

Modulation of Lag Time of Sodium Alginate Based Programmed Delivery of Water Soluble Drug from Tablet in Capsule Device

Mukesh Lal Sah*, Vijay Juyal

Department of Pharmaceutical Sciences, Bhimtal Campus Kumaun University, Nainital, Uttarakhand, India.

Abstract

Three single layered tablets followed by effervescent mixture and lactose, were placed in the insoluble capsule body and soluble cap. Lactose was added as filler while effervescent mixture was used to hasten the release of drug after desired lag time. Two pulse drug release was successfully obtained by placing eudragit S-100 surface coated sodium alginate rate modulating tablet between upper and lower immediate release tablets. Lag time was dependent of thickness of the surface coated sodium alginate tablet, Contrary to previous studies no effect of the amount of lactose was observed on the lag time of drug. Immediate release of the drug was obtained successfully after desired lag time of six h.

Keywords: Circadian rhythm, lag time, sodium alginate, Eudragit S100, effervescent mixture.

Introduction

Oral route of drug delivery system was always considered the best among all drug delivery routes, as it has larger surface area and better patient compliance. Desired dose of drug at predetermined time was always remained the prime objective of the drug delivery system. Novel drug delivery systems have the potential to provide antihypertensive medication at the time when the need is greatest (Elliott and Prisant 1997, Prisant et al. 1992). Pulsatile release of the drug in the disease, which follows the circadian rhythm, was primary target for such delivery system. Cardiovascular diseases, which account for the greatest morbidity and mortality, are greatly affected by body rhythms (Muller 1999). It is now generally recognized that myocardial infarctions, sudden cardiac death, transient ischemic attacks, and cerebrovascular accidents occur at a higher frequency in the early morning hours. 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 and White 1998). 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). For the treatment of hypertension, this idea has the potential for a therapeutic paradigm shift. 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 BP (Prisant 2001). This technology incorporated initial 4-5 h delay, followed by the extended release of verapamil.

*Corresponding author: mukeshlalsah@gmail.com

Natural gums have been widely used as rate modulating layer in controlled/sustained release preparations. Release of drug from a hydrophilic matrix is governed by two mechanisms (Alderman 1984): (i) diffusion of water-soluble drug through the gel layer and (ii) release of water-soluble or water insoluble drug by erosion of outer gel layer as it becomes well hydrated. Sodium alginate has been widely used as rate controlling agent by direct compression method (Timmins et al. 1992, Hodsdon et al. 1995, Efenkatis and Buckton 2002, Moroni and Drefko 2002, Holte et al. 2003, Liew et al. 2003). In context of above principles need of dosage form was recognized, which will be able to release drug immediately after 6 h of desired lag time by using sodium alginate polymers.

Materials and Methods

Verapamil hydrochloride and cross linked PVP (cross povidone) was received as gift sample from Alembic Ltd. Vadodra, Guzrat, India. Empty capsule shells were received as gift sample from Erawat Pharma, Pithampur, Madhya Pradesh, India, Sodium alginate and formaldehyde were purchased from Loba chemie, Pvt. Ltd, Mumbai, India. Magnesium stearate, Citric acid, sodium bi carbonate, lactose and other chemicals purchased from S. D. Fine Chemicals, Mumbai, India. All the materials used were of analytical grade and used as procured.

Preparation of impermeable capsules body

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 hot air oven (Sropathy et al. 1999). Treated capsule body and the untreated soluble cap were stored in desiccators for further use. Prior to use, treated capsule body was studied for disintegration test and treated capsule body didn't show any sign of disintegration and used for the further study.

Preparation of single layered tablets

Accurately weighed amount of the powders, containing immediate release tablet and rate modulating tablet, were sifted through 80 mesh size, and then tablets were compressed in 7 mm single punch machine by hand filling.

Studies of lag time modulating tablet

Natural gums have been widely used to control the release of drug from the dosage form. Sodium alginate was chosen as candidates for the study, which is commonly used for controlled or sustained release. Sodium alginate at 100, 150, 200 mg weights were compressed (n=30). To get the mechanically stable tablets, 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).

