Formulation, Development and Evaluation of Dual Retard Floating Tablets of Amlopidine Besylate and Atenolol

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Abstract: Gastroretentive drug delivery systems have shown to be of better significance in controlling release rate for drug having site specific absorption. The purpose study was to develop an optimized dual retard floating tablet of amlopidine besylate and atenolol using optimization technique. Dual retard floating tablet comprised of two layers, i.e. immediate release layer of amlopidine besylate and sustained release layer of atenolol. Immediate release layer comprised of different superdisintegrant like sodium starch glycolate, cross carmellose sodium and kyorin T-314. Formulation containing 4% Kyron T-314 as a superdisintegrating agent was selected as optimized formulation which release 99.86% of amlopidine besylate within 30 min. Sustained release layer comprised of different polymers like HPMC K4M, HPMC K15M and HPMC K100M. Formulation containing 30% HPMC K100M was selected as optimized which release 90% of drug within 12 hours. Gas generating approach was used for floating purpose. A 3² factorial design was employed in formulating the GRDDS with conc. of HPMC K100M (X₁) and sodium bicarbonate (X₂) as independent variables while xanthan gum was added to maintain matrix integrity. FLT, Q15, T50, T75 and Q350 were selected as dependent variables. The granules were characterized by FTIR and DSC studies. There was no incompatibility observed between them. There was no significant change observed after following ICH stability guideline.

INTRODUCTION

The goal is to provide the drug concentration to reach very quickly above the minimum effective concentration and maintain for desired time period for longer time in the blood stream. Oral route is the best appealing route amongst all dosage forms. It is more acceptable because of several advantages like ease of manufacturing, accurate dosing, ease of handling and more stable than other dosage forms. In recent times, scientists focus on developing such a tablet dosage form that generated quick disintegration and as well as remained for longer time to produce therapeutic effect of desired time period. [1]

Dual retard Bilayer tablets are prepared for the challenging purpose that comprise of two layer of drug and release mechanism of drug from the dosage form is differ. It comprises of immediate release layer and sustained release layer. There is string consideration of combination therapy for the disease like hypertension, diabetes and asthma. Combination therapy has more advantages over monotherapy like less dose dumping, less toxicity, wider mode of action, synergetic effect etc. [2,3]

Hypertension and angina pectoris are most common disease which requires constant monitoring. Hypertension means high blood pressure in arteries. Many cardio vascular diseases are produces due to high blood pressure. Amlopidine besylate is calcium channel blocker and reduces hypertension by relaxing the smooth muscle in the arterial wall, decreasing total peripheral resistance and hence reducing blood pressure. [4,5] Atenolol is a selective β1 receptor antagonist, a drug belonging to the group of beta blockers. The formulation is developed as floating because of low absorption of atenolol is found in lower gastro intestinal tract. The ultimate aim is to develop the stable, safe and effective dosage form to control hypertension that produce quick action as well as longer time duration action. [6,7]

MATERIAL AND METHODS

Amlodipine besylate and atenolol were gift sample from Zydis Cadila Healthcare Ltd, Ahmedabad. Sodium Starch Glycolate, Cross Carmellose Sodium and All HPMC grade polymers were procured from Chemdyes Corporation, Ahmedabad. Kyron T-314 was obtained from Corel Laboratories, Ahmedabad. All other chemicals and reagents used were of analytical grade.

Preparation of Amlodipine Besylate as an Immediate Release Layer

Various formulations were prepared using different super disintegrating agents in different concentration by direct compression method using Micro Crystalline Cellulose (MCCP) and mannitol as filler. (Table 1)

After sifting (20#) of accurately weighed Amlodipine besylate, MCCP and mannitol, they all were mixed for 15 minutes. To this Mixer, super disintegrating agents, Talcum and Mg Stearate were added and mixed for 5 minutes. The prepared blend was passed through 20# sieve. The prepared blend was compressed using 6mm concave punch in Rotary tablet press machine. [8]

Preparation of Atenolol as Sustained Release Layer

Atenolol was prepared as sustained release by using hydrophilic polymer hydrophobic polymers as well as natural polymers. Wet granulation method was employed by using organic solution Iso Propyle Alcohol (IPA) as a vehicle and Poly Vinyl Pyrolidine K-30 (PVP K- 30) as a binder. Hydrophilic polymer Hydroxy Propyle Methyle Cellulose (HPMC) of different viscosity grades was selected as hydrophilic polymer, Eudragit RSP0 and Carbopol were selected as hydrophobic polymers and Xanthan gum and Guar gum were selected as natural polymers to retard the release rate. Accurately weighed Atenolol, polymers and lactose were passed through 20 # sieve. Shurry of PVPK - 30 IP (5 % w/w) was prepared in IPA by gentle stirring. All the
Dual Retard Tablet Technology: A Novel Drug Delivery System

