Research and Reviews: Journal of Pharmacy and Pharmaceutical Sciences

Formulation Development and Evaluation of Bi-Layer Sustained Release Tablets of Amlodipine and Metaprolol

Sindhu P1, Madhu Babu Sakshi2*, M.Trinadha Rao2

1Department of Pharmacy, Vaageswari institute of pharmaceutical sciences, Thimapur, Karimnagar, Telangana, India
2Department of Pharmaceutics, Vignan Institute of Pharmaceutical Technology, Beside VSEZ, Duvvada, Visakhapatnam-530 046, AP, India

Review Article

Received: 19/04/2014
Accepted: 21/05/2014
Published: 27/05/2014

*For Correspondence

Corresponding author’s affiliation:

Madhu Babu Sakshi, M. Pharmacy, Department of Pharmaceutics, Vignan institute of Pharmaceutical sciences, Visakhapatnam, Andhra Pradesh, India, Tel: 9491375747; E-mail: sakshi.madhu@gmail.com
Sindhu P, B-pharmacy, Vaageswari institute of pharmaceutical sciences, Thimapur, karimnagar, Telgana, India, Tel: 8121474344; E-mail: sindhureddy.pingili@gmail.com

Keywords: Bilayer tablets; Amlodipine besylate; Metoprolol succinate; Sustained release; Immediate release; Antihypertension; Combination therapy

ABSTRACT

Background and Objective: The objective of the present research, an attempt has been made to formulate bilayered tablets of Amlodipine besylate and Metoprolol succinate. The main objective for combination therapy is to encourage the use of lower doses of drug to reduce the patient’s blood pressure, to minimize dose dependent side effects and adverse reactions. When smaller doses of medication with different mechanism of action are combined, synergistic or additive effects on blood pressure are achieved.

Methods: Nine different formulations of bilayered tablets were prepared with Amlodipine besylate as immediate release layer and Metoprolol succinate as Sustained release layer. Tablets were prepared by direct compression technique. Immediate release layer was prepared by using Super desintegrant CCS. Sustained release layer was prepared by different ratios of polymers like HPMC K100M, Acacia and Combination of both. The prepared tablets were evaluated for pre and post compression parameters, drug content, in vitro dissolution studies and stability studies.

Results: All the evaluated parameters of the optimized formulation showed the metaprolol succinate drug release over a period of 16 to 20 hours and the amlodipine besilate (IR) release max drug in 60 minutes showed compliance with pharmacopoeial standards.

Interpretation and conclusion: The optimized formulation of bilayer tablets showed good release profile and are within pharmacopoeial limits. The extended release Metoprolol layer of optimized formulation follows first order and shows non-Fickian diffusion mechanism of release this formulation was subjected to stability studies. The stability studies were carried out for the optimized batch for three months and it showed acceptable results.

Introduction

In the recent days, multilayer tablets occupying the importance in the designing of oral control drug delivery systems. Bi-layer tablets are prepared with one layer of drug for immediate release while second layer designed to release drug later, either as second dose or in an sustained release manner. Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances, and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. The combination therapy is to encourage the use of minimize the dose dependent side effect and adverse reactions, decreasing dosing frequency [1-6].
Metaprolol succinate is a widely used β1 selective adreno receptor antagonist, is rapidly and completely absorbed from the gastrointestinal tract when administration in conventional dosage forms. The systemic availability after oral administration in, however, is only about 50% due to hepatic oxidative metabolism which is subjected to genetic polymorphism. Since metaprolol has a relatively short elimination half-life of 3-4 hours having bioavailability (12%), a simple once daily dosage regimen of a conventional tablet is not sufficient to sustain plasma levels and clinically effective β1 blockade over the entire day. For the patient compliance the metaprolol succinate as sustained release is necessary [7-13].

Amlodipine is a prototype second generation dihydropyridine calcium channel blocker that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. It has a longer duration of action (ie) half-life of 40 hours having bioavailability (64-90%), and the initial effects are cumulative over many days and more over for patient compliance in case of anti-angina patients, a rapid onset of action is necessary for immediate pain relief. Hence Amlodipine can be given as a single immediate release dose [14-21].

Formulation of Bi-Layer Sustained Release Tablets

Amlodipine besylate, Metaprolol succinate Mylan Laboratories, Hyderabad. Crosscarmellose sodium, Sunset yellow, Pvp k 30, Acacia gum, Dicalcium phosphate, Hpmck100m, Yarrow Chem. Products, Mumbai, Magnesium stearate, Talc, Molychem, Mumbai.

Preparation of Amlodipine besylate immediate release layer: Amlodipine is a hygroscopic material. Being an unstable compound, Amlodipine requires well directed stability approaches to formulate Amlodipine layer with reasonable stability. Hence Amlodipine layer (immediate release layer) was prepared by direct compression method.

Shifting: Amlodipine Besylate, Dicalcium phosphate and sodium starch glycolate were shifted through # 40 mesh. Magnesium Stearate was sifted through # 60 mesh sieves. Sunset yellow lake was sifted through # 100 mesh sieve [21-27].

Blending: Mix geometrically Amlodipine with Dicalcium phosphate, ccs and Sunset yellow lake. Mix for 15 minutes in double lined polybag.

Lubrication: The above blend was lubricated with Magnesium Stearate for 2 minutes. Preparation of Metoprolol succinate sustained release layer: Metoprolol layer (sustained release layer) was prepared by direct compression method.