Surface coating of the rate modulating tablet

Coating of the sodium alginate tablet was done by using eudragit S100. Composition of coating solution is shown below in Table 1. Sodium alginate tablets were exposed at the surface which was to be coated. All other sides of the tablet were covered by the aluminum foil. Exposed surface was coated manually by dip coating followed by evaporation of the solvent.

Table 1. Composition of the coating material

Ingredients	%
Eudragit S 100	12.5
TEC	20
Acetone q.s	100

Study of the amount of coating material on the lag time of drug

Maximum lag time of uncoated sodium alginate tablet was found to be 2.5 h at 200 mg weight hence, selected for further studies to obtain the desired lag time. Sodium alginate tablets (n=25) were surface coated by dipping in coating solution. Solvent was evaporated in open air and tablets were further coated to get the tablets of different coatings (coded as F₁-F₇), and stored in desiccator for further use. Mean Thickness (Table 2) of coating was determined by subtracting mean thickness of uncoated tablet from the mean thickness of coated tablets.

Table 2. Mean thickness of the surface coating

Formulation Code	Increase in weight (%)	Mean Thickness (mm)
F1	8	0.089± 0.012
F2	10	0.105± 0.056
F3	13	0.164± 0.094
F4	16	0.201±0.102
F5	18	0.254±0.145
F6	23	0.296±0.176

Studies of the amount of bulking agents on the lag time of drug

To ensure the proper position and to study amount of bulking agents on the lag time, lactose at different amount (150, 160, 170, 180, 190 and 200 mg) was placed at bottom of the tablets in the capsule. To hasten the release of drug from capsule body different amount (5, 10, and 15 mg) of effervescent mixture (sodium bicarbonate: citric acid, 1:1) was separately filled above lactose (n=3).

Fabrication of capsule device for two pulse drug release

Immediate release tablet, surface coated rate modulating tablet and immediate release tablet, followed by effervescent layer and lactose as bulking agents were snugly fitted in the impermeable capsule body and then soluble cap was placed on the body.

In vitro drug release studies of the capsules

A total of 900 ml of the dissolution medium (pH 1.2) was filled in the USPXXIII dissolution apparatus. The capsule (n=3) was placed in basket and the speed was adjusted at 100 rpm. The temperature of the dissolution medium was maintained at 37±0.5 °C. After 2 h agitation was stopped, basket was washed with distilled water and dissolution medium was replaced by, previously maintained at simulated body temperature, phosphate buffer (pH 7.4). 10 ml of aliquots were withdrawn after 15 min time intervals and same amount was replaced by the fresh dissolution medium.

Results and Discussion

Effect of the weight of polymer on the lag time has been studied by Mukesh and Sumitra (Gohel and Manhapra 2002). Results in Figure 1 showed that maximum lag time of 2.50 h was obtained at 200 mg weight which was reduced to 2 h at 150 mg and 1.25 h at 100 mg weight. It was found that without coating sodium alginate was not able to provide the desired lag time of 6 h. Particulate and porous nature, of the hydrated layer of gel formed after hydration of sodium alginate at simulate gastric fluid, was attributed for less lag time.

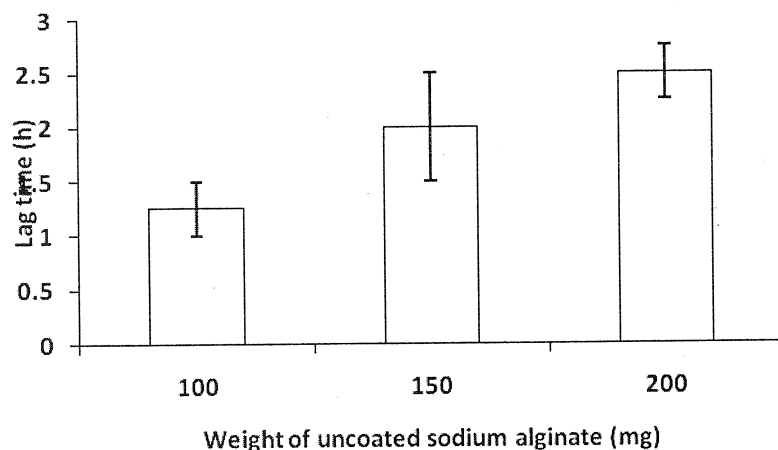


Figure 1. Lag time of uncoated sodium alginate rate modulating tablet n=3 (Mean \pm S.D.)