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Abstract: With advancement in technology and increase in awareness towards modification in standard tablet to achieve better acceptability as well as bioavailability, newer and more efficient tablet dosage forms are being developed. The main reasons behind formulation of different types of tablets are to create a delivery system that is relatively simple and inexpensive to manufacture, provide the dosage form that is convenient from patient's perspective and utilize an approach that is unlikely to add complexity during regulatory approval process. Dual retard is with combo features that provide dual release mechanism in single dosage form i.e. immediate release and sustained/fixed release. Pharmaceutical companies are also interested to develop because of patient convenience and compliance. Dual retard system can be developed for single therapy or two therapies may be of single component or dual components. Modified tablet presses are used to formulate dual retard tablets. This article describes the technology of dual retard, objective of dual retard and challenges of the same. Despite of the challenges like layer separation, insufficient hardness, poor weight control, lower yield, cross contamination etc., dual retard drug release tablet is very promising novel drug delivery technology.

INTRODUCTION
Dual retard technology of tablet has some distinct advantages as having two different release mechanism of API within the single dosage form. Dual retard technology in tablet dosage forms is produces by preparing bi-layered tablet. Two layers of two different API give different drug release pattern to overcome so many conflicts of single retard system. Bilayer tablets are commonly prepared to avoid physical incompatibilities of components by physical separation. Bilayer tablet comprises of one drug or two different drugs which may or may not of same pharmacological action. Dual retard system is novel controlled drug delivery technology in which drug release is predetermined by combining sustained drug release with immediate drug release. One layer acts as initial dose and the other acts as maintenance dose.

Objective of Development of Dual Retard Technology
1. To administer two API in single convenient tablet dosage form.
2. To control the drug release rate of each layer.
3. To provide immediate action as well as sustained action.

Advantages of Dual Retard Technology
1. Very fast symptomatic relief as well as for longer time.
2. Dose frequency is reduced which enhances patient compliance.
3. Dose dependent side effects can be minimized in compare with monotherapy.
4. Widen the therapeutic range of formulation as two drugs having different mode of action.
5. Low dose of two different drugs reduces the clinical and metabolic effects that may be of large dose of single agent.
6. In case of drugs having a low half-life, each of the two layers of the tablet respectively content a loading dose and maintenance dose of the same and thus increase the bioavailability of the drug.

Disadvantages
1. Less compression capacity due to amorphous nature or low density property.
2. Bitter drugs require encapsulation.
3. Dual dose sometimes difficulty in swallowing to pediatric patient.
4. Difference in physical properties of two API, leads to difficulty in compression as a whole.
5. Lack of bonding and adhesion at interface resulting in layer separation.

DUREDAS TECHNOLOGY
DUREDAS - Dual Release Drug Absorption System (Elan Corporation) utilizes bi-layer tabletting which have been providing different release rates from single dosage form. Dosage form tablet is prepared by separate compression step. It is the combination of immediate drug release layer and controlled matrix drug release layer. The immediate release layer quickly release the drug from the dosage form when it comes in contact with GI fluid in stomach by diffusion and dissolution mechanism while the control release matrix remains intact and slowly absorbs the fluid from GI tract and expands the dosage form. As the gel continues to expand, fluid penetrates further in dosage form, dissolving the drug and resulting in diffuse out the drug in controlled manner. Further extended DUREDAS technology is to produce controlled release dosage form of two different drugs in two different layers and drugs release in controlled manner to enhance the therapeutic effect. The DUREDAS technology initially used to produce over the counter controlled release analgesics.

DUAL RETARD TABLETS - QUALITY AND GMP REQUIREMENTS
It is very essential that the prepared dosage form meets the Good Manufacturing Practice parameters. Quality can only be managed by GMP way and validated process.
1. The press must be capable to prevent capping and separation of two layer.
2. The press must be capable of producing sufficient hardness.
3. The press must be able to prevent the cress contamination between two layers.
Certificate

This Certificate is awarded to

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