Design of polypill for treatment of type-II diabetes mellitus associated with dyslipidemia

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This study presents development of a bilayered tablet with sustained release (SR) of Metformin hydrochloride (MH) and immediate release of Atorvastatin calcium (AC), used as anti-hyperglycemic agent in patients with type 2 diabetes, by lowering both basal and postprandial plasma glucose and competitive inhibitor of HMG-CoA reductase. In SR layer, sodium carboxy methyl cellulose (Sodium CMC) and Hydroxy Propyl Methylcellulose K4M (HPMC K4M) were used as retarding material but Hydroxy Propyl Methylcellulose 15 Cps (HPMC 15 Cps) was used as channeling agent. Tablets were prepared by wet granulation method. FT-IR studies showed no interaction between drugs and polymers used in the study. Optimized formulation gave an initial burst effect and followed by SR for 8 h (92.53%), without any drug degradation during stability studies. Drug release from formulation was dose dependent and by diffusion mechanism.

Keywords: Atorvastatin calcium (AC), HPMC 15Cps, HPMC K4M, Metformin hydrochloride (MH), Sodium CMC

Introduction

Bilayered tablet requires fewer materials than compression-coated tablets, weigh less and may be thinner1. Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances, and also for sustained release (SR) tablet, in which one layer is immediate release (IR) as initial dose and second layer is maintenance dose2. Higher rate of mortality in patients with diabetes mellitus patients is mainly due to cardiovascular diseases3. Patients with type 2 diabetes have increased risk of atherosclerosis and it can be treated with statins4,5. Blood glucose level impairs endothelial function and promotes atherogenesis in diabetic patients, and combined administration of metformin and atorvastatin prevent Endothelium-dependent dilation in patients compared with metformin alone5,6. Mortality of diabetic patients after a cardiac event is significantly increased as compared to non-diabetics7. Drugs should be stable in gastro-intestinal tract as SR systems release their contents over entire length of gastro-intestinal tract. Metformin hydrochloride (MH; biological half-life, 2-4 h) is an orally administered biguanide, which is widely used in management of type-2 diabetes. It is a hydrophilic drug and is slowly and incompletely absorbed from gastrointestinal tract and absolute bioavailability of a single 500 mg dose is reported to be 50-60%1. SR formulation that maintains plasma levels of drug for 8-12 h might be sufficient for once daily dosing for MH. Atorvastatin calcium (AC) mimics activity of HMG-CoA reductase by blocking rate-limiting step of cholesterol biosynthesis. It reduces LDL cholesterol, apolipoprotein B and triglycerides and increases HDL in treatment of hyperlipidaemia. Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentration occurs within 1-2 h and half-life in humans is 14 h8.

This study presents development of a bilayered tablet with SR of MH and IR of AC, used as anti-hyperglycemic agent in patients with type 2 diabetes, by lowering both basal and postprandial plasma glucose and competitive inhibitor of HMG-CoA reductase.

Experimental Section

MH (mol wt, 165.62; plasma elimination half-life, 2-4 h; apparent volume of distribution, 654±358 l) was a gift sample from Apotex India Ltd. It is soluble in water and methanol and practically insoluble in acetone and methylene chloride. AC (mol wt, 1155.36; plasma elimination half-life, 14 h; mean volume of distribution,
381 l), a gift sample from Maithri Laboratories Pvt Ltd, India, is soluble in dimethyl sulfoxide. Sodium carboxymethyl cellulose (Sodium CMC) was obtained from Pioma Chemicals, India. Hydroxy propyl methylcellulose K4M (HPMC K4M) and hydroxy propyl methylcellulose 15 Cps (HPMC 15 Cps) were procured from Enar chemicals, India. Lactose was obtained from DMV international, Netherlands. Croscarmellose sodium was obtained from hetero drugs as gift sample. All other chemicals used were of analytical grade.

