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Research Article

FABRICATION OF PULSATILE DELIVERY MULTIPARTICULATE SYSTEM OF POORLY WATER SOLUBLE CARVEDILOL PHOSPHATE

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ABSTRACT:

Pulsatile drug delivery system is required to satisfy the needs of chronotherapy. Among solids, multiparticulates have its own advantages. Pulsatile drug delivery system provides better therapy with many of the actives. Rupturable pulsatile drug delivery system consists of a drug core; swelling layer of a super disintegrant; and an insoluble, water-permeable polymeric coating. Upon water ingress, the swellable layer expands, resulting in the rupturing of outer membrane followed by drug release. The active pharmaceutical ingredient selected was Carvedilol Phosphate, deposited on sugar pellets as first layer. The second layer composed of swelling excipient, had crospovidone, L–substituted hydroxy propyl cellulose and sodium starch glycolate. Third and the outer most layer was based on ethyl cellulose. The release after lag time was fast and complete, when crospovidone was used as a swelling agent. In contrast, a sustained release was achieved after the lag time, when L–substituted hydroxy propyl cellulose and sodium starch glycolate were used as swelling agents. Fast release would be preferable in the present case. Optimal level of crospovidone to achieve a fast and complete release of Carvedilol phosphate was 33%. Outer membrane, formed using aqueous dispersion of ethyl cellulose was suitable enough to rupture sufficiently ensuring fast drug release, compared to stronger ethyl cellulose membrane formed using organic solution. It was possible to design multiparticulates of carvedilol phosphate having a suitable release profile.

Key words: Rupturable, Pulsatile release, Multiple unit-systems, Chronotherapy, Carvedilol Phosphate.

INTRODUCTION:

In recent years there has been a significant interest in the development of controlled drug release system, to achieve optimal therapeutic effect of drugs. A typical oral controlled release system shows a pattern of drug release, in which its plasma concentration is maintained in the therapeutic window continuously for an extended period of time. But for several diseases (e.g. bronchial asthma, hypertension, rheumatic condition and myocardial infarction) as well as for control of body functions (e.g. blood pressure, levels of many hormones like aldosterone, rennin and cortisol) influenced by circadian rhythms delayed or pulsatile drug release might be the required option. Pulsatile release is also useful for the targeting of a drug irritating the stomach or degradable there in, as well as for drugs developing biological tolerance or with an extensive first-pass metabolism e.g. β blocker. This systems is characterized by a drug release at suitable rate after a predetermined lag time and repeating this cycle if required [1-3]. These can be classified as single unit (e.g. tablets) or multiparticulate (e.g. powder or pellets) systems [4]. A class of pulsatile drug delivery system contains a drug reservoir, surrounded by a barrier, which erodes, dissolves or ruptures[6]. Often a challenge in the development of pulsatile drug delivery system is to achieve a desired drug release after the lag time. There are various types of pulsatile delivery multiparticulates reported in the literature like Pulsincap® system, Port® system etc [5-8]. A chronotopic system generally works better for poorly water soluble drugs, because highly water soluble drugs could diffuse through the swollen barrier layer prior to its complete erosion [9]. Time Clock system is more suitable for the highly hydrophilic drugs, because of their hindered diffusion through carnauba wax or bee wax containing coating. The lag time in both the type of drugs is controlled by coatings thickness and is independent of the environmental pH. In the rupturable multiparticulate pulsatile product, drug containing inner core is layered by a swellable component followed by water insoluble polymer film as a top layer[10-12]. Upon water ingress, the swellable layer expands resulting in film rupturing with subsequent rapid drug release. In case of hard/soft gelatin capsules the lag time and completeness of drug release is independent of capsule content but influenced remarkable by core composition in case of tablets. Properties of swelling layer as well as composition and thickness of the outer membrane are reported as major factors, affecting the rupturing and release parameters [13-15]. Multiparticulate systems offer various advantages over single units. These include no risk of dose dumping, flexibility of blending units with different release patterns, as well as short and reproducible gastric residence time. As a rupturable multiparticulate pulsatile drug delivery system a "time controlled explosion system" has been presented[16]. The drug is layered on an inert core, followed by a swellable super disintegrant layer and finally a water insoluble polymer membrane as the outermost layer. Ethyl cellulose is well-known water-insoluble polymer and is often used as a rate-controlling membrane to modulate the drug release from dosage forms using organic or aqueous coating techniques. Irrespective of several advantages of aqueous coating over organic (lower raw material costs, environmental friendly, etc.) for the rupturable pulsatile delivery systems, so far only organic coatings are described[17-21]. Carvedilol phosphate is a racemic mixture in which nonselective β-adrenoreceptor blocking activity is present in the S (-) enantiomer and α1-adrenergic blocking activity is present in both R (+) and S (-) enantiomers in equal potency. Carvedilol phosphate has no intrinsic sympathomimetic activity. It is rapidly and extensively absorbed after oral administration with an absolute bioavailability of only 25% to 35% due to a significant degree of first-pass metabolism. According to b-iopharmaceutical classification it belongs to class II drug (low solubility and high permeability)[22-25].