Sifting: Sift Metoprolol Succinate through # 30 mesh sieve, Dicalcium phosphate HPMC K100m, pvp k30 through # 40 mesh

Blending: Blended Metoprolol Succinate and Dicalcium phosphate, acacia, and HPMC K100M, in a double cone blender for 20 minutes [27-28].

Tablet compression: The bilayer tablet compression was made using mm punch in a 6 station rotary tablet machine with single feed. In this, sustained release metoprolol succinate granules were introduced first in to the die cavity and a slight precompression was made so that the layer was uniformly distributed. After that immediate release amlodipine besilate granules were added through the feed and a final compression was made [29-33].

Characterization and evaluation of bilayered tablets

Pre compression parameters

Evaluation of powder blend for the bulk density, tapped density, Carr’s index, Hausner’s ratio and angle of repose. The results were optimized.

Post compression parameters: Tablets were tested for hardness, friability and weight variation. Thickness, of the tablets was determined by using digital vernier callipers.

Hardness of the tablets was tested using Monsanto hardness tester and friability of the tablets was determined in a Roche friabilator [34-40].
In vitro dissolution study: For Amlodipine besylate (IR): Dissolution parameters: Dissolution studies for amlodipine besylate were performed by using Medium: 0.1 N HCL Volume : 900 ml using dissolution apparatus type II of USP (paddle) (LABINDIA DS 8000) With Rotating speed : 50 rpm and Temperature : 370°C ± 0.50 C. samples of dissolution fluids were withdraw through a filter (0.45 µm ) at Time intervals 10, 20, 30, 45, and 60 Min. And the dissolution sample fluids were analysed by spectrophotometrically at 237 nm using UV Visible Spectrophotometer (ELICO SL 159). For amlodipine besylate drug content [41-50].

For metaprolol succinate (SR): Dissolution studies were performed by using 6.8ph buffer 900ml volume using dissolution apparatus type II of USP (paddle) (LABINDIA DS 8000) With Rotating speed : 50 rpm and Temperature : 370°C ± 0.50 C. samples of dissolution fluids were withdraw through a filter (0.45 µm ) at Time intervals 1,2,4,8,12,16,20 hours. And the dissolution sample fluids were analysed by spectrophotometrically at 222nm using UV Visible Spectrophotometer (ELICO SL 159). For metaprolol succinate drug content [51-57].

Results and Discussion

Bilayerd tablets of Metoprolol Succinate, and amlodipine besylate were Metaprolol succinate (SR) prepared by using different polymer like HPMC□K100M, Acacia, both combination of HPMC-K100M+acacia in the ratio 1:1. For Amlodipine (IR) CCS used as asuper diesintegrant. The tablets were fabricated using direct compression technique. The pre blended powders of the sustained release layer and the immediate release were characterized and the parameters were showed in the table . Content uniformity of all the prepared batches is within the limit (amlodipine besilate, and metaprolol succinate 100 ± 3% of the labelled content) [58-68]. The pre compression parameters and other post compressed parameters of tablets friability, hardness, weight variation and thickness are optimized [69-78]. We can conclude that all the batches of tablets prepared were of good quality with regard to hardness, friability and drug content [79-83].

In vitro dissolution study for amlodipine besilate (IR)
The in vitro drug release profiles of Amlodipine besilate were obtained. The in vitro release study showed satisfactory release of amlodipine besilate from the immediate release layer showed 100.02% release in 60 min.

In vitro dissolution study for metaprolol succinate (SR)
The in vitro drug release profiles of Metaprolol succinate were obtained. The in vitro release study showed satisfactory release of metaprolol succinate from the sustained release layer F7,F8,F9 containing HPMCK100M showed 93.47, 88.12, 85.15% drug release respectively in 20 hours [84-92].

Conclusion

Bilayer tablets of Amlodipine besylate and Metoprolol succinate were prepared by direct compression technique and were found to be good without chipping, capping and sticking. Infrared spectroscopic studies indicated that the drug is compatible with the polymers. The drug content was uniform in all the formulations of prepared tablets. Drug release (Metoprolol succinate) was found to approximately follows first order, non-Fickian diffusion. From the reproducible results obtained from the executed experiments it can be concluded that Increase in amount of CCS, in Amlodipine layer increases the release of Amlodipine. ccs 20% is sufficient for complete release of Amlodipine in 45min [93-100]. Increase in the amounts of HPMC K100M and pvpk30 in Metoprolol layer decreases the release of Metoprolol. HPMC K100m (%) and PVPK30 (%) are suitable for sustain release of Metoprolol over a period of 20 hours. On the basis of in-vitro release studies and its kinetic data was selected as optimized formulations for designing Bilayer tablets of Amlodipine besylate and Metoprolol succinate. SBased on mathematical models, it was concluded that formulation F7, F8, and F9 fitted into first order and show non-Fickian diffusion mechanism of Metoprolol release. Short-term stability studies indicated no appreciable changes in the drug content and in vitro drug release rates of formulation. Thus Bilayer drug delivery system can be considered as one of the promising formulation technique.
REFERENCES


75. Werner FM, Covenas R (2014) Might Combined GABAA Agonists and NMDA Antagonists have a Therapeutic and maybe a Prophylactic Effect in Alzheimer’s and Parkinson’s Disease?. J Cytol Histol 6: 298.