



Selection of a suitable polymeric matrix for chronotherapeutic drug delivery: a comparative study

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Abstract

The aim of study was to prepare a chronomodulated press coated tablet having pulse release pattern with the desired lag time for chronic heart disorder. The prepared time-dependent pulse release system consisted of a core drug layer surrounded by polymeric coat. The core consisted of Atenolol (25 mg), while the coating layer consisted of polymer blends of Carbopol 971P:Hydroxypropyl cellulose and Carbopol 971P:Hydroxypropylmethyl cellulose K15M combinations in various ratios. Both combinations were studied for mucoadhesion, swelling. The mucoadhesion for Carbopol 971P:Hydroxypropyl cellulose combination was found to be satisfactory. Increased in the adhesion force was observed as proportion of Carbopol increased for Carbopol 971P:Hydroxypropylmethyl cellulose K15M combination. The swelling rate was increased in both combinations as Carbopol 971 increased. For drug release study pulsatile release pattern was observed for Carbopol 971P:Hydroxypropyl cellulose with lag time up to 12 h. For Carbopol 971P:Hydroxypropylmethyl cellulose K15M combination pulse and sustained release pattern was observed with lag time up to 7 h and sustained release over a period of 16 h. From the obtained results of polymer studies and *in vitro* release profile, the tablet prepared with Carbopol 971P:Hydroxypropyl cellulose combination was found to be more suitable for the development of a chronotherapeutic drug delivery system.

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INTRODUCTION

It is well established that considerable daily variations exist in all body functions including those influencing the pharmacokinetic parameters. The onset and extent of several diseases like asthma, myocardial infarction, angina pectoris, hypertension, ulcer and arthritis shows circadian dependency. With the knowledge when the disease shows peak time, controlled release dosage forms can be developed.^[1] Various chronotherapeutic dosage forms have been developed which include enteric coated systems, osmotic systems, pulsincaps, multi-particulate systems and layered systems.^[2-5] Atenolol, a β_1 -selective adrenergic receptor antagonist widely used in treatment of hypertension, angina pectoris, cardiac arrhythmias and myocardial infarction.^[6, 7] The prepared mucoadhesive press coated tablet consisted of a core with the drug Atenolol and coat made up of various polymer ratios of Carbopol 971P:Hydroxypropyl cellulose (HPC) and Carbopol 971P:Hydroxypropyl methyl cellulose K15M (HPMC K15M) combination.^[8, 9]

MATERIALS AND METHODS

Atenolol B.P. (from M. J. Biopharm. Pvt. Ltd., Navi Mumbai) and Carbopol 971P (from Lubrizol Advanced Materials India Pvt. Ltd.) were obtained as gift sample. HPC (low substituted), HPMC K15M, sodium starch glycolate, dibasic calcium phosphate and magnesium stearate (IP grade) were purchased from S. D. Finechem Ltd. Other solvents and chemicals used in the study were of analytical grade.

Polymer studies:

Various polymer blends in following ratios (20:80, 30:70, 40:60, 50:50, 60:40, 70:30, 80:20) of Carbopol 971P:HPC and Carbopol 971P:HPMC K15M in combination were prepared and physically evaluated. Prepared blends were compressed in to tablet for study of mucoadhesion and swelling.^[10, 11]

Mucoadhesion:

Mucoadhesive force was assessed with modified pan balance apparatus. The intestinal tissue of Wistar rat of either sex was cut in to 1cm² piece and stuck to the apparatus with the mucus layer facing up. The compressed polymer tablets were hydrated for 2 min in phosphate buffer pH 6.8 and placed on the mucus surface. Another tissue layer of same dimension was placed on the tablet surface in such a way that the tablet was placed in between two mucus layers. The system was pressurized for 10 min with 5 g weight for initial contact. The total

weight required to detach the tablet from the mucus surface was measured in terms of force of detachment^[12, 13].

Swelling and erosion:

The tablet was weighed (W_1) and immersed in water at zero time. The swollen tablet was weighed again after each hour time interval (W_2) and % swelling (increase in size of tablet) was calculated. The swollen polymer tablets were dried at 60⁰ for 24 h in an oven and kept in desiccators for 48 h. The dried tablet was weighed (W_3) to calculate % erosion^[14].