The objective of the present study was to develop and evaluate a multiparticulate pulsatile drug delivery system consisting of carvedilol phosphate core, layered with a swelling composition made up of L–substituted propyl cellulose, sodium starch glycolate and crospovidone and

coated with an insoluble polymeric membrane using ethyl cellulose.

MATERIALS AND METHODS

Materials

Carvedilol phosphate (CP) from Cadila Pharmaceuticals Ltd. Ahmadabad, India; Sugar spheres (Pharma-a-spheres 20/25) from Hanns G. Werner GmbH, Germany; Ethyl cellulose (Ethocel standard 10 and standard 100) from Colorcon Asia Pvt. Ltd. Goa, India; Hydroxy propyl methyl cellulose (HPMC, Methocel E6 premium) from Colorcon Asia Pvt. Ltd. Goa, India; Crospovidone (Polyplasdone XL-10) from Ashland Specialty Ingredients, USA; Sodium starch glycolate (Glycolis) from Roquette freres, France; Low-substituted hydroxyl propyl cellulose from Shin-Estu Chemical Company Ltd., Japan; Polyoxyl hydrogenated castor oil (Chemosphere RH 40) BASF, Germany and Dibutyl sebacate from Morflex Inc, Greensboro, USA were received as gift samples. Methanol and Methylene chloride were of analytical grade.

PREPARATION OF PULSATILE MULTIPARTICULATE DRUG DELIVERY SYSTEM

Drug Coating

CP was coated on sugar spheres using 10% (w/w) solution in methanol and Dichloromethane (3:7 w/w) containing HPMC E6 premium in a fluidized bed coater (Pam Glatt CPCG 1.1, Mumbai, India) to achieve 10% (w/w) drug content. Batch size was 200 g, pre-warming of the core pellets at 40° C for 15 min and the layering parameters were: inlet air temperature 40° C, product temperature 28° C, air flow 140 m^3/h, nozzle diameter 1.2 mm, spray pressure 1.2 bars, spray rate 8-10 g/min. Final drying of pellets was done at for 30 min at 40° C. (Table 2)

Coating of swelling layer

Drug containing pellets were coated with a 8 % (w/w) suspension of crospovidone, sodium starch glycolate or Low-substituted hydroxyl propyl cellulose in a 3 % (w/w) HPMC E6 solution in 96% (v/v) ethanol using the fluidized bed coater to achieve required weight gain. The process conditions were: batch size, 200 g, pre-warming of the cores at 40° C for 15 min; spray nozzle diameter, 1.2 mm; atomizing air pressure 1.5 bar, air flow rate, 140 m^3/h; inlet air temperature, 40° C; product temperature, 28° C; spray rate, 10-15 g/min. Final drying of pellets was done at for 15 min at 40° C. (Table 3)

