

Programmed delivery of verapamil hydrochloride from tablet in a capsule device

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The aim of the present work was to develop a programmed drug delivery system which would be able to release the drug after 6 h of lag time by use of hydrophilic polymers. The capsule body was made impermeable by use of formaldehyde vapor treatment, while the cap was untreated. The capsule was filled with two layered tablets (tablet-in-capsule), followed by a sodium bicarbonate: citric acid mixture (SBCM) and lactose as bulking agent. Sodium alginate, chitosan, HPMC K15 and chitosan: sodium alginate complex (CSAC) were used as the rate modulating layer. Through combined use of HPMC K15 and adjusting the ratio of CSAC, the desired lag time of 6 h was obtained. The effect of the bulking agents on the lag time were also studied and it was found that the lag time was decreased with higher amounts of lactose, and delayed dissolution and decreased lag time was observed at higher amount of effervescent mixture.

Uniterms: Circadian rhythm. Chitosan/sodium alginate complex. HPMC K15. Lactose. Effervescent mixture.

O objetivo do presente trabalho foi desenvolver sistema de liberação programada de cloridrato de verapamil capaz de liberação imediata do fármaco após 6 h de intervalo de tempo usando polímeros hidrofílicos. O corpo da cápsula foi impermeabilizado por tratamento de vapor de formaldeído, enquanto a tampa não foi submetida ao tratamento. Dois comprimidos foram inseridos na cápsula (comprimidos em cápsula) seguido de mistura de bicarbonato de sódio: ácido cítrico e lactose, utilizados como excipientes. O alginato de sódio, a quitosana, o HPMC K15 e o complexo quitosana: alginato de sódio foram utilizados para modular a razão de liberação do fármaco. A combinação entre o HPMC K15 e o ajuste da proporção do complexo quitosana: alginato de sódio permitiu a liberação do fármaco após 6 h. O efeito dos excipientes na liberação do fármaco foi também avaliado. Verificou-se que o tempo de latência foi reduzido na presença de maior quantidade de lactose, enquanto o menor tempo foi observado empregando maior concentração da mistura efervescente.

Unitermos: Ritmo circadiano. Quitosana/complexo de alginato de sódio. HPMC-K15. Lactose. Mistura efervescente.

INTRODUCTION

The delivery of the desired dose of a drug at a predetermined time has always been the prime objective of drug delivery systems. Novel drug delivery systems have the potential to provide antihypertensive medication at the time when the need is greatest (Elliott, Prisant, 1997; Prisant *et al.*, 1992). The disease symptoms, such as hypertension,

ischemic heart disease, asthma and rheumatoid arthritis, exhibit circadian rhythms (Lemmer, 1991; Traynor *et al.*, 1992; Vyas *et al.*, 1997). Cardiovascular diseases, which account for the greatest morbidity and mortality, are greatly affected by body rhythms (Muller, 1999). Moreover, treatment outcomes may be affected by body rhythms. Failure to recognize these points may account for chronopathological events, including anterior ischemic optic neuropathy (Hayreh, 1999) and cerebrovascular accidents among persons with hypertension whose blood pressure falls markedly during the night ("extreme dippers") (Kario *et al.*, 1996). It

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is recognized that myocardial infarctions, sudden cardiac death, transient ischemic attacks and cerebrovascular accidents occur at a higher frequency in the early hours of the morning. Most cardiovascular medicines are designed to achieve a constant, or near-constant, effect throughout the 24-hour dosing interval. In many cases, however, the requirement for medication is not the same at nighttime as it is during the day (Anwar, White, 1998). Many drugs have been studied with respect to their pharmacokinetics and chronopharmacology, including analgesics, anticancer drugs, antibiotics, psychoactive drugs, local anesthetics, antiasthmatics, anticonvulsants and beta-blockers (Ritschel, Forsuz, 1994).

In general, the release rate of a drug is controlled by using a polymer with opposite solubility to the drug, or by combining polymers of different solubilities, as the drug will diffuse out easily from the dosage form if the fabricated by polymer, or polymers, have the same solubility as the drug. This concept was used to deliver verapamil (Verelan PM) by using water soluble and insoluble polymers. The chronotherapeutic oral drug absorption system (CODAS) verapamil PM, (Verelan PM, Schwarz Pharma, Inc., Mequon, WI) was designed to provide a drug-release profile that complements the circadian pattern of blood pressure (Prisant, 2001). This technology incorporated an initial 4-5 h delay, followed by the extended release of verapamil.

