DESIGN, DEVELOPMENT AND CHARACTERIZATION OF SUSTAINED RELEASE OF METFORMIN AND GLICLAZIDE BILAYERED TABLETS

Kotta Kranthi Kumar*1 M. Mahesh1, K. Sasikanth2

Department of Pharmaceutics, 1Narsaraopet Institute of Pharmaceutical Sciences of Pharmacy, Narsaraopet. 2Nova College of Pharmacy, JRD. Andhra Pradesh.

ABSTRACT

Hyperglycemia means an increased amount of glucose in blood. Metformin hydrochloride and gliclazide both are antihyperglycemic agents. The present investigation was aimed to the development of bilayered tablet of Metformin hydrochloride and gliclazide are sustained release by using HPMC as release retarded for polytherapy of diabetes. HPLC and preformulation studies shows that API’s is compatible with excipients. Tablets are prepared by wet granulation method., The best formula was selected by physical evaluation of tablets, dissolution profile of Metformin hydrochloride was 101%, where as Glucophage XR (Reference) was 101% after 24 hours and gliclazide was 99%, Diamicron MR (innovater) 100% after 24 hours and similarity factor (f2) correlation studies 70.9% for Metformin hydrochloride and 67.2% for gliclazide when compared with the innovater products. Bilayered tablets of Metformin hydrochloride with gliclazide was successfully formulated and evaluated.

Keywords: Metformin hydrochloride, Gliclazide, Magnesium stearate, Zinc stearate.

INTRODUCTION

Over the past 30 years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled release drug delivery systems. The attractiveness of these dosage forms is due to awareness to toxicity and ineffectiveness of drugs when administered or applied by conventional method in the form of tablets, capsules, injectables, ointments etc.

* Corresponding Author

Kotta Kranthi Kumar
Email: mddhanaraju@yahoo.com

Usually conventional dosage form produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. This factor such as repetitive dosing and unpredictable absorption led to the concept of controlled drug delivery systems. The goal in designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. The primary objective of sustained release drug delivery is to ensure safety and to improve efficacy of drugs as well as patient compliance. If the drug is given in conventional dosage form, it has to be administered several times a day to produce the desired therapeutic effect. Because of the frequent dosing fluctuation in plasma drug level occurs.
If the drug-dosing interval is not in accordance with biological half-life, large peaks and valleys are possible with time-drug concentration in blood curve. The pronounced fluctuations resulting from the conventional drug administration are likely to yield period of no therapeutic effect when drug concentration fall below minimum therapeutic level.

The main objective of present study is to develop polytherapy for the treatment of NIDDM. Though there are numerous drugs for treating type II diabetes, sulphonyl ureas and biguanides are used commonly by a wide section of patients. Gliclazide is a second generation of sulphonyl urea; Whereas Metformin Hydrochloride belongs to biguanide group. Hence the combination of Gliclazide/Metformin Hydrochloride would help in treatment of NIDDM and probably prevention of its associated macromolecular and microvascular complications (Gwen M et al., 1996; Thomas et al., 2001; Li VHK et al., 1987; Welling PG et al., 1987; Crank J, 1996; Hopfenberg HB, 1976).

MATERIALS AND METHODS
(Gwen M Jantzen and Joseph R Robinson, 1996)

Preparation of Mixed blend of Drug Excipients

Preparation of GLICLAZIDE Blend:
1. Gliclazide was weighed accurately and passed through #40mesh.
2. Methocel K15 M, MCC-102 was passed through #60 & #30 mesh.
3. HPMC 6cps was dispersed into purified water.
4. Intra granular materials were dry mixed in RMG for 10 minutes.
5. Granulation was carried out by using binder solution in RMG.
6. Granules were dried in rapid drier for 60 mins at 60°C to get LOD bellow 2% w/w.
7. Methocel K 15 M & MCC 102(extra granular materials) were passed through #60 & #30 mesh mixed with dried granules and blended for 25 mins
8. Magnesium Stearate and Iron oxide Yellow was passed through #80 mesh adds to blender for 5 mins.
9. Final blend was compressed by using Bilayer compression machine using 20mm X 9mm punches.

Preparation of METFORMIN HCl Blend:
1. Metformin HCl was weighed accurately and passed through #40 mesh.
2. Methocel K100 M, PVP K 90 D passed through #60 & #30 mesh.
3. HPMC 6cps was dispersed into purified water prepared as binder solution.
4. Step 1 and Step 2 were dry mixed in RMG for 10 minutes.
5. Granulation was carried out by using binder solution.
6. Granules were dried in rapid drier (Fluidized Bed Dryer) for 60 mins at 60°C to get LOD range1.5% w/w – 2.0% w/w.
7. Dried granules were milled by using multi-mill with 1.5 mesh slow speed and forward direction. Retains were milled through 1.0-mm SS sieve if necessary.
8. Retains were passed through #20mesh.
9. Methocel K 100 M & MCC 102 were passed through #60 & # 30 mesh used as extra granular materials.
10. Dried granules and extra granular materials were blended for 25 minutes.
11. Mg. Stearate was passed through #80mesh and adds to blender for 5min.
12. Final blend was compressed by Bilayer compression machine using 20X 9-mm punches.

Steps in preparation of Metformin HCl and Gliclazide blends:

Binder solution preparation:
PVP K90D dissolved in IPA: Water (9:1) by using stirrer. HPMC 6 cps was dispersed in 80% of 80 C of water and adds remaining 20 % of cool water into it and mixed well and keeps it aside for some time to from clear solution.