Coating of ethyl cellulose

The pellets coated with the swelling polymer were further coated with a 5 % (w/w) ethyl cellulose grade 10 or 100 in 96% (v/v) ethanol, plasticized with 3% (w/w) Dibutyl sebacate based on the weight of the polymer. Coating was performed in the fluidized bed coater to achieve required weight gain. The process conditions were: batch size, 200 g, pre-warming of the cores at 40° C for 15 min; spray nozzle diameter, 1.2 mm; atomizing air pressure, 1.5 bar, air flow rate, 140 m^3/h; inlet air temperature, 40° C; product temperature, 28° C; spray rate, 2-6 g/min. Final drying of pellets was done at for 15 min at 40° C. The coated pellets were cured in an oven at 45-50° C for 24 h. (Table 4)

DRUG RELEASE

The dissolution of drug loaded pellets was studied using USP 26 Type 2 dissolution test apparatus, Electrolab TDT-06 P, India, containing 900 ml of pH 1.2 HCl maintained at 37 ±0.5° C and stirred at 100 rpm for 12 hours. Samples were collected periodically and replaced with a fresh dissolution medium. All readings were made in triplicate.

MICROSCOPY

An optical image generated through macro option of a digital camera (Nikon coolpix L18). The image contains ethylcellulose shell after brusting of the pellets shown in association of mm scale for size judgment) Fig (4). The illumination has created shadows of the pellets remnants which are to be neglected.

Table 1: Formulation Optimization

Batch .No.	CP 1	CP 2	CP 3	CP 5	CP 6	CP 7
Drug layering						
Carvedilol Phosphate	80.0	800.0	800.0	800.0	800.0	800.0
Sugar sphere	200.0	200.0	200.0	200.0	200.0	200.0
HPMC E6 CPS	3.0	3.0	3.0	3.0	3.0	3.0
Methanol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Dichloromethane	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Coating of swelling layer						
Crospovidone	5.0	…	…	…	…	35.0
Low-substituted hydroxyl propyl cellulose	…	5.0	…	25.0	…	…
Sodium starch glycolate	…	…	5.0	…	25.0	…
Methocel E6 CPS	3.0	3.0	3.0	3.0	3.0	3.0
Ethanol w/w	q.s.	q.s.	qs	q.s.	q.s.	q.s.
Coating with ethyl cellulose						
Ethyl cellulose standard 10	15.0	…	…	…	…	…
Ethyl cellulose standard 100	…	15.0	20.0	20.0	20.0	25.0
Dibutyl sebacate	…	2.0	0.75	0.75	0.75	0.75
Polyoxyl hydrogenated castor	4.0	…	…	…	…	…
Purified water	…	…	…	…	q.s.	….
Ethanol w/w	q.s.	q.s.	q.s.	q.s.	….	q.s.

Table 2: Process parameter for coating of drug layer

1	Inlet air temperature	40° C
2	Bed temperature	28° C
3	Exhaust temperature	35° C
4	Atomizing air pressure	1.5 Kg/cm2
5	Spray rate	8-10 g/ min
6	Blower RPM	1800 rpm

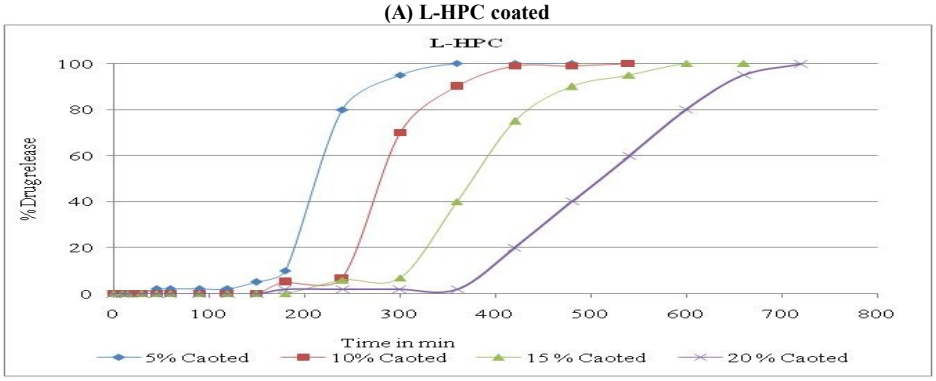
Table 3: Process parameter for coating of swelling layer

