



In vitro evaluation of once a day chronotherapeutic drug delivery system of *Gymnema sylvestre*



Nimisha Jain^{a,*}, V. Kusum Devi^b

^a Al-Ameen College of Pharmacy, Hosur Road, Bangalore, India

^b Vice Principal and HOD of Pharmaceutics, Al-Ameen College of Pharmacy, Hosur Road, Bangalore, India

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ABSTRACT

Gymnema sylvestre is a potent antidiabetic plant used in indigenous system of medicine. It targets several of the etiological factors connected with diabetes and obesity and thus can offer holistic treatment. However the dosage form in which it is administered is traditional and conventional resulting in reduced efficacy of the drug. The method by which a drug is delivered can have a significant effect on its efficacy, if the modern drug delivery technology is applied to *G. sylvestre*, it has a potential to synergize benefits of both the drug and the delivery system. Diabetes is one of the diseases where the constant drug levels are not preferred but needs a pulse of therapeutic concentration when the blood sugar levels are high. Chronotherapeutic drug delivery systems has a specificity in delivering therapeutic amount of drug in a burst at circadian timings correlated with specific pathological need to achieve maximum drug effect. The objective of the current study is to apply chronotherapeutic drug delivery based on time controlled approach to *G. sylvestre*. The drug delivery system is designed to achieve three pulsatile drug deliveries from a single formulation at the time when the blood sugar levels are high. The various components of the system were formulated, evaluated and optimized for the desired drug release. Also, as one of the main mechanisms of action of *Gymnema* is inhibition of glucose absorption which is exerted in the small intestine and as oral use of *Gymnema* may cause irritation of the gastric mucous membrane and reflux, the chronotherapeutic formulations were modified so as to make the drug available at the site of action and probably the site of absorption, as well as to prevent the side effects in the stomach. The developed system was able to achieve the objective of integrating modern method of drug delivery with herbal drug for once a day therapy of *G. sylvestre* with enhanced therapeutic efficacy. But further clinical studies should be warranted to test the efficacy of this system.

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1. Introduction

The potential of Ayurveda and herbal medicines is being realized in the recent years. These medicines have a lot of advantages over chemical pharmaceuticals. However, the drug delivery system used for administering the herbal medicine to the patient is traditional and out-of-date, resulting in reduced efficacy of these drugs.

Diabetes mellitus is a disorder of carbohydrate, fat, and protein metabolism, characterized by chronic hyperglycemia. Diabetes and obesity are cause and complication of each other, a single phytoconstituent that could be used in the treatment of both the diseases/conditions simultaneously would be a tremendous advantage. Gymnemic acid from *Gymnema sylvestre* fulfills this criterion.

It targets several of the etiological factors connected with diabetes and obesity and no single oral hypoglycemic drug presently available exerts such a diverse range of effects. It has long history as a treatment for diabetes and it not only prevents or delays the development of type 2 diabetes, but more important, reverses the effects of the disease. *G. sylvestre* can offer holistic treatment of both the diseases diabetes and obesity which are cause and complication of each other (Baskaran et al., 1990; Leach, 2007; Shanmugasundaram et al., 1990; Sugihara et al., 2000).

If the novel drug delivery technology is applied in herbal medicine, it may help in increasing the efficacy and reducing the side effects of various herbal compounds and herbs. Novel drug delivery systems for diabetes have lot of advantages over conventional drug delivery systems. Patient compliance and patient's acceptance to treatment can be improved by reducing the doses required per day and also by reduction of adverse effects. As *Gymnema* has lot of potential to be used as antidiabetic and antiobesity

* Corresponding author.

E-mail address: nimijain@gmail.com (N. Jain).

