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 [17]

Effect of outer polymer concentration and water uptake performance

To study the effect of outer polymer layer concentration on lag time, core tablets were coated with different levels of ethyl cellulose (3,4,5,6%w/w and inner swelling layer remained the same. The % water uptake capacity of tablets was determined in the container filled with 100ml of 0.1N Hcl placed in a biological shaker at 37°C. Speed of shaker was adjusted to 75 rpm.Tablets were removed from containers at pre-determined regular intervals, blotted with tissue paper, weighed and again placed in medium till the outer coating of tablet started to rupture. The % water uptake was calculated using the formula, %Water uptake=((Wt-Wo))/Wo, where Wt is weight of wet tablet at time t and Wo is weight of dry tablet [18].

Effect of inner swelling layer on lag time

Core tablets were coated with 20, 30,40 and 50%w/w of HPMC K100M as inner swelling layer and subjected to dissolution study. Outer polymer remained the same (EC). Effect of swelling layer concentration over lag time and release behaviour was observed using a spectrophotometer as described in method under *in vitro* drug release studies.

Drug- excipient Interaction

The IR spectrum of the coated tablets was recorded and compared with that of metformin Hcl to confirm the chemical integrity of the drug in the coated tablets [19]. The powdered mixture was taken in a diffuse reflectance sampler and the spectra recorded by scanning in the wavelength of 400 to 4000cm^{-1}in a FTIR spectrophotometer-430 (Jasco, Japan).

Stability studies

The stability study of the optimized batches in which the tablets were monitored upto 3 monthsas 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.

RESULTS AND DISCUSSION

All the formulations had different lag times followed by a burst release of metformin Hcl. Formulation F1 achieved 3h lag timewith 54% drug releasefollowed by 99% drug release in 7th hour of dissolution media pH6.8. F2 achieved lag time at 3.5th h with 59% drug releaseand was 99% at 8.5h.F3 achieved lag time at 3.5th h with 58% drug release and was 98% at 8.5h. F4 achieved lag time at 4.5thh with 59% drug release and was 98% at 8.5h. F5 achieved lag time at 5.5th h with 56% drug release and was 99% at 8.5h. F6 achieved lag time at 5.5th h with 62 % drug release and 98% at 8.5h. F7 achieved lag time at 6th h with 96% drug release and increased gradually to 100% at 8.5h(Figure 1).

The rupturable pulsatile drug delivery system consisted of a core, a drug containing reservoir, inner or intermediate swelling layer and outer water insoluble layer but permeable coating. The swelling layer consisted of HPMC(HPMC K100M) and was chosen because of its swelling nature and its eroding behaviour and was applied by direct compression method.

The rupturable coating consisted of a plasticized mixture of EC as it forms a mechanically weak and semipermeable film, which could rupture easily upon exposure to the dissolution media and was water insoluble and pH independent film former.

Water influx was through the semipermeable rupturable outer coating which leads to the expansion and erosion of an intermediate layer, which ultimately resulted in rupture of the outer coating. The drug was released with in a short time after a definite lag time period.

The dissolution studies were carried out to investigate the release behaviour of the developed system. Metformin Hcl is a freely water soluble drug. There was no drug release prior to the breaking of outer coating. The lag time of the tablet decreased with increasing level of swelling layer. As the amount of swelling agent (HPMCK100M) increased, it exerted more pressure over the outer layer resulting in rapid rupturing of the tablet. The expanded swelling layer facilated the entry of dissolution medium to the core containing the drug and ruptured the outer layer. After breaking of the outer layer, the drug release from the time release tablet formulations were observed.Among

all the formulations formulation F7 with 20%w/w HPMC of the pure drug and 6%w/w of EC showed lag time of 6h which was desirable as the aim of the work was to prepare pulsatile drug delivery system of Metformin Hcl with lag time of 6h and a immediate release of drug after a lag time.

