DEVELOPMENT OF BIPHASIC PULSATILE RELEASE MINI-TABLETS SYSTEM OF POORLY WATER SOLUBLE CARVEDILOL PHOSPHATE

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ABSTRACT:

Objective:

Carvedilol Phosphate is indicated for the treatment of mild-to-severe chronic heart failure of ischemic or cardiomyopathic origin. The ultimate goal of pulsatile release mini-tablets to deliver a drug to the specific site and then to maintain the desired plasma drug concentration at particular site in chronotherapeutic manner. Among solids, multiparticulate delivery have its own advantages. Pulsatile drug delivery system provides better therapy with many of the actives. Rupturable pulsatile mini-tablet consists of a drug core; swelling layer of a super disintegrant; an insoluble, water-permeable polymeric and enteric coating. Upon water access, the swellable layer expands, resulting in the rupturing of outer membrane followed by drug release. There were no drug release ob served in acid phase. The active pharmaceutical ingredient selected was Carvedilol Phosphate, in core mini-tablets. The second layer composed of swelling excipient, had crospovidone, Croscarmellose sodium and sodium starch glycolate. Third and the outer most layer was based on ethyl cellulose and enteric polymer. 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 croscarmellose sodium 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 30%. Outer membrane, formed using ethyl cellulose was suitable enough to rupture sufficiently ensuring fast drug release in upper portion of small intestine. It was possible to design multiparticulate of carvedilol phosphate having a suitable release profile.

Key words: Mini-tablets, Biphasic pulsatile release, multiple unit-systems, Chronotherapy.

1. INTRODUCTION:

Progress in formulation development started with first generation immediate release dosages forms but these suffered from disadvantage such as no control over release rate of drug, frequent dosing was needed. Therefore, second generation modified release dosage form with controlled release were developed, which release drug at continuous and and /or constant rate.[1] This formulation had an advantage of reducing dose frequency and patient compliance as compared to conventional drug delivery. But many of controlled release formulation having numerous problems such as development of resistance, tolerance and side effect and undesirable blood level when symptoms are at peak.[2-5] Thus came in the development were new drug delivery system which release the drug at desired rate, specific time and to the targeted site. Pulsatile drug delivery systems are designed to release the drug at desired rate and selected time to mimic the biological which occur during specific day and night time. In modern era, pulsatile release formulation has become more and more popular within the pharmaceutical industry. A number of products have reached global markets and several high-profile brands have generated considerable revenues. Significant advances have been attained in developing and commercializing oral modified release products. [6-8]

The term Modified release drug product is used to describe products that alter the timing and/ or the rate of release of the drug substance.[9] Whereas the Extended release dosage forms allows at least a two fold reduction in dosage frequency as compared to that drug presented as an immediate release form. Extended release dosage forms are formulated in such manner as to make the contained drug available over an extended period of time following administration. Expressions such as controlled release, prolonged action, repeat action and sustain-release have also been used to describe such dosage forms.[10-14] A typical controlled release system is designed to provide constant or constant drug levels in plasma via reduce fluctuations via slow release over an extended period of time.[15]

Multi-particulate pulsatile mini tablets systems have several performance advantages over single unit dosage forms. After ingestion, Multi-particulate units are released from the capsule in the stomach, predictably transit to

the small intestine and spread along the gastrointestinal tract resulting in a consistent drug release with reduced risk of local irritation and dose dumping. Multi-particulate formulations generally have a more reliable in-vivo dissolution performance when compared to a single unit dosage form, resulting in more uniform bioavailability and clinical effect. [16-21].

