



## Design and Evaluation Core in Cup Pulsatile Tablet of Amlodipine Besylate for Early Morning Hypertension

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### ABSTRACT

The purpose of present work is to develop a pulsatile dosage form of amlodipine besylate for treating early morning hypertension. Now a day the one of the main reasons behind the mortality in cardiac patients is early morning hypertension or nocturnal hypertension, this is because capillary resistance, vascular reactivity are higher in the morning and platelet agreeability is increase in early morning. But it is tough to overcome this risk by taking regular dose at night. This problem can be overcome by present pulsatile drug delivery system with pre regulated lag time. The pulsatile tablets were formulated by core in cup design taking drug in core tablet which is again punched by covering three sides with water insoluble polymers like ethyl cellulose, cellulose acetate propionate, and upper face is with hydrophilic polymers like Na CMC or disintegrating polymers like pectin and gelatin with 5% of xanthum gum. Main challenge in developing pulsatile dosage form is maintaining lag time; this can be achieved by modifying concentration of upper hydrophilic polymer. The formulated tablets were studied for physical parameters like hardness, weight variation, drug content determination, swelling index and dissolution profiles. The results concluding that as the concentration of polymer in upper layer increases the lag time will also increase.

**Keywords:** Cellulose acetate propionate, Core in cup tablets, Early morning hypertension, ethyl cellulose, Na CMC, Pulsatile drug delivery system, Xanthum gum.

### INTRODUCTION

Chronotherapeutics<sup>1-5</sup> is defined as a treatment system where the in vivo drug availability has been timed in accordance to cyclic rhythms of drug related biological phenomena to create maximum benefit minimizing harm. In the present day many diseases are related to circadian rhythms<sup>6</sup> of human body so it is important to treat the disease with respect to body's circadian rhythm. A number of common diseases are affected by chronobiology. Such diseases include angina<sup>7</sup>, hypertension<sup>8</sup>, rheumatoid arthritis, allergic rhinitis<sup>9</sup> and cancer.<sup>10</sup> Asthma<sup>11</sup> may be the most common disease with the largest circadian variation. The activity of the lung exhibits a circadian rhythm with a maximum around 4 pm and a minimum around 4 a.m. In asthmatic patients, the intensity of variation in lung function is as much as 50% in a day. In cardiovascular diseases capillary resistance and vascular reactivity are higher in the morning and decreases latter in the day; platelet agreeability is increase leading to a state of hypercoagulability of the blood, because of this reaction the frequency of myocardial infraction and sudden cardiac death are more porn in early morning.

Amlodipine besylate<sup>12</sup> is a dihydropyridine derivative and is a long acting calcium channel blocker acts by inhibiting the Trans membrane influx of calcium ions in to vascular smooth muscle and cardiac muscle. Oral absorption of Amlodipine besylate<sup>13</sup> is 70% ±10. Volume of distribution is 21 l/kg and plasma protein binding is 92-95%. Pre systemic metabolism is 2.5% ±2.5 and metabolism is reported extensive by liver. Renal Excretion accounts for 62% and plasma half-life is 30-60 hr. Since it can controls

the vascular reactivity and capillary resistance faced in the early morning it is desirable to formulate as pulsatile drug delivery system<sup>14-19</sup> to control the early morning hypertension.

In the present work core in cup<sup>20</sup> type of tablets were prepared by taking amlodipine besylate in core tablet along with microcrystalline cellulose, sodium bi carbonate. The core tablets were prepared by direct compression method. Then the formulated core tablet is again compressed by covering three sides with hydrophobic polymers and fourth side with either hydrophilic or erodible polymer to get core in cup tablet. The purpose of this surrounding hydrophobic layer is to prevent escape of drug and the use of hydrophilic<sup>21</sup> or erodible polymer is to maintain the lag time for desirable single pulsatile drug release.

### MATERIALS AND METHODS

#### Materials

Amlodipine besylate is obtained as a gift sample from Dr. Reddy's Laboratories, Hyderabad, India. Polymers ethyl cellulose, and Sodium carboxy methylcellulose, pectin were procured from Yarrow Chem. Products, Mumbai, India. Sodium bicarbonate was procured from Reachem Laboratory Chemicals Pvt. Ltd., Chennai, India. Lactose, magnesium stearate and talc I.P were procured from Molychem, Mumbai, India. All other chemicals were of analytical grade.

