

## ABSTRACT

Synchronizing the drug release to the rhythm of the disease activity is the basic principle of chronotherapy. One way to improve pharmacotherapy efficiency is to administer medications when they are very well tolerated. Blood pressure has a well-documented 24-hour rhythm with a morning surge, which could explain the morning increase in unfavorable cardiovascular events. Morning doses of antihypertensive medication have traditionally been used to reduce daytime blood pressure rises. However, the absence of nocturnal dropping blood pressure has also been linked to an increased risk of cardiovascular disease. Effectively lowered nocturnal blood pressure can counteract the morning spike in BP. Chronotherapy in hypertension reduces the risks of early morning sudden increase in blood pressure, drug associated side effects and increases drug efficacy and patient compliance. The current research aims to design, develop and evaluate the acceptability of chronotherapeutic delivery of a core in cup metoprolol tablet and a mucoadhesive core in cup atenolol tablet.

The objectives of the research work are

To design a core in cup delivery system of metoprolol and a mucoadhesive core in cup formulation of atenolol, Preparation and evaluation of the designed formulation to identify the feasibility of the designed formulation to achieve chronotherapeutic delivery of the drug, Preformulation studies: characterization of drugs by analyzing solubility and melting point. Identification and compatibility studies using DSC and FTIR, Formula development and optimization using statistical methods, Formulation development of metoprolol core in cup tablet and atenolol mucoadhesive core in cup tablet

Evaluation of the developed formulation: hardness, friability, weight variation, disintegration time, in vitro and in vivo drug release. A time-adjustable pulsatile release system containing atenolol as an active pharmaceutical agent was developed for bedtime dosage administration and release of the medicine in the early morning to manage elevated blood pressure. The system contained an immediate release (IR) core, a sustained-release (SR) plug, and a mucoadhesive cup layer and it was designed by the cup and core technique. The immediate-release layer was composed of atenolol, croscarmellose sodium, microcrystalline cellulose (MCC), sorbitol, talc, and magnesium stearate. The SR plug was composed of hydroxyl propyl methylcellulose (HPMC), polyvinyl pyrrolidone (PVP), MCC, Lactose, talc, and magnesium stearate. The mucoadhesive cup contains polycaprolactone and mucoadhesive polymer chitosan. Bilayer tablets were punched by applying different compressive forces. Based on the Release data of the drug from each layer F5 and S5 were selected for the preparation of the bilayer tablet. Cup composition containing 3% of chitosan provided the highest mucoadhesion time up to 10h. Pulsatile delivery of the drug from

the formulation was observed at 300 min after the administration of the drug. The constructed pulsatile delivery systems were compared to that of commercially available atenolol IR tablet. The comparison demonstrated that the formulation is suitable for the intended chronopharmaceutical delivery of antihypertensive drugs.