Carvedilol phosphate is a third-generation, non cardioselective β-blocker that also possesses α 1-adrenergic blocking, antioxidant, and calcium antagonist properties (Fig 4). Carvedilol phosphate blocks β1- and β2-adrenergic receptors, improves myocardial function, and attenuates (or reverses) the undesirable ventricular remodeling that marks heart failure. Unlike usual β blockers, which as a rule do not reduce peripheral resistance, Carvedilol phosphate decreases peripheral vascular resistance, in part, by antagonizing α1-adrenergic receptors. Carvedilol phosphate lacks intrinsic sympathomimetic activity and does not demonstrate high levels of inverse agonist activity, which may contribute to its favorable tolerability profile in patients with heart failure. Moreover, it has a distinctive metabolic profile compared with other β blockers. Among other mechanisms, may also be due to the inhibition of activation and accumulation of polymorphonuclear leukocytes in the ischemic myocardium and the antioxidant activity of the drug. In various studies in patients with chronic stable angina pectoris, it was both efficacious and safe. In patients with congestive heart failure of both ischemic and non ischemic origin, it improved cardiac function, clinical symptomatology, and survival and was effective and safe given early after myocardial infarction. Carvedilol Phosphate was shown to protect against *in vivo* low-density lipoprotein oxidation in hypertensive patients and had mild beneficial effects, comparable to those of Captopril, on lipid profile in a cohort of hypertensive patients with dyslipidemia.[22-25] The safety of the higher recommended doses of Carvedilol Phosphate in both younger and elderly patients adequately respond to the lower dose, as well as higher dose on the basis of a risk/benefit assessment.[26-27] Metoprolol was chosen as comparative agent as it is one of the most widely used β blockers and is devoid of distinct additional pharmacologic properties, such as vasodilatation.[26] The present work describes such delivery system, which will improve the biological half-life and provides all the advantages of multiple unit drug delivery system, thus improving patient compliance. Carvedilol Phosphate innovator is Glaxo Smith Kline GSK) and marketed worldwide under the brand name Coreg CR. The half-life of Carvedilol Phosphate is 5-10 hrs [27-31]. The present work describes such delivery system, which will improve the treatment regimen and provides all the advantages of Multiparticulate drug delivery system, thus improving patient compliance.

The major objective of the this 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 Croscarmellose sodium, sodium starch glycolate and crospovidone and various ratio of coated with an insoluble polymeric membrane using ethyl cellulose and enteric polymer Eudragit L100.

2. MATERIALS AND METHODS

2.1. Materials

Carvedilol phosphate (CP) from Cadila Pharmaceuticals Ltd. Ahmadabad, India; Lactose monohydrate 200M (GranuLac 200) from Maggle Pharma, Germany; Microcrystalline cellulose (Avicel PH101) from FMC BioPolymer, USA; Polyvinylpyrrolidone (Kollidon 30) from BASF Germany; Crospovidone (Polyplasdone XL-10) from Ashland Specialty Ingredients, USA; Sodium starch glycolate (Glycolis) from Roquette freres, France; Croscarmellose sodium (Ac-di-sol) from FMC BioPolymer, USA; Ethyl cellulose (Ethocel standard 10) from Colorcon Asia Pvt. Ltd. Goa, India; Methacrylic acid co-polymer (Eudragit L-100) from Evonik Rohm GmbH, Germany and Triethyl citrate TEC (Morflex, Greensboro, NC, USA); All the remaining materials used were of analytical grade.

2.2. PREPARATION OF PULSATILE MINI-TABLETS

2.2.1. Preparation of mini-tablets

1. **Dispensing of Raw Materials**: Drug substance and excipients are dispensed as per the required quantity.

2. **Sifting:** Weighed quantity of Carvedilol Phosphate, Lactose monohydrate 200M, Microcrystalline cellulose PH101, were co-sifted through #40 sieve .

3. **Dry mixing:** Load the sifted material into the Rapid mixer granulator (RMG) and mixing for 15 minutes at slow speed of impeller and chopper off.

4. **Binder solution Preparation:** Disperse Povidone K30 in purified water and stir till a clear solution is obtained.

5. **Granulation:** Granulate the dry mix with the binder solution in Rapid Mixer Granulator with impeller on slow speed and chopper off. After complete addition of solution, continue granulation for appropriate period of time till to get desired granules by keeping impeller and chopper at slow speed. If required add additional quantity of water to get the required granules.

6. **Drying :** Unload the wet mass to the bowl of fluidized rapid Dryer (FBD) and fluidize it for 5 to 10 minutes with air, then dry it at inlet temperature of 60°C for the appropriate period of time till loss on drying is 3.0 to 5.0% (at 105°C, for 5 min).

7. **Sizing:** Pass the dried granule through # 30 sieves manually.

8. **Blending:** Blending of sized granule were carried out for 15 minutes in a one liter blender.

9. **Lubrication:** Lubrication were carried out of the sized granules with Magnesium Stearate (Sifted 60#) in the same blender for 5 minutes.