#### Preparation of core in cup tablet

The core tablet of amlodipine besylate was prepared by direct compression method with drug, excipients as



mentioned in table 1 by using 7mm flat tablet punch. The core in cup tablet was prepared by using 9mm tablet punch. 100mg of water insoluble polymer ethyl cellulose is filled in die cavity and core tablet is placed, then the sides of tablet was filled with 75mg of ethyl cellulose so that the surrounding surface of core tablet was fully covered. On the top of blend various polymers were placed as mentioned in table 2 and compressed in to tablet.

**Table 1:** Formulation table for core tablet

| Ingredients         | Core tablet |
|---------------------|-------------|
| Amlodipine besylate | 10          |
| Lactose             | 90          |
| Cross povidone      | 5           |
| Sodium bicarbonate  | 5           |
| Talc                | 2%          |
| Magnesium stearate  | 2%          |

### Evaluation of Tablets

#### Physical characteristics

All the physical parameters like weight variation, thickness, hardness, and friability were measured by following USP. Weight variation of tablets was measured by taking 20 tablets and weighed individually and mean variation was calculated. Tablet thickness was measured by using vernier calipers and hardness of tablet was measured by Monsanto hardness tester.

The friability of tablets was measured by Roche friabilator at a fixed rate.

$$\% \text{ Friability} = 100 (W_o - W) / W_o$$

Where  $W_o$  is initial weight of tablet and

$W$  is final weight of tablet

#### Drug content estimation

Randomly ten tablets were selected and crushed. Drug equivalent to 100mg is placed in 100 ml conical flask and drug was extracted with 100 ml of 7.4 pH phosphate buffer and filtered with whatmann filter paper, then filtered solution was analyzed for drug content with suitable dilutions at 361 nm spectrophotometrically.

#### Swelling studies

The tablets were taken in dissolution apparatus using dissolution medium pH 7.4 phosphate buffer at 50rpm and  $37 \pm 0.5^\circ\text{C}$ . All the formulations were taken out individually at interval of 30 min. excess water on the tablet was removed with help of filter paper and the tablets were weighed. The increase in the tablet weight represents water uptake efficiency.

#### In vitro release studies

The *in-vitro* dissolution study was carried out in the USP type 2 dissolution test apparatus with 900 ml of the dissolution medium (Phosphate buffer pH 7.4), temperature was maintained at  $37 \pm 0.50^\circ\text{C}$ . The speed of the paddle was set at 50 rpm. 5ml of the dissolution

medium was withdrawn and the same amount of fresh medium was replenished to the dissolution medium. The samples were analyzed by using the UV Spectrophotometer (Elite UV- 150 double beam spectrophotometer) at 361nm and the drug content was determined from calibration value of amlodipine besylate.

## RESULTS AND DISCUSSION

### Tablet physical properties

All the physical parameters like hardness, friability, thickness, and weight variation, were studied and mentioned in the table 3. The formulation prepared with NaCMC had greater hardness than formulations prepared with pectin and the hardness was increased with increased concentration of polymer. The hardness of formulations with NaCMC was  $5.2 \pm 0.14$ ,  $6.2 \pm 0.18$  and  $6.8 \pm 0.2$  Kg/cm<sup>2</sup> for FC1, FC2 and FC3 respectively. The formulations prepared with pectin were  $4.5 \pm 0.2$ ,  $5.2 \pm 0.17$ ,  $5.8 \pm 0.16$  Kg/cm<sup>2</sup> for FP1, FP2 and FP3 respectively. Friability of all the formulations was within limits, 0.22 to 0.42 and the thickness of tablets were from  $5.0 \pm 0.2$  mm to  $6.4 \pm 0.2$  mm. From the values it is shown that all the formulations were within the limits.

### Drug content estimation

Drug content from all formulations was studied. The drug content of core tablet formulations was found to be in the range of  $96.2 \pm 0.95$  to  $99.3 \pm 0.2$ , and the results were mentioned in table 3.