One should not assume that a drug dosed in the morning will have the same antihypertensive effect as a drug dosed in the evening (Lemmer, 1996). Oral pulsed or delayed delivery systems are designed to elicit programmable lag phases preceding a prompt and quantitative, and either repeated or prolonged release of the drug (Maroni, 2010). Therefore, the present study was aimed to develop a drug delivery system, using hydrophilic polymers only, which would be able to release the drug immediately after the desired lag time of 6 h. Verapamil was chosen as a representative drug, which is a potent calcium channel blocker and has been used for the treatment of essential hypertension and time related occurrence of disease symptoms (Lemmer, 1991).

MATERIAL AND METHODS

Material

Verapamil hydrochloride and HPMC K-15 were received as gift samples from Alembic Ltd. Vadodra, Gujarat, India. Empty capsule shells were received as gift samples from Erawat Pharma, Pithampur, Madhya Pradesh, India. Chitosan with 85% deacetylation was purchased from Marine chemicals, Kochi India. Sodium

alginate was purchased from Loba chemie, Pvt. Ltd, Mumbai, India. All other reagents were of analytical grade and used as purchased.

Preparation of impermeable capsules body

For controlling the release of the drug from a novel tablet in capsule device, the body of the capsule was made impermeable, while the cap of the capsule remained soluble, so that dissolution fluid may enter from the soluble part of capsule. The body and the cap of the gelatin capsule (size 0) were separated. The body of the capsule was exposed to formaldehyde vapor for 6 h at room temperature and dried at 50 °C for 48 h in a hot air oven (Sroopathy *et al.*, 1999). The treated capsule body and the untreated soluble cap were stored in desiccators until used. Prior to use, the treated capsule body was studied for disintegration test and the treated capsule body did not show any signs of disintegration and was therefore used for the further study.

Preparation of two layered tablets

An accurately weighed amount of the powders, containing the immediate release layer and the rate modulating layers, were sifted through 80 mesh size, and then tablets were compressed in a 7 mm single punch machine by hand filling. The immediate release layer was composed of verapamil: lactose: cross povidone: magnesium stearate (20:65:10:5), while the rate modulating membrane was composed of polymers only.

Studies of the rate modulating layer

To select the material for the modulating layer, HPMC K15, chitosan and sodium alginate were chosen as candidates for the study, which are commonly used for controlled or sustained release (n = 6).

Studies of weight of rate modulating layer on the release of drug

HPMC K15, chitosan and sodium alginate alone, and chitosan and sodium alginate in different proportions at different weights (100, 150, 200 mg) were compressed. To obtain mechanically stable tablets, the rigidities of the tablets were kept in the range of 8 - 10 kg/mm², as no significant effect of hardness was observed on the release of drug by Bin Li and co workers (Li *et al.*, 2008). HPMC K15 has been studied for lag time by Mukesh C. Gohel (Gohel, Manhapra, 2002), which was further studied at the same weights to obtain the desired lag time (n = 6).

Studies of the amount of bulking agent on the release of drug

To study the amount of bulking agent on the release of drug, lactose and sodium bicarbonate: citric acid (1:1) were used as bulking agents. 150, 175 and 200 mg of lactose and 20, 30 and 40 mg of the effervescent mixtures were selected to study the effect of the amount of bulking agent on the release of drug ($n = 6$).

Fabrication of the capsule device for two pulse drug release

Two layered tablets containing the immediate release and the rate modulating layer, followed by the effervescent layer and lactose as filler were snugly fitted in the impermeable capsule body (Fig. 1), and then the soluble cap was placed on the body. The first two layered tablet (A) was placed in the capsule body in such a way that the immediate release layer was facing the outer side, while the rate modulating layer faced inside. The layers (rate modulating and immediate release layer) of the second two layered tablet (B) were position facing the opposite way to first two layered tablet.

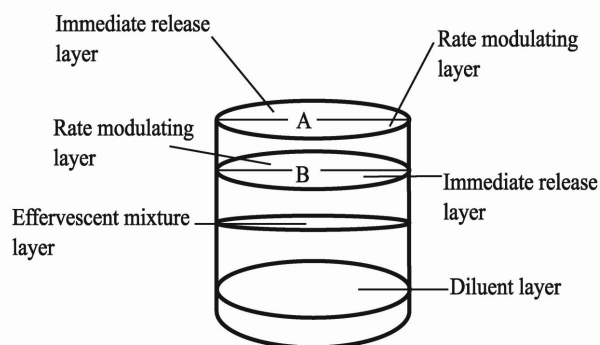


FIGURE 1 - Schematic presentation of the bi-layered tablets in the impermeable capsule body.

In vitro drug release studies of the capsules

A total of 900 mL of the dissolution medium (pH 1.2) was used to fill the USPXXIII dissolution apparatus. The capsule ($n = 6$) was placed in a basket and the speed was adjusted to 100 rpm. The temperature of the dissolution medium was maintained at 37 ± 0.5 °C. After 2 h stirring was stopped, the basket was washed with distilled water and the dissolution medium was replaced by phosphate buffer (pH 6.8), which had previously been maintained at simulated body temperature. Aliquots (10 mL) were withdrawn at 15 min time intervals and the same volume replaced by fresh dissolution medium.