Granulation:
Granulation was carried out in Rapid Mixing Granulator. Impeller rpm and time adjusted for dry mixing of intragranular materials & check for content uniformity if necessary and continuously add the binder solution to the dry mixture, chopper is used for prevent the formation of lumps. Granulations affect intragranular and intragranular pore structure by changing the degree of packing with in the granules. Metformin HCl is hygroscopic, highly water soluble and forms large wet mass in aqueous granulation. Therefore non aqueous granulation was taken.

Drying:
Rapid dryer (Fluidized bed dryer) is used for drying of wet granules. A film of a binding agent covers fluidized bed granules posses greater porosity and granule surface area. Adjust the temperature and time for drying the granules. Note the LOD in % w/w.
Milling:
Multimill is used for size reduction of the larger granules to maintain the equal size by applying slow speed and forward direction of motor blades. The blades were surrounded by stainless steel screen (size 1.5mm and 1.0 mm), from this granules were forcibly come out with various angles.

Sifting:
Mechanical sifter is used for reducing the granule size by passing through the mesh #20 for Metformin HCl and #30 for Gliclazide. Particle size, Bulk density, Tapped density, Compressibility index and Hunsler ratio are calculated for observing the floe properties of the granules.

Blending:
The granules are mixed with extra granular materials and placed in Double cone blender or Octagonal blender, adjust the rpm and time.

Lubrication:
Lubricants reduce friction between granulation and die wall during compression and ejection.

Compression of Bilayer Tablets: (Bilayer Compression Machine)
A tablet bilayer press is simply a tablet press that has been modified so that it has 2 die filling and compression cycles for each revolution of the press.

In short, each punch compress twice, once for the first layer of a two-layer tablet and a second time for the second layer. If the first layer is compressed so hard that the second layer will not bond it, or will bond so poorly that upon ejection the layers are easily separated for weighing. Once the proper weight adjustments have been made by adjusting the die fill, the pressure is adjusted to the proper tablet hardness and bonding of the layers.

In this two-layer tablet press, two hoppers above the rotary die table feed, granulated material to two separate feed frames without intermixing continuous, gentle circulation of the materials. Through the hoppers and feed frames assures uniform filling without segregation of particle sizes that would otherwise carryover to the second layer and affect layer weight, tablet hardness, so use colored granulation taken for one layer (Burnette RR, 1987).

Evaluation of tablets

Weight variation:
20 tablets were selected randomly from the lot and weighted individually to check for weight variation.

Hardness:
Hardness or tablet crushing strength (f_c) (the force required to break a tablet in a diametric compression) was measured using Monsanto tablet hardness tester. It is expressed in kg/cm² (Kroge I, Bodmeier R, 1999).

Thickness:
The thickness of the tablets was measured using verniercaliber.

Friability (F):
Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at height of 6 inches in each revolution. Reweighed sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were de dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula (Guruvinder Singh Rrekhi et al., 1999).

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F = \frac{W_{\text{initial}} - W_{\text{final}}}{W_{\text{initial}}} \times 100
\]

Physical Characteristics of Fabricated Metformin Hydrochloride and Gliclazide Bilayer tablet (Trial-7 – Trial-12)

IN- VITRO RELEASE STUDY

In-Vitro drug release studies were carried out using Tablet dissolution test apparatus USPXXIII at 50 rpm. The dissolution medium consisted of 900 ml of Standard buffer pH 1.2 for the first 2 hrs, followed by pH 7.5 for remaining period of time. Temperature maintained at 37±1. The sample of 5ml was withdrawn at predetermined time intervals and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced (Li VHK et al., 1987). From that 5 ml sample, 1 ml sample was withdrawn and placed in a 10 ml volumetric flask the diluted samples were assayed at 232 nm against reagent blank and results are shown in
Comparative Dissolution Profile of Diamicron-MR with Trail 4-9

Table: --1

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<th>S.NO</th>
<th>INGREDIENTS</th>
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<td>1</td>
<td>Metformin hydrochloride, Gliclazide and Iron oxide yellow</td>
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<td>Lactose, Maize starch, Plasdone S-630, Plasdone K-90, Mannitol.</td>
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<td>Talc Magnesium stearate</td>
<td>Signet chemicals, Mumbai</td>
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<tr>
<td>4</td>
<td>Stearic acid, Aerosil, Dicalcium phosphate</td>
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Table: --2

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<th>B.No.</th>
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<td>0.008</td>
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<td>6.58-6.62</td>
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<td>Trial 5</td>
<td>1141- 1152</td>
<td>0.030</td>
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<td>Trial 8</td>
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Comparative Dissolution Profile of Diamicron-MR with Trail 4-9

Table: --3

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Fig No:-1
Discussion

Granules were evaluated for tests LOD, Bulk density, tapped density, compressibility index, and Hausner ratio and sieve analysis before being punched as tablets. Tablets were tested for weight variation, thickness, hardness and friability as per I.P. procedure. In vitro dissolution tests and F2 values are found for 3 batches. From these results Trial-6 (Metformin HCl + HPMC K100M) and Trial-4 (Gliclazide + HPMC K15M) was selected for preparation of bilayered tablets. In Trial-6, the release retardant HPMC-K-100M and HPMC K15M was used as extra and intra granular polymer. Dissolution profile matched in Trial-7 (Metformin HCl) and Trial-9 (Gliclazide) with marketed product and F2 value was 70.9 and 67.2 respectively. As there was no marketed Bilayered Sustained Release tablet of the same combination. Dissolution profile was compared with Glucophase XR (Metformin HCl ER) and Diamicron MR (Gliclazide) tablets.

References