1	Inlet air temperature	40° C
2	Bed temperature	32° C
3	Exhaust temperature	35° C
4	Atomizing air pressure	1.5 Kg/cm2
5	Spray rate	10-15 g min
6	Blower RPM	1800 rpm

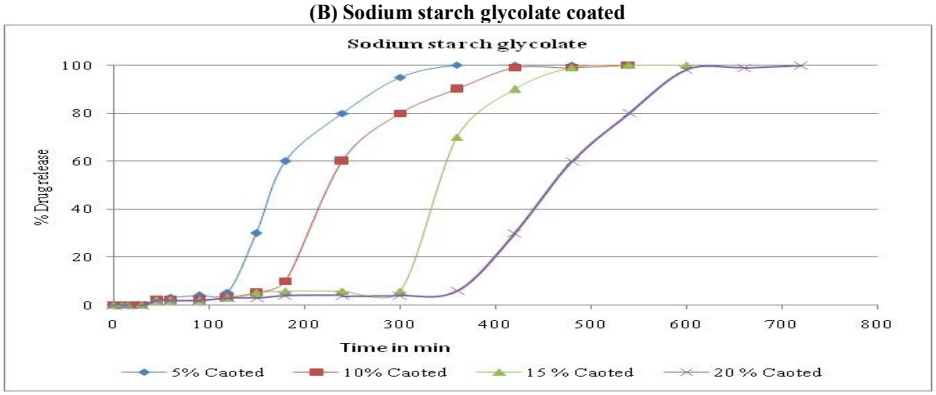
Table 4: Process parameter for coating of ethyl cellulose

1	Inlet air temperature	35° C
2	Bed temperature	32° C
3	Exhaust temperature	30° C
4	Atomizing air pressure	1.5 Kg/cm^2
5	Spray rate	2 -6 g min
6	Blower RPM	1800 rpm

Figure 1: Drug release from carvedilol phosphate coated sugar core:
(A) L-HPC coated



(B) Sodium starch glycolate coated



(C) crospovidone coated

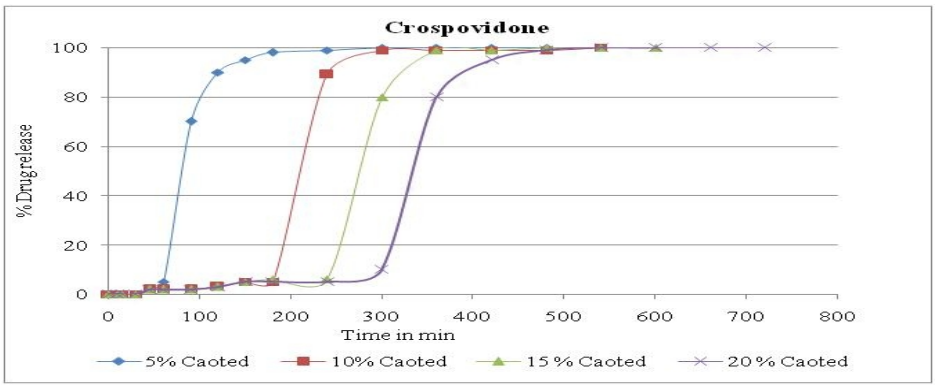


Figure 2: drug release from aqueous and non aqueous ethyl cellulose coated pellets