Preparation of the final press coated tablet:

Final press coated tablet composed of centrally placed active core surrounded by polymeric coat layer. The core consisted of the drug Atenolol-25 mg, sodium starch glycolate-4 mg (super-disintegrant) and dibasic calcium phosphate quantity sufficient to 50 mg. The core layer is of diameter 5 mm and low hardness. The coating layer was applied by dry compression technique using prepared ratios of Carbopol 971P:HPC and Carbopol 971P:HPMC K15M. The tablets prepared with the Carbopol 971P:HPC ratios had a diameter of 8.5 mm, hardness 6 kg/cm² and a total weight of 200 mg whereas, tablets prepared with Carbopol 971P:HPMC K15M ratios had a diameter of 7.5 mm, hardness 4-6 kg/cm² and a total weight of 100 mg^[15].

In vitro release profile:

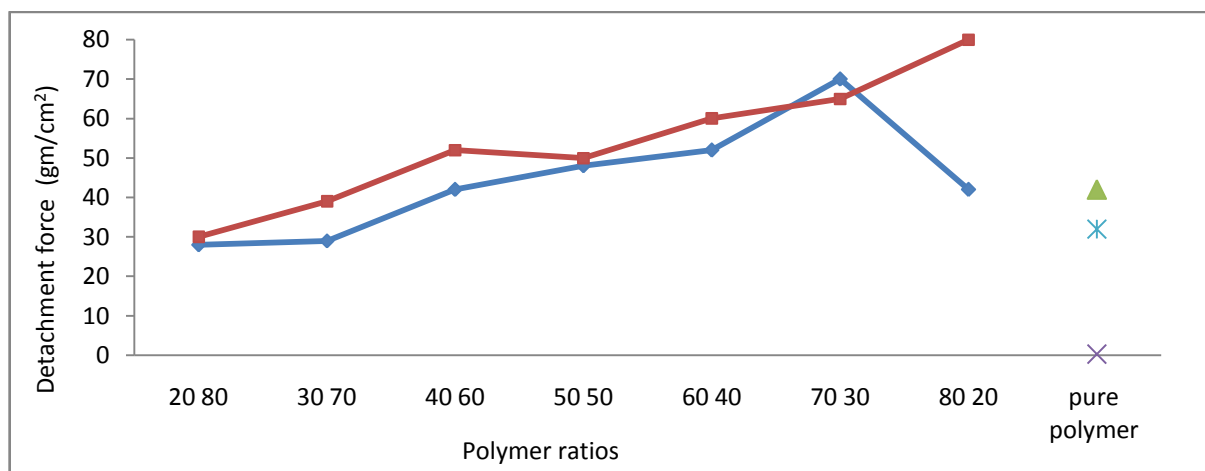
The release of Atenolol from the press-coated tablets was determined using the USP dissolution apparatus type II. The test was performed at 37±0.5⁰, 50 rpm using 0.1 N HCl (first 2 h) followed by phosphate buffer pH 6.8. According to the sampling plan 5 ml was withdrawn at pre-decided time intervals and replaced with an equal volume of same media. The sample was further diluted and analyzed by U.V. spectrophotometer at 225 nm^[16].

Rupture test:

Rupture behavior of tablet was observed visually using the USP dissolution apparatus type II with 900 ml of 0.1 N HCl for initial 2 h and then phosphate buffer pH 6.8 at 37±0.5⁰ at 50 rpm during dissolution study.^[17]