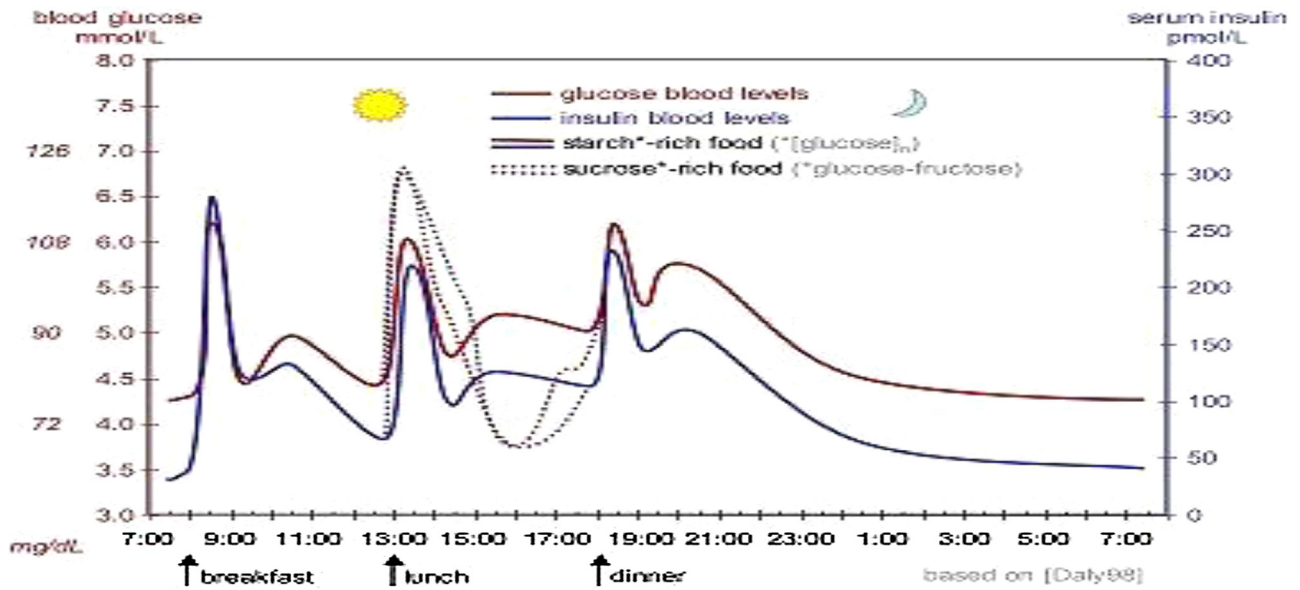


Fig. 1. Circadian variations of glucose and insulin in a healthy human being.

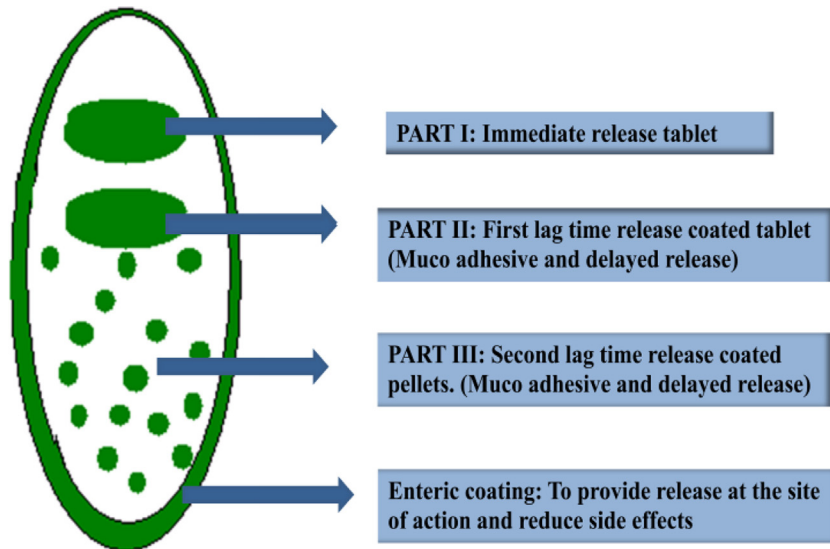


Fig. 2. Design of chronotherapeutic drug delivery system for *Gymnema sylvestre*.

agent, novel drug delivery systems are designed to get its maximum benefits with minimum side effects (Devi et al., 2010).

As *Gymnema* should also be taken 2–3 times a day, a controlled drug delivery system (one which delivers the drug continuously and at a constant rate) which provides for once a day administration would be suitable. But as diabetes treatment is chronic in nature, the drug will have more intense side effects if it is continuously present in the system. Also the possibility of tolerance and toxicity increases if the drug levels are held constant. Moreover living organisms require different amounts of drug at predictably different time within circadian cycle which will maximize desired and minimize undesired drug effects. Chronotherapeutic systems are designed over the concept of chronopharmaceutics in which there is specificity in delivering higher amount of drug in a burst at circadian timings correlated with specific pathological disorder to achieve maximum drug effect. In these systems there is a transient release of certain amount of drug within a short period of time immediately after a predetermined off-release period. Diabetes is one of the disease where the constant drug levels are not

preferred but needs a pulse of therapeutic concentration when the blood sugar levels are high i.e., after the meals which can be seen from the figure. Circadian variations of glucose and insulin in diabetes have been extensively studied and the clinical importance of insulin substitution in diabetes has been well exploited and evident from Fig. 1 (Daly et al., 1998; Malherbe et al., 1969).

As one of the main mechanisms of action of *Gymnema* is inhibition of glucose absorption which is exerted in the small intestine and as oral use of *Gymnema* may cause irritation of the gastric mucous membranes and reflux (Leach, 2007), it is decided to enteric coat the proposed formulations so as to make the drug available at the site of action and probably the site of absorption, as well as to prevent the side effects in the stomach. A once a day enteric coated chronotherapeutic drug delivery system is designed for the treatment of diabetes by *G. sylvestre*. The proposed therapy combines the benefits of both herbal drugs and novel drug delivery technology to provide a more patient friendly, holistic treatment for diabetes and obesity with *G. sylvestre*. The ultimate aim of this research work is to design and develop novel drug delivery systems of *G. sylvestre*

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