When sodium alginate tablets were surface coated with eudragit S100 then lag time was found to be increased (Figure 2). Increment of lag time was proportional to the coating thickness. Lag time of formulations were found to be increased, but not to the desired period of 6 h, as the coating was dissolved in pH 7.4. When thickness of the coating was increased lag time was found to be increased. F₆ formulation showed the lag time of 6 h, only 8.5% drug was released which satisfies the lag time criteria. Complete release of the drug was found after 8 h. Linearity between thickness of coat and lag time was observed ($y=15.594x+1.6178$, $R^2 = 0.9553$).

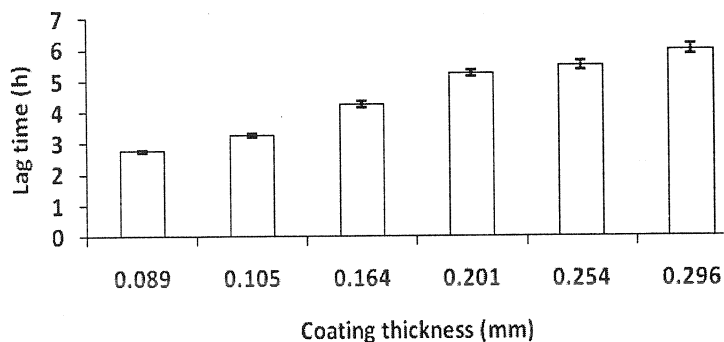


Figure 2. Lag time of coated sodium alginate rate modulating tablet n=3 (Mean \pm S.D.)

To hasten the release of drug after desired lag time effervescent mixture was added at different amount of 15, 20, 25 and 30 mg. The pressure generated in the system by CO₂, after dissolution of effervescent mixture, causes push of the gel matrix of sodium alginate. 25 mg of the effervescent mixture was found to be able the release drug after desired lag time. When effect of the weight of the effervescent mixture on the lag time was studied then no effect was observed on the lag time of drug. Lactose was added separately as bulking agent to ensure the proper position of tablet in capsule device. Lactose when added in 160, 170, 180, 190 and 200

mg then 180 mg lactose was found to be suitable as bulking and contrary to the previous studies, no significant effect ($p>0.05$) was observed on the lag time of drug.

Two pulse release was successfully obtained by placing immediate release tablet, surface coated rate controlling tablet and immediate release tablet followed by effervescent mixture and lactose. Lag time of 6 h was obtained, only 8.5% drug was released during this period which satisfied lag time criteria, followed by immediate release of drug. Complete release of drug was obtained in 6.5 h.

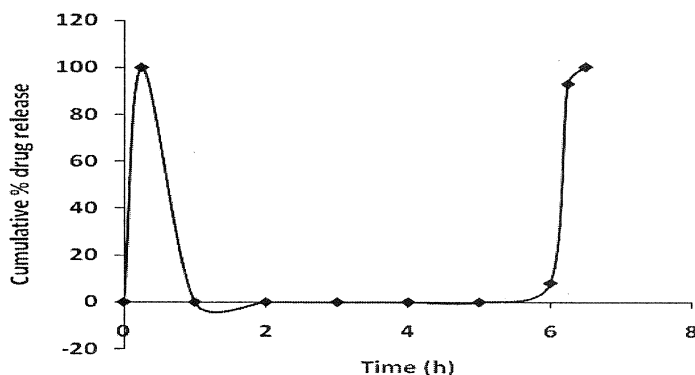


Figure 3. Two pulse release of drug containing eudragit S-100 surface coated sodium alginate rate modulating tablet, effervescent mixture and lactose.

Conclusion

Two pulse release was successfully obtained by using above system. Coated sodium alginate delivered the drug after desired lag time. By controlling the thickness of the coat above system can be used as once daily at 10 p.m., which will deliver drug at 4 a.m. This system is beneficial for the conditions where early morning dose is essential.

Acknowledgements

Authors acknowledge, Dr. Neelesh Chachda and Mr. Ashutosh Jamloki for providing the gift samples of gelatin capsule shell and verapamil hydrochloride.

Declaration of Interest

The authors report no declarations of interest.

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Received: 04.05.2011
Accepted: 04.11.2011