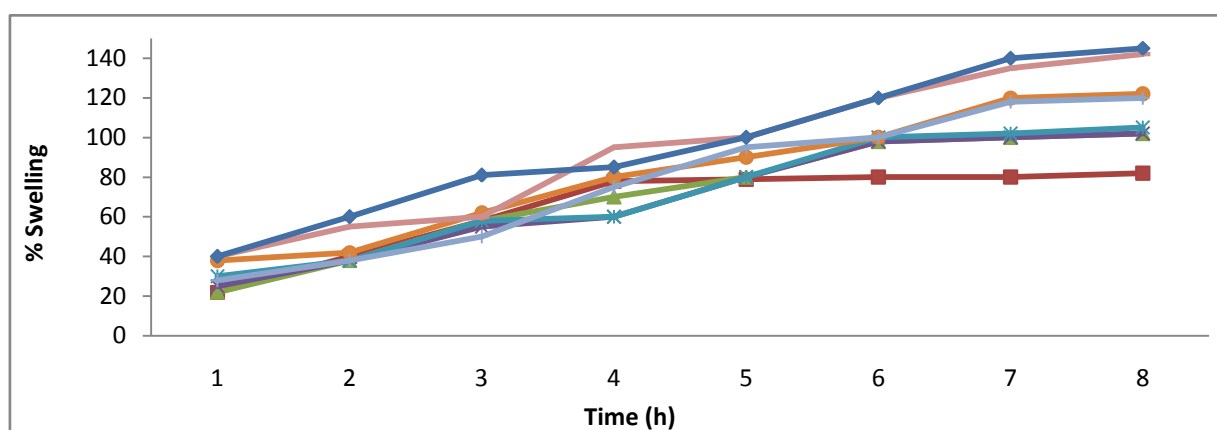
RESULT AND DISCUSSION

The prepared polymer combinations in various ratios were white to off-white in color and homogeneously mixed in the prepared ratios. The pH of a



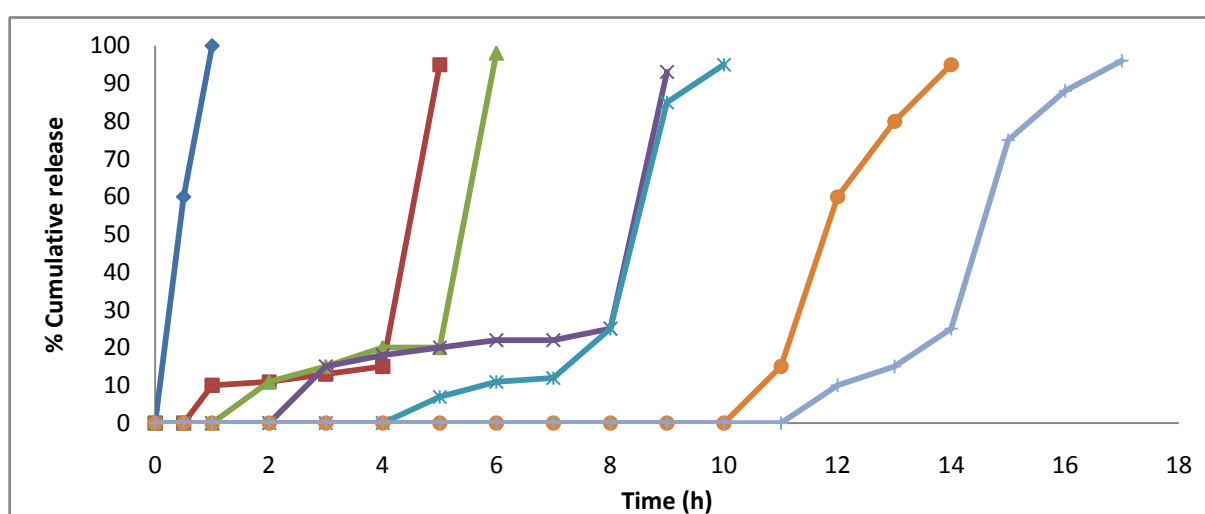
(—♦—) Carbopol 971P:HPC, (—■—) Carbopol 971P:HPMC K15M, (—▲—) Carbopol 971P, (—×—) HPC, (—*—) HPMC K15M.

Fig 1: Detachment force for various ratios of Carbopol 971P:HPC and Carbopol 971P: HPMC K15M in combination.



(—■—) 20Carbopol 971P:80HPC, (—▲—) 20Carbopol 971P:80HPMC K15M, (—×—) 40Carbopol 971P:60HPC, (—*—) 40Carbopol 971P:60HPMC K15M, (—○—) 60Carbopol 971P:40HPC, (—♦—) 60Carbopol 971P:40HPMC K15M, (—■—) 80Carbopol 971P:20HPC, (—♦—) 80Carbopol 971P:20HPMC K15M.

Fig 2: Swelling behavior of Carbopol 971P:HPC and Carbopol 971P: HPMC K15M in various ratios.



(—♦—) 20Carbopol 971P:80HPC, (—■—) 30Carbopol 971P:70HPC, (—▲—) 40Carbopol 971P:60 HPC, (—×—) 50Carbopol 971P:50 HPC, (—*—) 60Carbopol 971P:40HPC, (—○—) 70Carbopol 971P:30HPC, (—♦—) 80Carbopol 971P:20HPC.