RESULTS AND DISCUSSION

The aim of the study was to develop a pH independent dosage form with a lag time of 6 h and fast release thereafter. The total weight of the layered tablet was kept at 200 mg for the study.

Effect of individual polymer on lag time

Results in Figure 2 show that only HPMC K15 was able to provide a lag time of 6 h. Only 7.5% of the drug was released after 6 h, which satisfies the lag time criteria, but slow release was obtained thereafter, with only 20% of the drug being released after 8 h, and complete release being seen after 10 h. Lactose was added to the HPMC to reduce the swelling of HPMC gel at 10%, 20%, 30%, 40% and 50% w/w, but lag time was not controlled.

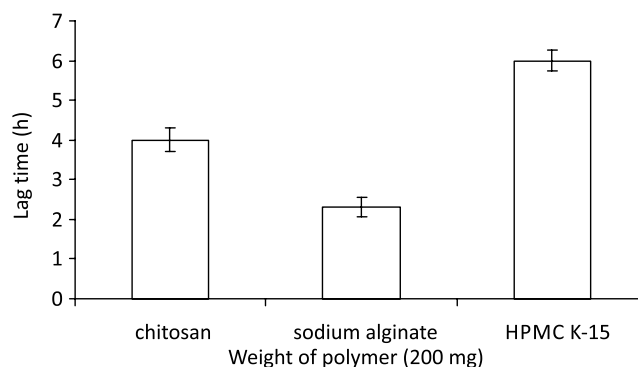


FIGURE 2 - Lag time of sodium alginate, chitosan and HPMC K15 at 200 mg weight.

From Figure 2, it was also seen that chitosan and sodium alginate were not able to produce the desired lag time at maximum weight, and that lag time was dependent on the pH of the medium. Sodium alginate rapidly forms a viscous gel on contact with aqueous media. Because of its high dissolution characteristics, the drug rapidly diffuses through the gel and released all of its active ingredient in 3 h, at the highest weight of polymer. Chitosan dissolves to some extent in inorganic mineral acids, hence providing the higher lag time of 4 h and the drug was released by initial low dissolution and then erosion of chitosan.

Effect of CSAS

A combination of chitosan with sodium alginate for sustaining the release of theophylline has also been studied, and release was found to be independent of the pH of the dissolution medium (Yamota *et al.*, 1994). From the results, shown below (Figure 3), it was found that a lag time

of 3 h was obtained from CSAS at a 50:50 ratio at 200 mg weight. When the ratio of chitosan was increased then lag time was also increased, but significant increase ($p < 0.05$) was not observed. The complex produced by combining the chitosan and sodium alginate had no significant effect over chitosan and sodium alginate alone. Similar results were also obtained by Jittima and co-workers (Chatchawalsaisin *et al.*, 2004).

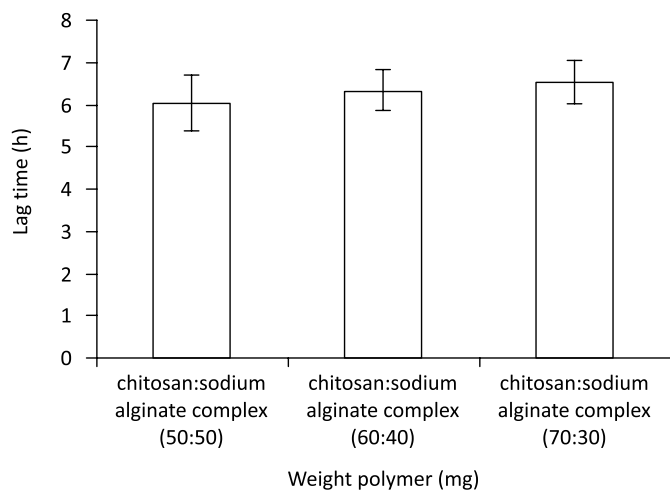


FIGURE 3 - Lag time of chitosan:sodium alginate polymer complex, in different ratio, at 200 mg weight.

Effect of HPMC K 15 and CSAS

HPMC K-15 and CSAS, when used alternately as the rate modulating layer, gave the desired lag time of 6 h, with only 8% of the drug being released from the formulation, which satisfies the lag time criteria. Lag time was found to be independent of pH and the drug was released mainly by diffusion, although through a dissolution/erosion mechanism.

Effect of the SBCM on lag time/dissolution

SBCM was added to hasten the release of drug after the desired lag time. No effect was observed at low amounts of SBCM (Figure 4), but at higher amounts the lag time was found to be reduced due to the pressure generated in the system by CO_2 after dissolution of SBCM causing pressure on the gel matrix. Verapamil is a basic drug which is why the dissolution of the drug was also reduced as SBCM was increased.