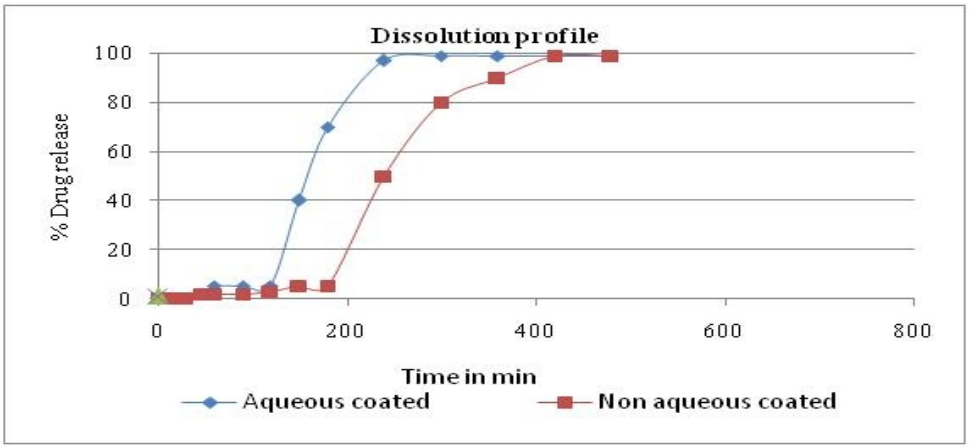


Figure 3: ffect of the ethyl cellulose coating level

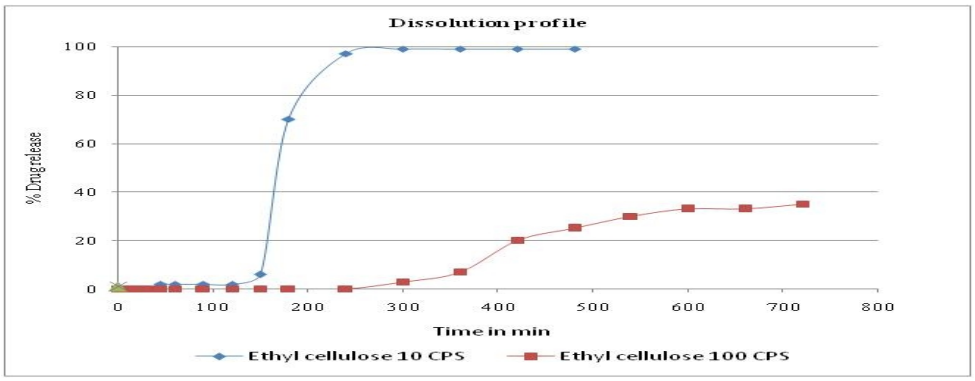
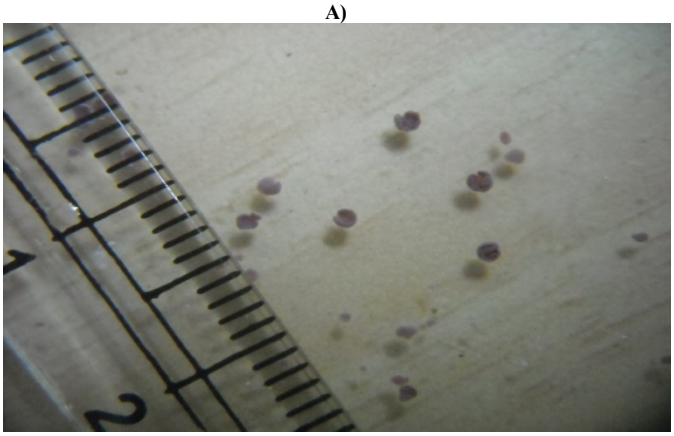


Figure 4: microscopical observation

A)



B)