### Swelling studies

The prepared tablet when gets in contact with water the top layer consisting of soluble hydrophilic layer starts to swell by absorbing the liquid thereby creates a gel layer which acts as barrier preventing the liquid from reaching the tablet core. Concentration of polymer on the top layer will influenced the extent of swelling and liquid uptake. The formulations prepared with NaCMC were showed good swelling properties whereas the tablets prepared with pectin does not showed any swelling values. This is because the pectin shows only gelling property not the swelling property and is concluded from the results. The formulation SC1 with least polymer (Na CMC-50mg) concentration gave least swelling and formulation SC3 with polymer much concentration of Na CMC (150mg) gave maximum swelling. After the swelling reaches a maximum point the upper layer starts to separate and inner core tablet exposed to dissolution medium resulting in Sharpe increase in the drug release. From the Figure 1 it can be clearly observed that swelling process starts the moment tablet touches the liquid surface and it is higher for formulations with much concentration of polymer.

### In vitro dissolution studies

The dissolution profile of all formulations were studied and shown in figure 2. From the figure it is evident that the formulation with lower concentration of CMC, FC1



showed lag time of 2 hours, formulation FC2 showed a lag time of 3.5 hours and the formulation FC3 showed a lag time of 5 hrs. On other hand formulations with pectin have prolonged lag time than the formulations with Na CMC. The formulations FP1, FP2, FP3 showed a lag time of 1.5 hours, 2 hours, 6 hours lag time respectively. From the formulations FC1, FC2, FC3 there is diffusion of drug taking place within lag time whereas from the formulations prepared with pectin there is no such diffusion observed. The formulations with higher

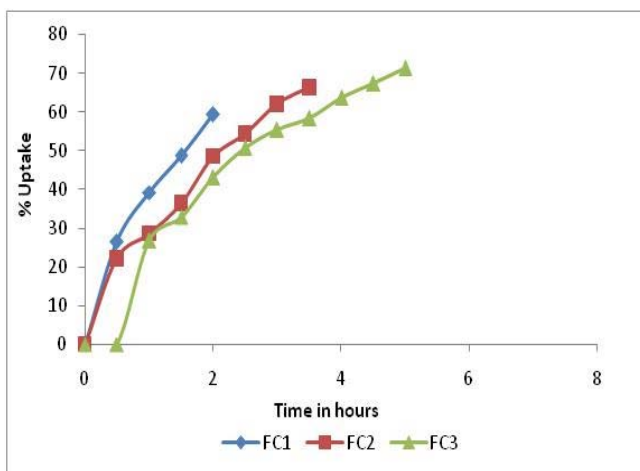
concentration of polymer showed greater lag time, the lag time is more for pectin than Na CMC and there is no or less diffusion of drug observed in case of pectin. Time required to release 70% of drug T70 was calculated for FP1, FP2, FP3, FC1, FC2, FC3 and is 2Hrs, 2.5Hrs, 6.7Hrs, 2.5Hrs, 3.8Hrs, 5.4 Hrs respectively. Time required to release 90% of drug is T90 and is 2.5Hrs, 2.8Hrs, 6.9Hrs, 2.6Hrs, 4Hrs and 5.6Hrs for FP1, FP2, FP3, FC1, FC2 and FC3 respectively.