Table 1. Composition of core tablet

Drug and Excipients(mg)	F1	F2	F3	F4	F5	F6	F7
Metformin HCl	500	500	500	500	500	500	500
HPMC	250	225	200	175	150	125	100
MCC	50	50	50	50	50	50	50
PVP	13	15	17	19	21	23	25
Magnesium Stearate	10	10	10	10	10	10	10
Talc	5	5	5	5	5	5	5

Table 2.Composition of coating solution

Excipients	F1	F2	F3	F4	F5	F6	F7
Ethyl cellulose(%w/v)	3	3.5	4	4.5	5	5.5	6
Triethyl citrate(%w/w)	13	13	13	13	13	13	13
Acetone	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Figure 1.*Invitro* drug release studies

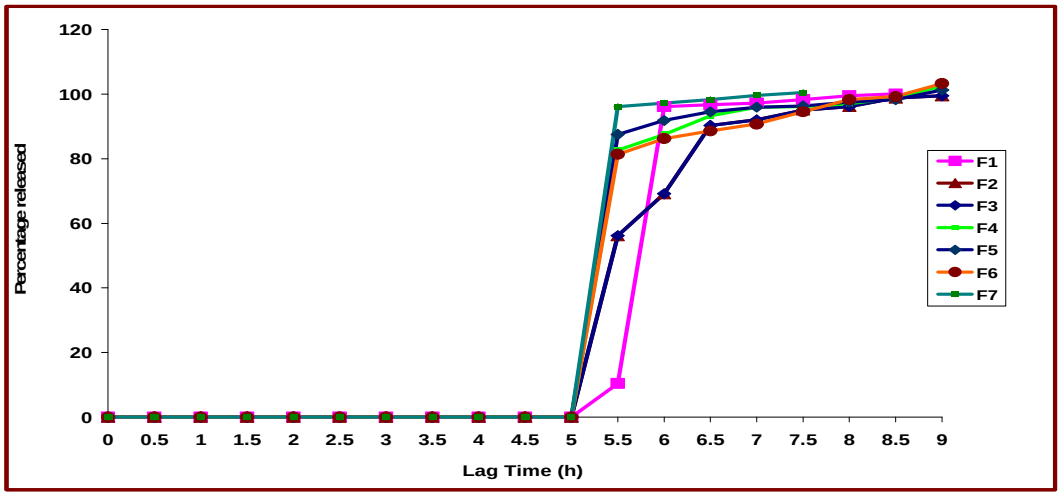
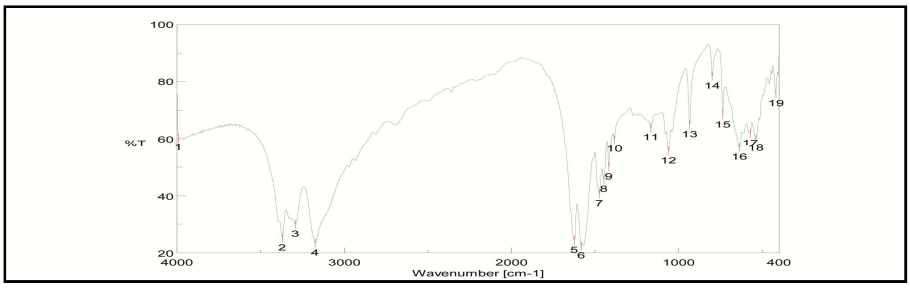


Figure 2. . IR spectrum of Metformin hydrochloride



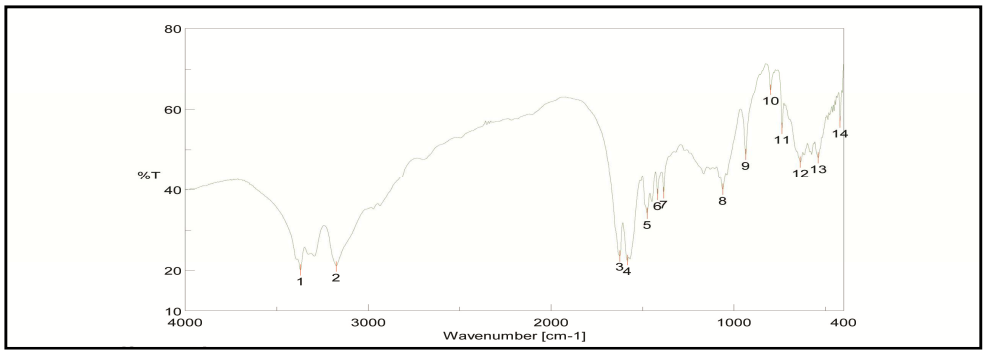
The water uptake capacity and drug release before the rupture of tablet was dependent on outer EC polymer film coating. The lag time increased with increased outer coating level.