Fig 3: Drug release profile for Atenolol tablets prepared using various ratios of Carbopol 971P:HPC in combination.

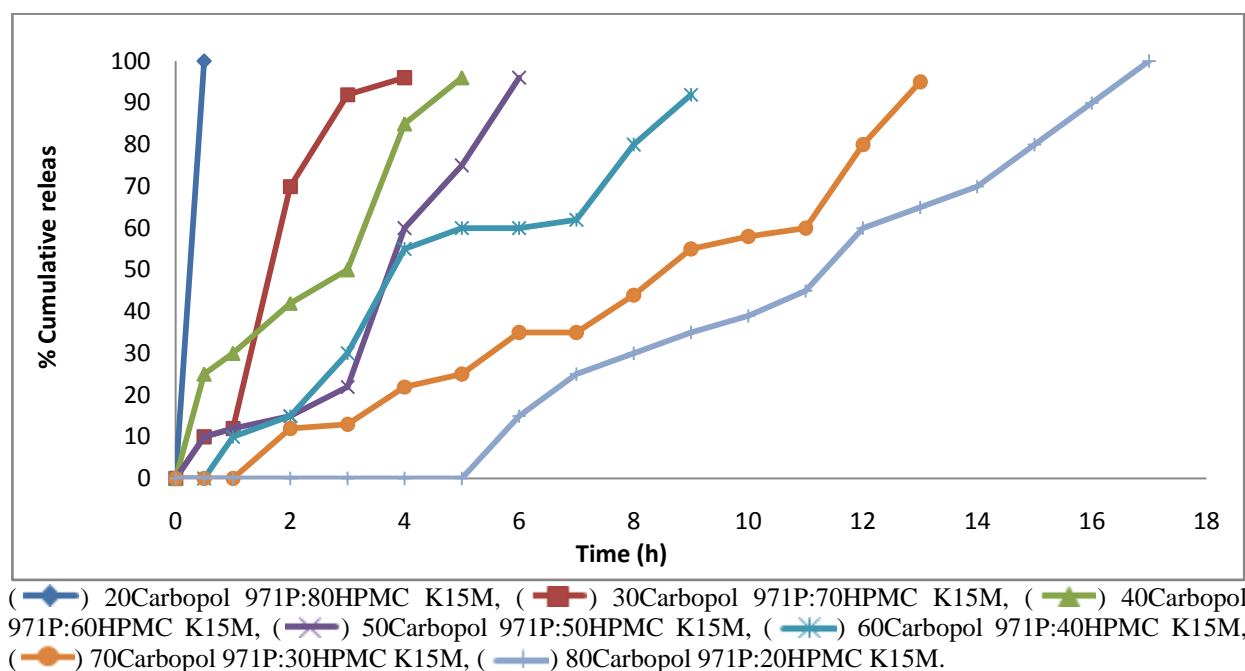


Fig 4: Drug release profile for tablets prepared using Carbopol 971P:HPMC K15M in combination.

0.5 % w/v solution of both the polymer combinations was found to be in the range 4.0-5.0.

Molecular weight, concentration, polymer flexibility, number of bond forming group, water absorption is the overall factors responsible for mucoadhesion. In case of Carbopol 971P:HPC combination Carbopol 971P exhibits higher mucoadhesion than HPC. Carbopol 971P has slower hydration and maximum swelling power. This increases the spreading of the system on the mucus surface and thus adhesion with the biological layer. HPC shows lesser swelling and faster erosion due to which HPC is not an effective mucoadhesive polymer. pH influences the charges on the polymers and affects hydration. The carboxylic groups remain unionized at gastric pH. There is increase in the hydration of Carbopol 971 between pH 4 to 7. Carboxylic group of Carbopol 971P are responsible for the formation of hydrogen bonds with the mucus layer. However, HPC has weak hydrogen bonding potential hydroxyl groups and thus a low interaction with the mucus molecule resulting in less mucoadhesion. Considering the Carbopol 971P and HPMC K15M combination, both polymers have high molecular weight, good swelling and hydrogen bond forming groups, HPMC K15M has less mucoadhesion than Carbopol 971P. Increase in viscosity of the polymer indicates extensive chain entanglement (diffusion theory), molecular bonding (absorption theory) and thus improved mucoadhesion [18-24]. Comparison of the detachment force of prepared polymer ratios with individual polymer is shown in