10. **Compression:** Lubricated blend were compressed into 25 mg weighing mini-tablets using 3 mm round concave punches in a rotary tablet press (Cadmach, Ahmadabad)

2.2.3. Coating of swelling layer

Core mini-tablets were coated with a 10 % (w/w) suspension of crospovidone or sodium starch glycolate or Croscarmellose Sodium and Kollidon K30 as binder in 96% (v/v) ethanol using the fluidized bed coater to achieve required weight gain. The process conditions were: batch size, 250 g, pre-warming of the cores at 40° C for 10 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, 32° C; spray rate, 10-12 g/min. Final drying of mini-tablets was done at for 15 min at 40° C. (Table 1)

2.2.4. Coating of modified release polymer

The Mini-tablets coated with the swelling polymer were further coated with a 7 % (w/w) ethyl cellulose grade 10 in 96% (v/v) ethanol, plasticized with 10% (w/w) Triethyl citrate based on the weight of the polymer. Subsequent coating of enteric polymer were carried out on ethyl cellulose coating. Eudragit L100 coated with a 20 % (w/w) in solvent system of Isopropyl alcohol, Acetone, purified water and plasticized with 10% (w/w) Triethyl citrate 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, 250 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, 32° C; spray rate, 2-6 g/min. Final drying of pellets was done at for 30 min at 40° C. The coated pellets were cured in an oven at 45-50° C for 24 h. (Table 2)

2.3. DRUG RELEASE

The dissolution of mini-tablets 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. Fig (1A-C).

2.4 MICROSCOPY

An optical image generated through macro option of a digital camera (Nikon coolpix L18). The image contains enteric coated ethylcellulose shell after brusting of the pellets shown in association of mm scale for size judgment) Fig (2). The illumination has created shadows of the pellets remnants which are to be neglected.

3. RESULTS AND DISCUSSION

3.1 Granule characteristics

The angle of repose for the granules of core mini-tablets was found to be 21.12 ± 0.11 º. The values for both loose bulk density and tapped bulk density were found to be 0.55 ± 0.01 and 0.65 ± 0.01 gm/cc respectively. The value of compressibility index for the blend was found to be 15.38 ± 0.31 %. The value for Hausner's ratio was found as 1.18 ± 0.05. These results indicate that the granules were of good flow properties.

3.2 Physical characteristics of core mini-tablets

The mean weight of mini-tablets was 20 ± 0.13 mg. The hardness of core mini-tablets was 2.92 ± 0.22 kg/cm2. Friability was 0.57 ± 0.04 % and it also showed that mini-tablets have sufficient mechanical strength. The thickness was 2.20 ± 0.03 mm. Good uniformity in drug content was observed in the uncoated core mini-tablets, and percentage drug content was 99.8± 0.04 %. The uncoated mini-tablets also passed the disintegration test as they disintegrated within 3 ± 0.56 min

3.3. 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.

3.4 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. 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.

3.5 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.

3.6 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.

3.4 Formulation stability

When optimized enteric coated mini-tablets batch F12 was subjected for evaluation of drug content, it was found that the drug was by 98 ± 0.55 % in a period of 6 months suggesting that the drug was stable. When stability studies were performed for in-vitro drug release profile it was observed that there was very small variation (i.e., < 1 %) in both lag time and drug release profile for the optimized formulation F12. While performing statistical analysis it was found that there was no significant difference during before and after stability studies ($p \leq 0.05$).

4. CONCLUSION

The pulsatile release mini-tablets with a swelling layer, rupturable ethyl cellulose coating and enteric coating were developed. The system released the drug rapidly after a certain lag time due to the rupture of the ethyl cellulose film. Précised lag time was observed with enteric coating over ethyl cellulose coating. The lag time of the system could be modified by several factors such as level of swelling layer, rupturable coating and enteric coating.

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Table 1: Formulation Optimization

Batch .No.	**F1**	**F2**	F3	F4	F5	F6
Core mini-tablets						
Carvedilol phosphate	80.00	80.00	80.00	80.00	80.00	80.00
Lactose monohydrate	145.00	145.00	145.00	145.00	145.00	145.00
Microcrystalline Cellulose PH101	75.00	75.00	85.00	71.00	71.00	71.00
Polyvinylpyrrolidone K 30	3.00	3.00	3.00	3.00	3.00	3.00
Magnesium Sterate	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Coating of swelling layer						
Crospovidone	15.00	…	…	…	…	20.00
Croscarmellose Sodium	…	15.00	…	20.00	…	…
Sodium Starch glycolate	…	…	5.00	…	20.00	…
Polyvinylpyrrolidone K 30	3.00	3.00	3.00	3.00	3.00	3.00
Ethanol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Coating with ethyl cellulose and enteric polymer						
Ethyl cellulose standard 10	55.08	55.08	55.08	48.08	48.08	48.08
Eudragit L 100	5.95	5.95	5.95	11.95	11.95	11.95
Triethyl citrate	5.97	5.97	5.97	5.97	5.97	5.97
Isopropyl Alcohol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Acetone	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Purified water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