Effect of lactose on lag time

Lactose was added as a bulking agent separately

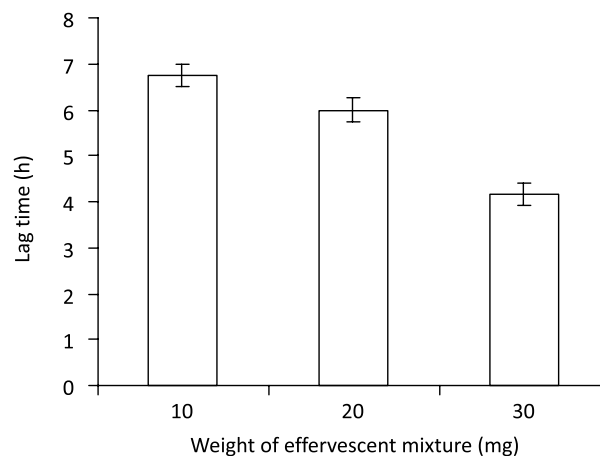


FIGURE 4 - Effect of the amount of effervescent mixture on the lag time of the rate modulating layer containing HPMC K15 and CSAC (50:50) at different weights.

to ensure the proper position of the tablet in the capsule device, but a significant effect on the lag time of drug due to the amount of lactose was observed (Figure 5). The increasing hydrodynamic pressure in the system, due to dissolution of lactose, shortened the lag time.

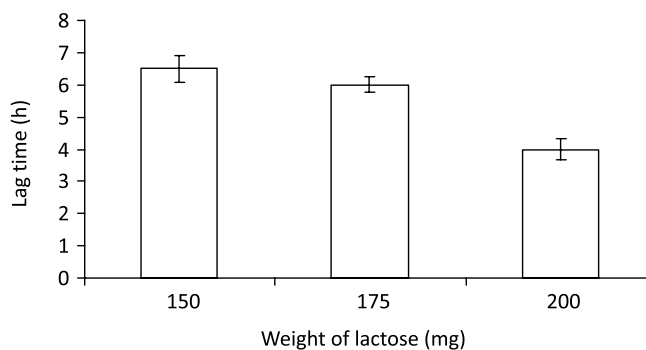


FIGURE 5 - Effect of the amount of lactose on the lag time of the rate modulating layer containing HPMC K15 and CSAC (50:50) at different weights.

Investigation of two pulse release

From the above results, two pulse release was successfully achieved (Figure 6) by using a bi-layered tablet containing 100 mg of immediate release layer and 100 mg of HPMC K 15 as a rate modulating layer, followed by 100 mg of CSAC (50:50) as a rate modulating layer, 100 mg of immediate release layer, and 20 mg SBCM and 175 mg of lactose. After 6 h of lag time, 85% release of drug was obtained within 15 min. Complete release was obtained within 30 min and the release was reproducible.

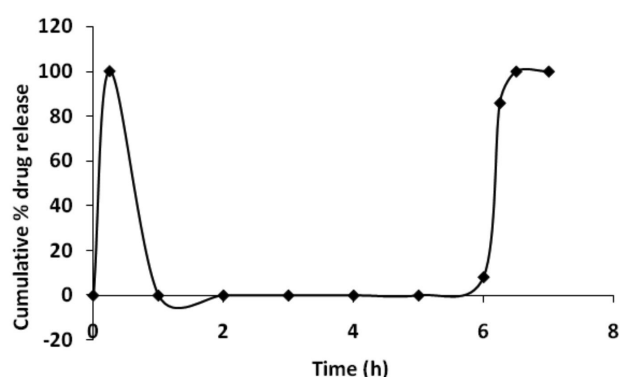


FIGURE 6 - *In vitro* release profile of two pulse release system, containing HPMC K15 (100 mg) and CSAC 50:50(100 mg) as rate modulating layers, CBCM (20 mg) and lactose(175 mg).

CONCLUSIONS

Pulsed release of a drug with variable lag time has been studied by various scientists. Lag time can control by using a polymer of opposite solubility to the drug, or by combining hydrophilic and hydrophobic polymers. A higher lag time for a water soluble drug using a hydrophilic polymer is always difficult, as diffusion of the drug from the polymer is not controlled easily. The present system is capable of delivering the drug after 6 h of desired lag time. It is known that in most people with high blood pressure, there is a definite rise in blood pressure upon awakening (also termed the “A.M.” surge), and that blood pressure then goes down starting in mid-afternoon, hence the proposed system could be used successfully, as a once daily does taken at night time, i.e. 10 p.m., which would enable delivery of the drug in the early morning i.e. 4 a.m.

AUTHORS' STATEMENTS

The authors declare no conflict of interest.

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