**Table 2:** Formulation table for core in cup tablet

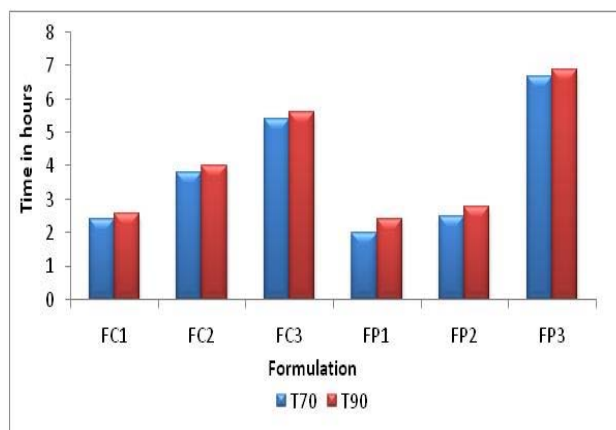
| Ingredients        | FC 1   | FC 2 | FC 3   | FP 1   | FP 2   | FP 3   |
|--------------------|--------|------|--------|--------|--------|--------|
| Na CMC             | 50     | 100  | 150    | -      | -      | -      |
| Pectin             | -      | -    | -      | 50 mg  | 100 mg | 150 mg |
| Xanthan gum        | 2.5 mg | 5 mg | 7.5 mg | 2.5 mg | 5 mg   | 7.5 mg |
| Isopropyl alcohol  | Q.S.   | Q.S. | Q.S.   | Q.S.   | Q.S.   | Q.S.   |
| Magnesium stearate | 1%     | 1%   | 1%     | 1%     | 1%     | 1%     |
| Talc               | 1%     | 1%   | 1%     | 1%     | 1%     | 1%     |

**Table 3:** Physical properties of tablets

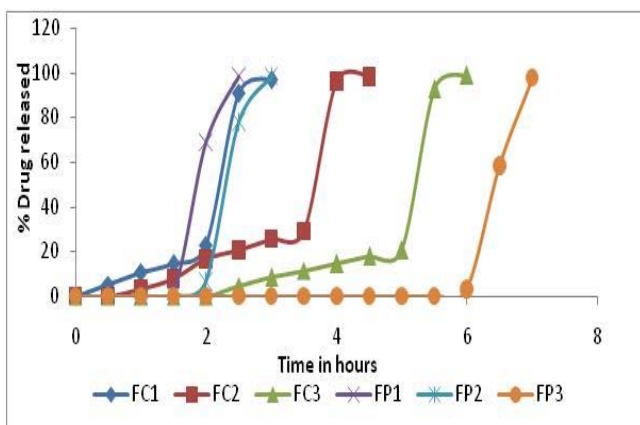
| Physical property                 | FC 1      | FC 2     | FC 3      | FP 1      | FP 2     | FP 3      |
|-----------------------------------|-----------|----------|-----------|-----------|----------|-----------|
| Hardness(Kg/cm <sup>2</sup> ) ±SD | 5.2±0.14  | 6.2±0.18 | 6.8±0.2   | 4.5±0.2   | 5.2±0.17 | 5.8±0.16  |
| Weight variation test             | Pass      | Pass     | pass      | Pass      | Pass     | pass      |
| Friability                        | 0.22      | 0.25     | 0.28      | 0.34      | 0.38     | 0.42      |
| Drug content ±SD                  | 96.2±0.95 | 98.4±0.5 | 96.8±0.98 | 97.4±0.64 | 99.3±0.2 | 98.6±0.94 |
| Thickness (mm)                    | 5.0±0.2   | 5.6±0.1  | 6.2±0.2   | 5.2±0.1   | 5.7±0.1  | 6.4±0.2   |



**Figure 1:** Swelling studies of core in cup tablets



**Figure 3:** Time required for T70% and T90% drug release



**Figure 2:** Dissolution profile of core in cup tablets

**CONCLUSION**

The core in cup tablets prepared with Na CMC showed lag time up to 5 hours and there is slight diffusion of drug takes place during the dissolution whereas the formulation prepared with pectin does not show any diffusion of drug and showed lag time up to 6hours. Formulation FP3 prepared with 150mg of pectin and 5% of xanthan gum exhibits a lag time of 6 hours, and if a patient takes a tablet at night the drug is released after a lag time of 6 hours and the concentration of drug is sufficiently high in the early morning when the possibility of heart attack is very high. The formulation is useful to significantly reduce the mortality rate in cardiac patients. The formulation with increased concentration of polymer showed more lag time implying that the lag time of

formulations increases with increased concentration of polymer.