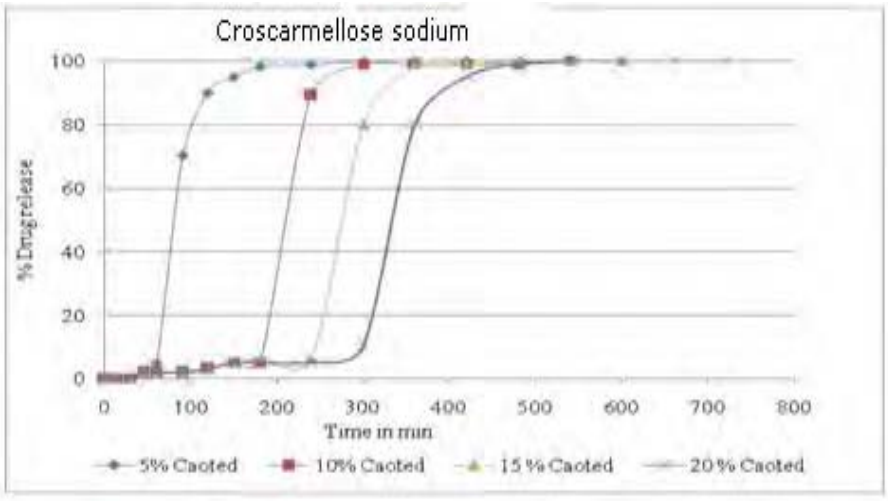
Table 2: Process parameter for coating of swelling layer

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	10-12 g min
6	Blower RPM	1800 rpm

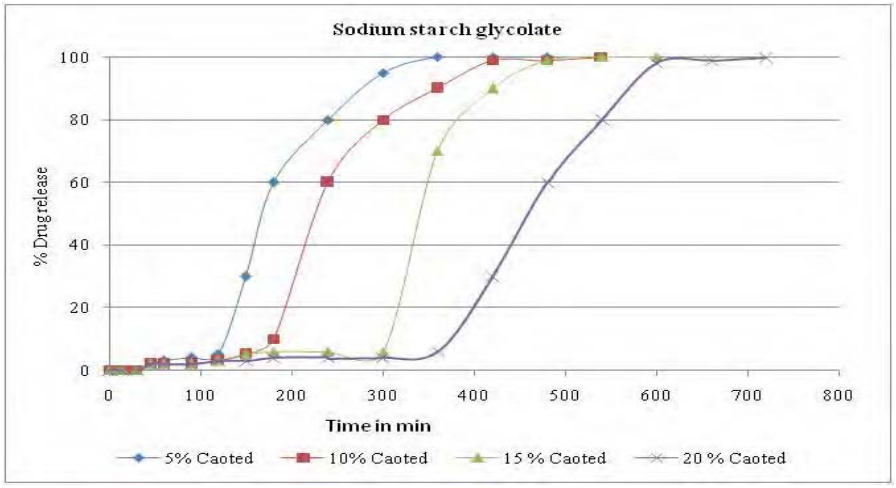
Table 3: Process parameter for coating of ethyl cellulose

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

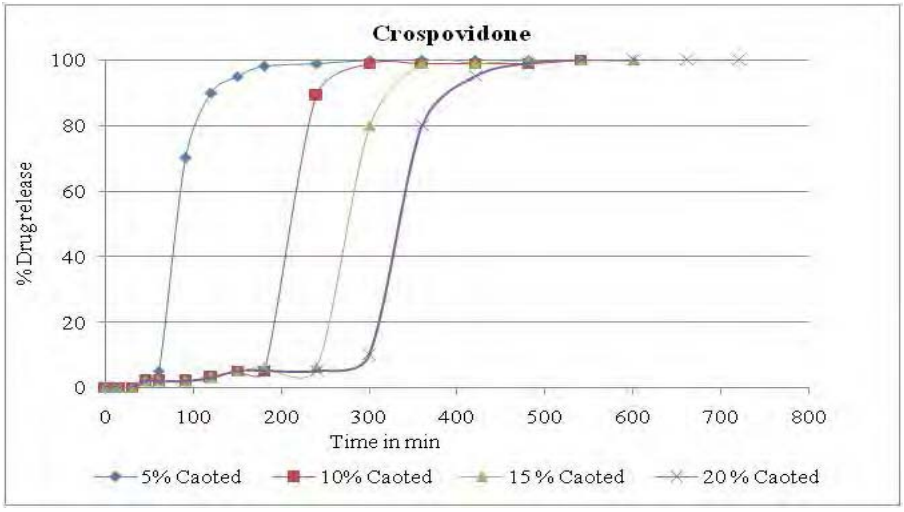
Figure 1: Drug release from carvedilol phosphate coated sugar core:



(A) Croscarmellose sodium coated



(B) Sodium starch glycolate coated



(C) crospovidone coated

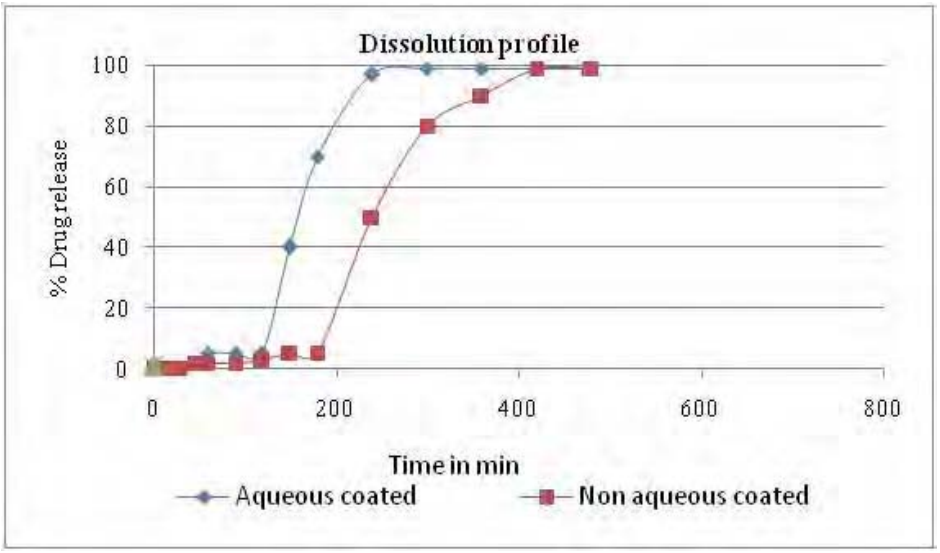


Figure 2: drug release from aqueous and non aqueous ethyl cellulose coated pellets

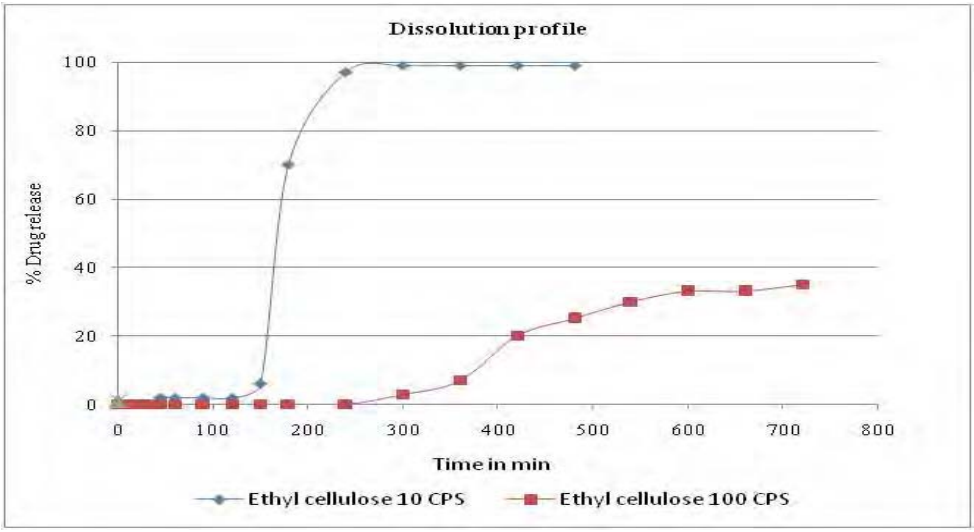


Figure 3: ffect of the ethyl cellulose coating level

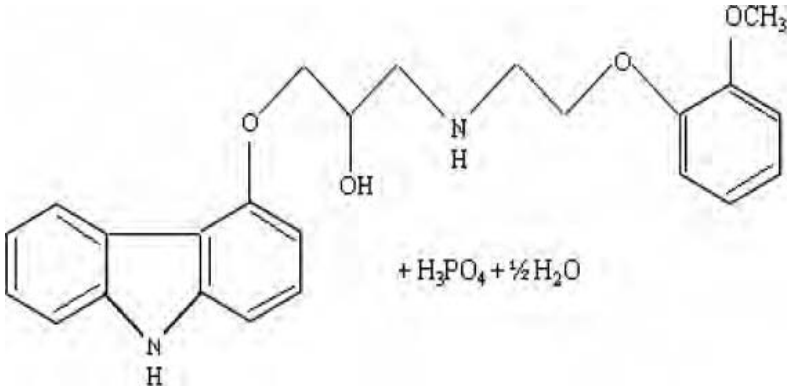


Figure 4: Chemical structure of carvedilol phosphate