Drug-excipients Compatibility Studies
MH and AC were taken in glass vials individually and along with various excipients (1:1). All mixtures of drug and excipients were kept at various accelerated condition (30ºC/65% RH and 40ºC/75% RH) in stability chamber for one month. At 2 weeks time interval and at the end of 4th week, samples were withdrawn and checked out for any changes in physical character like color. Finally, combination of excipients with no colour change was selected for formulation.

Preparation of Sustained Release Layer of Metformin Hydrochloride (MH)
SR layer of Metformin, each containing MH (500 mg), were prepared by a conventional wet granulation technique (Table 1). All ingredients (MH, HPMC K4M, HPMC 15Cps, sodium CMC, dicalcium phosphate anhydrous) were passed through sieve no. 40. Povidone (K-30) was dissolved in purified water. Granules were prepared in rapid mixer granulator by adding binder solution to mixture of above ingredients and mixing at slow speed. MH granules were transferred to double cone blender. Colloidal silicon dioxide was sifted through 40 mesh sieve, and magnesium stearate and talc were sifted through 60 mesh sieve and added to double cone blender and mixed for 2 min.

Preparation of Immediate Release Layer of Atorvastatin Calcium (AC)
IR layer of AC were prepared by wet granulation process (Table 2). Weighed AC, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium and colloidal silicon dioxide were sifted through 40 mesh sieve and ponceu 4R supra was sifted through 100 mesh sieve. These ingredients were loaded into planetary mixture and mixed for 15 min at fast speed. Binder solution, prepared by dissolving polysorbate-80 in purified water, was added slowly to mixed contents in planetary mixer and mixed at slow speed for 5 min. Wet granules were loaded into fluidized bed dryer and dried at 50-60ºC. Produced granules were sized by sifting through 20 mesh sieve. In lubrication step, magnesium stearate, talc and sodium bicarbonate were sifted through 60 mesh sieves and croscarmellose sodium was sifted through 40 mesh sieve. Then, granules and lubricants were loaded into double cone blender and mixed for 3 min at slow speed. Prior to compression, granules were evaluated for characteristic parameters (bulk density, tapped density, compressibility index and hausner’s ratio). Carr’s compressibility index was calculated from bulk and tapped densities using a digital tap density apparatus (Electrolab Ltd. India).

Preparation of Bilayer Formulation
Final bilayer tablets (Fig. 1) were compressed as one layer only for MH (SR7) and second layer for AC (FR5) using 19.2 mm x 8.9 mm oblong shaped punch in
27 station tablet compression machine (Cadmach, India). MH granules were introduced first into die cavity and slightly pre compressed. After that, AC granules were added and a final compression was made.

**Film Coating of Bilayer Tablets of MH and AC Coating Solution Preparation**

Over head stirrer was operated containing sufficient quantity of isopropyl alcohol and methylene chloride to form a mixture. To this, Transparent Coat IC-U-6638 was added in vortex without formation of lumps and continuously stirred for 45 min for homogenization. Coating solution was filtered through 200 mesh nylon cloth and used for coating of bilayer core tablets.

**Film Coating of Tablets**

Compressed tablets were loaded into Neocota coating machine containing pan and tablets were film coated to get the build of 2.0% with following parameters: pan speed, 5 rpm; gun type, spray gun; inlet temp., 40-45°C; outlet temp., 30°C; and spray rate, 3 ml/min.

**Physical Tests for Bilayer Tablets**

Standard physical test for bilayer tablets were performed and average values were calculated. Weight variation was determined by weighing 20 tablets individually, average mass was calculated and variation% of each tablet was calculated. Hardness was determined by taking 6 tablets from each formulation using a Monsanto hardness tester (Tab machine Ltd., India) and average pressure (kg/cm²) applied for crushing tablet was determined. Friability was determined by weighing 20 tablets after dusting and placing them in a roche friabilator (Electro lab ET-2, India), which was rotated for 100 revolutions. After dusting, total remaining mass of tablets was recorded and friability% was calculated.