The addition of MCC in the inner core can improve the bond and flow prosperties of the excipients during direct compression. It also acts as an disintegrant.

The IR spectra of the anhydrous Metformin Hcl and the coated tablets of Metformin Hcl are shown in (Figure 2and Figure 3). This drug-excipient interaction study by FTIR ruled out the possibility of chemical interaction between the Metformin Hcl 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 Metformin Hcl tabletsbefore or after 3 months of storage either in the physical properties of the drug or in its dissolution profile.

Figure 3. IR spectrum of coated tablet of Metformin hydrochloride



CONCLUSION

Metformin Hcl are administered once daily as extended SR forms may not be able to counteract the early morning hyperglycemia due to dawn phenomenon. Since the time of administration of the drug plays a key role in the treatment of diabetes for effective therapy, it is always necessary to provide maximum drug concentration at maximum intensity of disease condition.Hence in the present research work a novel chronotherapeutic approach has been made to formulate pulsatile release tablets of Metformin hydrochloride with a lag time of about 6 h to control the early morning hyperglycemia in non-insulin dependent diabetic patients. Thus this new dimensional approach of pulsatile tablet of metformin hydrochloride taken at bed time, releasing drug in the morning hours can prove to be a revolution in the treatment of early morning hyperglycemia.

Acknowledgement
The authors wish to thank Dr.M. Gopal Rao, Head, Department of Pharmaceutics, College of Pharmacy, SRIPMS,Sri Ramakrishna Hospital Campus,Coimbatore for providing necessary facilities to carry out this work.

REFERENCES

[1] SS .Davis, L. Illum , **1998**, *Int. J. Pharm*, 176, 1-8.
[2] Lemmer B, **1991**, *J ControlRelease*, 16, 63–74.
[3] Youan B-BC (ed.), *Chronopharmaceutics*, New Jersey: JohnWiley & Sons, **2009.**
[4]Mayank Nagar, Sanjay Singhai, V. S. Chopra, Namrata Gautam, Piyush Trivedi, **2010**, *International Journal of Pharmaceutical and Clinical Research*, 2,10-19.
[5] A.Arora, J.Ali , A.Ahuja , Baboota, J.Qureshi , **2006**,*Indian J. Pharm. Sci*. 68, 295-300.
[6] S.Sungthangjeen , S.Puttipipatkhachorn ,O. Paeratakul, A. Dashevsky, R. Bodmeier. **2004**, *J Control Release.* 95, 147-159.
[7]. B.U .Janugade, S.S.Patil, S.V.Patil, P.D. Lade, P.D. **2009,***International Journal of Chem. Tech Research*, 1,690-691.
[8]S.Survase, N.Kumar,**2007,***Current Research & Infor. Pharm.Sci*,8,27-33.
[9] American Diabetes Association. Standards of Medical Care in Diabetes— 2009. Diabetes Care **2009,** 32 , 13–61.
[10] J.P. Sheehan, Fasting hyperglycemia: etiology, diagnosis, and treatment, **2004**, *Diabetes Technol Ther*,6, 525–533.
[11]**G**eremia B. Bolli, John E. Gerich,**1984,***N Engl J Med*, 310,746-750.
[12]Mohit D.Bauskar, Santosh Y. Nandedkar, Rajendra D. Wagh ,**2011,***Int J Pharm Pharm Sci*, 3, 218-223.
[13]Suresh V. Gami , Mukesh C. Gohel, Rajesh K. Parikh, Laxman D. Patel, Vipul P. Patel, **2012**, *Pharma Science Monitor*,3, 171-181
[14]Javed Qureshi, Mohd. Amir, Alka Ahuja, Sanjula Baboota, J. Ali, **2008**, *Indian Journal of Pharmaceutical Sciences*,70,351-356.
[15] Y.Zhang, Z.Zhang, Fang Wu, **2003**, *J.Control Release*, 89,47-55.
[16] H.N. Shivakumar, S.Suresh , B.G.Desai , **2007,** *Indian J Pharm Sci*, , 69,73-79.