## REFERENCES

- Smolensky MH, Lemmer B *et al.* Chronobiology and chronotherapeutics of allergic rhinitis and bronchial asthma, *American j .Respi.crit care med*, 59, 2007, 852–882.
- Makoni A, Zema L, Oral pulsatile delivery: rational and chronopharmaceutical formulaion, *International journal of Pharmaceutics*, 398, 2010, 1–8.
- B. Lemmer, The clinical relevance of chronopharmacology in therapeutics, *Pharmacol. Res*, 33 (2), 1996, 107–115.
- B. Lemmer, Chronopharmacokinetics: implications for drug treatment, *J. Pharm. Pharmacol*, 51(8), 1999, 887–890.
- Youan BC, "Chronopharmaceutical drug delivery systems: Hurdles, hype or hope", *Adv. Drug Deliv. Rev*, 62, 2010, 898–903.
- Youan BC, Chronopharmaceutics: gimmick or clinically relevant approach to drug delivery, *J. Control. Release*, 98, 2004, 337–353.
- Bjorn L, The importance of circadian rhythms on drug response in hypertension and coronary heart diseases, *Pharmacology and therapeutics*, 111, 2006, 629–665.
- B. Lemmer, Genetic aspects of chronobiologic rhythms in cardiovascular disease, in: M. Zehender, G. Breithardt, H. Just (Eds.), *From Molecule to Men*, Darmstadt, Germany, 2000, 201–213.
- Romacn CH, Ayala DE *et al.*, Chronotherapy of hypertension: administration time dependent effects of treatment on circadian pattern of blood pressure, *Advance drug delivery reviews*, 59, 2007, 923–939.
- Smolensky MH, Lemmer B *et al.*, Chronobiology and chronotherapeutics of allergic rhinitis and bronchial asthma, *American j .Respi.crit care med*, 59, 2007, 852–882.
- M. Mormont, F Levi, Cancer chronotherapy: principles, applications, and perspectives, *Cancer*, 97(1), 2003, 155–169.
- "Amlodipine besylateBesylate", The American Society of Health-System Pharmacists, Retrieved 3 April 2011.
- Luksa J, Josic D, Kremser M, Kopitar Z, Milutinovic S (December 1997). "Pharmacokinetic behaviour of R-(+)- and S-(-)-amlodipine besylate after single enantiomer administration", *J. Chromatogr. B Biomed. Sci. Appl*, 703 (1-2), 185–193.
- Gurny R, Junginer HE, Peppas N, Eds., In; *Pulsatile Drug Delivery; Current Applications and Future Trends*, Wissensheftliche Verlagsgessell schaft, Stuttgart, Germany, 1993, 36.
- Roy P, Shahiwala A, Multiparticulate formulation approach to pulsatile drug delivery current perspective, *Journal of controlled release*, 134, 2009, 74–80.
- Article, pulsatile drug delivery: current scenario :SachinSurvase and Neeraj Kumar. Department of Pharmaceutics National Institute of Pharmaceutical Education and Research (NIPER) CRIPS, 8(2), April-June 2007.
- Petereit HU, Pulsed release drug delivery, [www.iptonline.com](http://www.iptonline.com). 2003:101-104. *Indian journal of pharmaceutical sciences*, Article. Pulsatile drug delivery, 69, 2007.
- P. Percel, K.S. Vishnupad, G.M. Venkatesh, Timed Pulsatile Drug Delivery System, U.S. Patent 6627223, September 30 2003.
- C.M. Chen, Pulsatile particles Drug Delivery System, U.S. patent 5260069, November 9, 1993.
- Efentakis M, Koligliati S, Vlachou M. Design and evaluation Efentakis M, Koligliati S, Vlachou M. Design and evaluation of a dry coated drug delivery system with an impermeable cup, swellable top layer and pulsatile release. *Int J Pharm*, 311, 2006, 147-156.
- A.Kikuchi, T. Okano, Pulsatile drug release control using hydrogels, *Adv. Drug Deliv. Rev*, 54(1), 2002, 53–77.
- Meghal AK, Chaudari PS, Mathur VB, Formulation and evaluation of enteric coated HPMC capsule of diclofenac sodium, *Res J Pharm BiolChem Sci*, 2, 2011, 790–798.
- MconviIJT, Rose Ac *et al*, The effect of wet granulation on the erosion behavior of an HPMC lactose table, used as a rate controlling component in pulsatile drug delivery capsule formulation, *European journal of Pharmaceutics and biopharmaceutics*, 57, 2004, 541–549.

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