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### Table 2—Ingredients (mg/tablet) for Atorvastatin Calcium immediate release layer

<table>
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<tr>
<th>Ingredients</th>
<th>FR1</th>
<th>FR2</th>
<th>FR3</th>
<th>FR4</th>
<th>FR5</th>
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<tr>
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<td>Croscarmellose sodium</td>
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<tr>
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<tr>
<td>Croscarmellose sodium</td>
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Fig. 1—Bilayer tablets of Metformin HCl (MH) and Atorvastatin Calcium (AC): a) heap of tablets; and b) sides of tablets
Thickness (mm) was determined by digital vernier caliper (Mitutoyo corp., Japan).

**In vitro Dissolution Studies**

Release of MH was determined using a dissolution apparatus type I of USP (Basket) at 100 rpm. Dissolution was studied at 37 ± 0.5°C using 900 ml of phosphate buffer (pH 6.8). Samples (5 ml) were withdrawn at different intervals (1, 4 and 8 h) and filtered through 0.45 µm membrane filter. Filtrate was collected after discarding first few ml of filtrate. Sample solutions were analyzed by high performance liquid chromatography (HPLC) using UV detector under following chromatographic conditions: column, C8 (250 mm x 4.6 mm) 5µ SS column; wavelength, 254 nm; flow rate, 1.0 ml/min; mobile phase, filtered and degassed mixture of buffer and acetonitrile (400: 600) and adjusted pH 2.5 with Trifluoro acetic acid solution; and buffer, dissolved sodium dihydrogen phosphate (13.8 g) in 1000 ml water.

Release data obtained were treated according to zero-order (cumulative amount of drug release vs time), first-order (log cumulative% drug remaining vs time), Higuchi (cumulative% release vs “time” and Korsmeyer-Peppas (log cumulative% drug release vs log time) equation models.

**Stability Studies**

Promising formulation was tested for 3 months at 25°C and 40°C with 60% RH and 75% RH. At the interval of 15 days, tablets were withdrawn and evaluated for thickness, hardness, friability, weight variation, content uniformity, in vitro drug release and assay.
Results and Discussion
MH and AC were used as a model drugs for treatment of type-2 diabetes mellitus with associated dyslipidemia. Preformulation studies of MH and AC were evaluated for various physical properties individually (Table 3) and flow was found poor in the case of both drugs. In drug excipients compatibility studies, there was no incompatibility in drugs alone or with excipients. Bulk densities for granules of optimized formulation (Table 4) indicated good packing character. Compressibility index

Fig. 2—Drug release (%) profile of: a) Metformin Hydrochloride (MH) tablet matrices; and b) Atorvastatin Calcium (AC) tablet matrices

Fig. 3—First order kinetics, Higuchi model, Zero order kinetics and Peppas model of formulation F-7
were found to be good without chipping, capping and polysorbate-80 for IR layer by wet granulation method sustaining layer and croscarmellose sodium and swellable polymers HPMC and Sodium CMC as retarding agent. Granules of AC IR layer were prepared by using super disintegrants, croscarmellose sodium and polysorbate-80 as surfactant. Drug polymer ratios were found to influence the release of drug from SR layer of formulation. As the amount of polymer increases, drug release was found to decrease. In case of IR layer, as the concentration of surfactant was increased, drug release was also found to be increased. Drug release from optimized formulation SR7 was found to follow First order release kinetics. Thus release of drug from dosage form was found to be dose dependent. Formulation SR7 containing Sodium CMC (23.66% w/w), HPMC 15 Cps (1.18% w/w) and HPMC K4M (7.1% w/w) in following ratios releases the drug at desired rate. One month short term stability studies performed for optimized formulation at 25ºC and 40ºC with 60% RH and 75% RH indicated no appreciable changes in drug content% and in-vitro drug release studies.

References