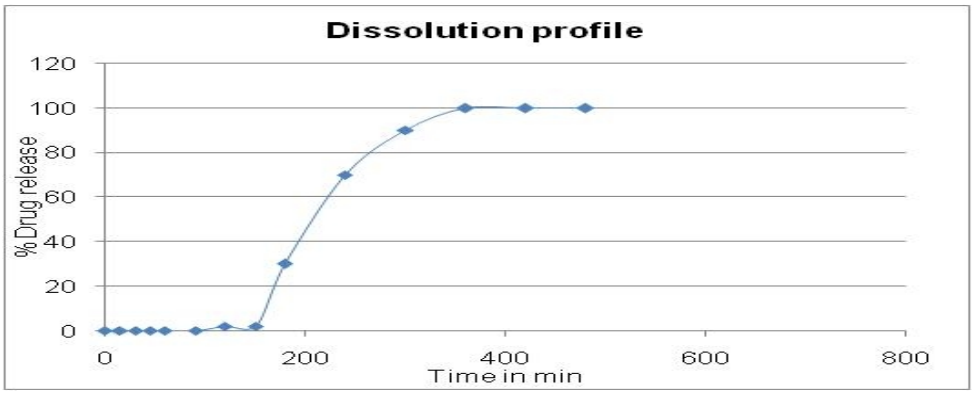
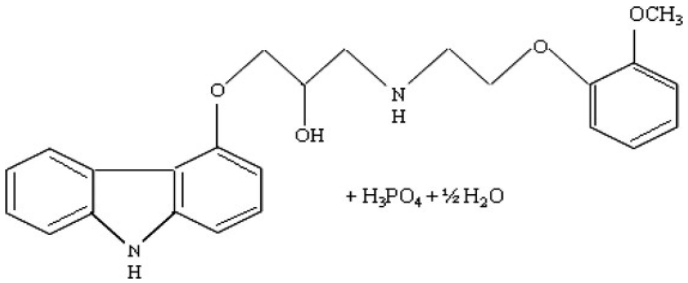


Figure 5: Chemical structure of carvedilol phosphate



RESULTS AND DISCUSSION

Swelling layer

First, core pellets containing CP (10%, w/w) were layered with crospovidone, sodium starch glycolate or Low-substituted hydroxyl propyl cellulose respectively and top-coated to different coating levels of swelling polymer and ethyl cellulose. The rupturing of the outer membrane was poor resulting in slow release, when sodium starch glycolate was used as a swelling agent as in Fig. (1b). In contrast, desired pulsatile release profile with a clear lag time, followed by rapid and complete release was obtained with crospovidone for all investigated coating levels Fig. (1c). This might be because of higher swelling energy of crospovidone compared to SSG. The lag time was slightly increased and the following drug release was remarkably faster by increasing crospovidone amount from 10 to 20%. It might be that, further higher amount of crospovidone would absorb more water showing better outcome. However, both the lag time and the following release were unchanged by further increase of crospovidone level. In addition, dissolved drug layer and probably sugar core had low mechanical resistance and swelling pressure towards the outer membrane is again diminished. A clear lag time having rupturing of membrane and complete release was achieved by increasing the coating level of crospovidone up to 30 %. Besides the water permeability, the mechanical properties of the outer most membrane are very important for the performance of the pulsatile system. In general, mechanically weak and non-flexible films are suitable, while highly flexible films expand and often do not rupture during release test. Ethyl cellulose was selected to form the outer membrane, because of the brittleness of the membrane prepared there from, which was advantageous for completeness of the rupturing. The plasticizers, usually added to ensure the film formation, improve flexibility of the films. Therefore plasticizer content should be carefully selected. Immediate release was achieved for all coating levels with low amount of polyoxyl hydrogenated castor oil (10%, w/w), because of insufficient film formation on the contrary, high amount of this plasticizer **(**35%, w/w) result in flexible, not rupturable films and therefore very slow release at coating levels over 20% (w/w). Optimal plasticizer amount for investigated system seemed to be 25% (w/w) of polyoxyl hydrogenated castor oil**,** because of sufficient film formation (ensuring integrity of the ethyl cellulose coat dosage form during the lag time) and with suitable mechanical properties (brittleness) to achieve complete rupturing.