Fig 1. Carbopol 971P:HPC combination with 20 % Carbopol 971P shows low mucoadhesion, 40 % Carbopol 971P has similar mucoadhesion as pure Carbopol 971P while blends with 50 to 70 % Carbopol 971P show maximum adhesion. At the highest concentration of Carbopol 971P the polymer chains highly interact with each other leads to inflexible conformation of the polymer without active participation in adhesion with the mucus molecule and thus a decrease in adhesive force is observed. In case of Carbopol 971P:HPMC K15M combination increase in adhesion is observed.

Under static condition swelling is dominant initially. A balance is maintained between swelling and erosion up to 6 hours. Erosion is predominant after 6 hours. Increase in fluid dynamics assists in polymer chain relaxation and thus erosion of the system. Swelling also produces the surface drag effect on the swollen polymer mass tending to pull out the polymer molecule. Swelling behavior of prepared ratios is shown in Fig 2. For the Carbopol 971P:HPC combination erosion increases as the concentration of HPC is increased. 2-7 % erosion is observed in the case of Carbopol 971P:HPMC K15M combination [25-28]. High swelling and negligible erosion is observed for the 80:20 ratios of both the polymer combinations.

The drug release from the polymeric barrier is by the contributions of both diffusion and erosion. Complete wetting of the system was achieved in the first 3 hours. The macromolecular chains of the polymer swell at the tablet surface and form a gel

layer around the core tablet which is the closely packed swollen polymer. Continuous swelling of the polymer further increases the thickness of the polymer gel inhibiting water penetration to the deeper part of the tablet resulting in reduction of drug release. In case of Carbopol 971P:HPC, the polymeric coat undergoes simultaneous swelling and erosion. Thus release of drug through the matrix is negligible and lag time is maintained [29-33]. For the Carbopol 971P:HPMC K15M combination the polymer erosion is less thus the fully swollen polymer is acting as the diffusion front which slowly releases the drug over an extended time and pulse release of the drug is not observed. The release pattern of Atenolol with prepared ratios of Carbopol 971P:HPC and Carbopol 971P:HPMC K15M in combination is shown in fig. 3 and fig. 4. In Carbopol 971P:HPC combination pulsatile release pattern is observed with all ratios whereas with Carbopol 971P:HPMC K15M combination a sustained release pattern is observed. With high Carbopol 971P proportion a lag time of 7 hours is observed with sustained release of the drug over a period of 16 hours.

The tablets prepared with Carbopol 971P:HPC ratios, the outer swollen polymeric layer forms a porous gel through which small amounts of drug is release over a period of lag time. After lag time, the tablet was burst into smaller fragments and released the remainder of drug rapidly. In case of the tablet prepared with the Carbopol 971P:HPMC K15M ratios pulse and sustained release pattern was observed. The drug is release through porous gel in sustained manner. Outer polymer layer broke in to two halves and residual drug was released

CONCLUSION

If release pattern of the drug is designed in a controlled manner, it results in more effective treatment and a better quality of life for patients suffering from chronic disorders. The chronomodulated drug delivery system for the treatment of chronic heart disorders was developed using Carbopol 971P:HPC and Carbopol 971P:HPMC K15M in combination. Release of the drug in the form of a pulse with desired lag period is designed in such a way that less amount of drug is released during the lag time followed by rapid and complete release. Based on the polymer studies and release profile of the formulations prepared using Carbopol 971P:HPC and Carbopol 971P:HPMC K15M in combination, it was observed that Carbopol 971P:HPC is a more suitable combination for pulsatile drug delivery system and can provide an ef-

fective and easily prepared system for pulsatile chronotherapeutic drug delivery.

Abbreviations and Symbols

Hydroxypropyl cellulose : HPC
 Hydroxypropylmethyl cellulose K15M : HPMC K15M
 Weight: w
 Volume: v
 Kilogram: kg
 Gram: g
 Milligram: mg
 Centimeter: cm
 Millimeter: mm
 Nanometer: nm
 Hour: h
 Minutes: min
 Revolution per minutes: rpm
 U V: Ultra violet
 Figure: Fig.

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Competing Interests

None declared.

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