Drug release was typically pulsatile. The lag time could be controlled by coating level. The lag time was shorter and the release was slightly quicker using a water soluble plasticizer polyoxyl hydrogenated castor oil, compared to water insoluble Dibutyl sebacate. This might be because of complete leaching of polyoxyl hydrogenated castor oil from EC films in the dissolution medium, which affects the permeability and the mechanical properties of the polymeric coating during dissolution. The outer membrane became more brittle by addition of 10% (w/w) of talc (based on the total solid content of dispersion), indicated by reduced puncture strength and elongation. Therefore lag time of the pellets, coated with ethyl cellulose by addition of the talc, decreased and the following release was faster.

Effect of the coating system (aqueous versus organic)

A higher coating level 20% was needed by coating with ethyl cellulosestandard 10 aqueous system (25%, w/w polyoxyl hydrogenated castor oil) compared to coating with ethanolic solution (plasticized with 5% Dibutyl sebacate) to achieve comparable drug release profiles as in Fig (2). This could be explained by higher brittleness of films prepared from aqueous dispersion of EC compared to films prepared from its ethanolic solution of ethyl cellulose.

Effect of the Ethyl cellulose coating level

The importance of the brittleness of outer membrane could be underlined by comparison of different molecular weights of ethyl cellulose for outer membrane formation. Drug release decreased after lag time remarkably by increasing of coating level of ethyl cellulose 10, which might be result of mechanically stronger outer membrane. Drug release was extremely slow in case of coating with higher molecular weight ethylcellulose standard 100, due to decreased brittleness, compared to ethyl cellulose standard 10 as shown in Fig 3.

Imaging to show drug release mechanism

Clear correlation between rupturing time and drug release onset was noted through imaging of the pellets during the release. Drug release onset and first cracks on the surface of the outer membrane were observed after 2 h. This stage corresponded to the pressure exerted by the swelling layer exceeding the mechanical resistance of the membrane at the end of the lag time. Progressing water flux into the swelling layer caused a further expansion in the cracks spreading over the pellet surface after 2.5 h and enlarged after 3 h. Drug release was completed within 4 h after lag time Fig (4).

CONCLUSION

To achieve pulsatile drug release profile crospovidone as swelling agent with optimum layering amount 30% (w/w) was needed for poorly soluble carvedilol phosphate. Outer membrane, formed using aqueous dispersion of ethyl cellulose was brittle and ruptured sufficiently for complete drug release, compared to membrane formed by ethyl cellulose from ethanol solution. The lag time could be controlled by coating level. Use of water soluble plasticizer (polyoxyl hydrogenated castor oil) resulted in slightly shorter lag time and faster release, compared with water insoluble plasticizer (Dibutyl sebacate) due to leaching. Drug release mechanism controlled by rupturing of outer membrane was confirmed by microscopical observation of pellet behavior during release. Thus, the designed option could be considered a promising formulation for multiparticulate pulsatile drug

delivery systems and hence in chronotherapeutic management of cardiac disorder by opening a "new extended life" to an existing drug molecule.

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REFERENCES:

1. Lachman L, Lieberman HA, Kanig J. The Theory and Practice of Industrial Pharmacy. 2nd ed. Mumbai: Varghese Publishing House, 1976;293.
2. Chein YW. Novel Drug Delivery Systems. 2nd ed. New York: Marcel Dekker. Inc, 1992;1-139.
3. Chivate AK, Poddar SS, Shajahan A, and Savant S. Evaluation of Sterculia foetida Gum as Controlled Release Excipient. AAPS PharmSciTech 2008; 9 (1)
4. Bussemer T, Otto I, Bodmeier R. Pulsatile drug delivery systems. Critical Review of Therapeutic Drug Carrier System. 2001;18(5):433-458.
5. Paeratakul O, Bodmeier R. Mechanical properties of dry and wet cellulosic and acrylic films prepared from aqueous colloidal polymer dispersions used in the coating of solid dosage forms. Pharm. Res 1994; 11: 882–888.
6. Pozzi F, Furlani P, Gazzaniga A, Davis SS, Wilding, IR. The Time Clock® system: a new oral dosage form for fast and complete release of drug after a predetermined lag time. J. Contr. Rel. 31, 99–108.
7. Singh DK, Poddar AS, Nigade SU, Poddar SS "Pulsatile drug delivery system: An overview" Int. J. Curr. Pharm. Rev. Res. 2 (2), 2011, 55-80.
8. Lobenberg R, Kim JS, Amidon GL. Pharmacokinetics of an immediate release, a controlled release and a two pulse dosage form in dogs. Eur. J. Pharm. Biopharm, 2005;60:17-23.
9. Ueda S, Ibuki R, Kimura S., Murata S, Takahashi T, Tokunaga Y, Hata T. 1994b. Development of a novel drug release system, time-controlled explosion system (TES). III. Relation between lag time and membrane thickness. Chem. Pharm. Bull 1994 a. 42: 364–367.
10. Ritschel WA, Forusz H. Chronopharmacology: a review of drugs studies. Meth. Find. Exp Clin. Pharmaco 1994; 16: 57–75.
11. Sungthongjeen S, Puttipipatkhachorn S, Paeratakul O, Dashevsky A. Bodmeier R. Development of pulsatile release tablets with swelling and rupturable layers. J. Contr. Rel 2004; 95: 147–159.
12. Singh R, Poddar SS, and Chivate A. Sintering of wax for controlling release from pellets. AAPS PharmSciTech 2007; 8 (3) : 1-9
13. Feuerstein GZ, Hamburger SA, Smith ED. Bril A, Ruffolo Jr. RR. Myocardial protection with carvedilol. J. Cardiovasc Pharmacol 1992. 19 Suppl. 1 : S138–S141.
14. Wilding IR, Davis SS, Piozzi F, Gazzaniga A, Enteric coated timed released systems for colonic targeting. Int. J. Pharm. 1994; 111: 99–102.
15. Shimamura K, Zou LB, Moriyama K, Yamamoto K, Sekiguchi F, Sunano S. Effects of amiloride on the neutrally mediated contraction of mesenteric artery. Eur. J. Pharmacol 1997. 320: 37–42.
16. Niwa K, Takaya T, Morimoto T, Takada K, 1995. Preparation and evaluation of a time-controlled release capsule made of ethylcellulose for colon delivery of drugs. J. Drug Target 1995; 3: 83–89.
17. Shivakumar, HN, Patel PB, Desai BG, Ashok P, Arulmozhi S. Design and statistical optimization of glipizide loaded lipospheres using response surface methodology. Acta Pharm 2007. 57: 269–285.
18. Sungthongjeen S, Puttipipatkhachorn S, Paeratakul O, Dashevsky A, Bodmeier R, Development of pulsatile release tablets with swelling and rupturable layers. J. Control. Release 2004; 95 : 147–159.
19. Sriamornsak P, Thirawong N, Puttipipatkhachorn S. Emulsion gel beads of calcium pectinate capable of floating on the gastric fluid: effect of some additives, hardening agent or coating on release behavior of metronidazole. Eur. J. Pharm. Sci 2005; 24: 363–373.
20. Bodmeier R, Chen H. Evaluation of biodegradable poly (lactide) pellets prepared by direct compression. J. Pharm. Sci 1989; 78: 819–822.
21. Mustofa M, Suryawati S, Dwiprahasto I, Santoso B, The relative bioavailability of diclofenac with respect to time of administration. Br. J. Clin. Pharmacol 1991. 32: 246–247.
22. Ghebre-Sellassie I. Multiparticulate Oral Drug Delivery. Marcel Dekker 1994; New York.
23. Lemmer B. Chronopharmacokinetics: implications for drug treatment. J. Pharm. Pharmacol 1999; 51: 887–890.
24. Paeratakul O, Bodmeier R. Leaching of water-soluble plasticizers from polymeric films prepared from aqueous colloidal polymer dispersions. Drug Dev. Ind. Pharm 1992; 18: 1865–1882.
25. Singh, SK, Reddy IK, Khan, MA. Optimization and characterization of controlled release pellets coated with an experimental latex: II. Cationic drug. Int. J. Pharm 1996; 141: 179–195.

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