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DESIGN AND ASSESSMENT OF BILAYERED TABLETS OF METFORMIN HYDROCHLORIDE AS SUSTAINED RELEASE LAYER CONTAINING HP MCK 100M AND GLIMEPIRIDE

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Abstract

The formulation comprise of Glimepiride as immediate release layer formulated using super disintegrate and Metformin Hydrochloride as sustained release layer containing HP MCK100M. The present research work was envisaged to develop bilayered tablets to improve therapeutic efficacy for the treatment of diabetes mellitus. The combination of two drugs i.e., Metformin Hydrochloride and Glimepiride were used for the preparation of bilayered tablets which act against type 2 diabetes. Evaluation of bilayered tablets for the immediate release Glimepiride layer and sustained release Metformin Hydrochloride layer with optimization of excipients. The immediate release layer of Glimepiride showed complete release within 45 min and Metformin Hydrochloride release was extended up to 12 hours. The present study revealed that Metformin Hydrochloride and Glimepiride bilayered tablets were successfully developedfortheuseagainsttype2diabetes.

Keywords: Metformin, Glimepiride, Diabetes mellitus, Bilayered tablets.

Introduction

Diabetes mellitus is a metabolic disorder that is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency [1]. The main objective of combination therapy is to encourage the utilization of lower doses of drugs to treat patient's and also to minimize dose dependent side effects and adverse reactions. Bilayered tablets can be a primary option to avoid chemical incompatibilities between different drugs by physical separation and to enable the development of different drug release profiles [2][immediate release (IR) with sustained release (SR)]. Applications of bilayered tablets are mainly used in the combination therapy; to deliver the loading dose and sustained dose of the same or different drugs and are used to deliver the two different drug shaving different release profiles. Type2 diabetes mellitus is a progressive disease with multiple underlying patho-physiologic defects. Mono therapy alone cannot maintain glycemic

control and leads to treatment failure. Ideally, a combination of glucose-lowe ring agents should have complementary mechanisms of action that address multiple patho-physiologic pathways, can be use detail stages of the disease, and be generally well tolerated with no increased risk of hypoglycemia, cardiovascular events or weight gain [3].

Two classes of glucose-lowering agents that meet these criteria are Glimepiride (GM); second-generation sulfonylurea class [4] and Metformin Hydrochloride (MF) is a biguanide class [5].Glimepiride will stimulate the pancreatic beta cells to release insulin whereas Metformin Hydrochloride will decrease the glucose level by inhibiting the glucose production in liver.The combination of Glimepiride and Metformin Hydrochloride exhibit synergistic effect and decreases blood glucose level [6]. The aim of this present work is to formulate and evaluated bilayered tablet of Glimepiride (as IR layer) using super disintegrate Cross Carmel lose sodium and Metformin Hydrochloride (as SRlayer) using various extended release polymers Microcry stalline cellulose, HPMCK 100 M for the effective treatment of type2 diabetes mellitus[7,8].

Materials and MethodsMaterials

Glimepiride (GM) and *Metformin* Hydrochloride (MF) were obtained as gift samples from M/sYarrow Chemical Products, Mumbai, India. Cross carmellose sodium, HPMC K100M, Avicel102, Povidone K30, Magnesium stearate, Talc, Isopropyl alcohol (IPA), Quinoline yellow was purchased from Loba Chemie Pvt Ltd., Mumbai, India. All the excipients used in study are of pharmaceutical grade.

Preformulation studies

The overall objective of preformulation studies is to generate information useful to the formulator in developing stable and bioavaliable dosage forms. Preformulation solubility analysis was done to select a suitable solvent system to dissolve the drug as well as various excipients used for formulation and also to test drugs solubility in the dissolution medium, which was to be used. To check the drug-drug and drug-excipientinter actions, preformulation studies were performed. Drugs alone, incombination and along with excipients proposed to be used were filled in amber colored vials sealed with bromo butyl rubber stoppers and kept in environmental stability chamber (Remi Lab, Mumbai, India) foray celebrated stability condition at 40±2°Ctemperature and75±5% RH for a period of 30days. The IR absorption spectrum of Glimepiride and Metformin Hydrochloride was determined by Bruker FT-IR spectrophotometer and compared with the initial spectra of drugs using KBr dispersion method. The IR spectrum of the obtained sample of drug was compared with the standard IR spectra of the pure drug. FT-IR spectra help to confirm the identity of the drug and detect the interaction of the drug with polymers was carried out to check the compatibility between drug and polymers.

Standard calibration curve of Metformin in phosphate buffer Ph 6.8

Accurately weighed amount of 100mg Metformin Hydrochloride was transferred in to a 100mL volumetric flask. The volume was made up to 100 mL with phosphate buffer pH 6.8. The resulted solution has the concentration of 1mg/mL which was labeled as primary stock solution. From this primary stock solution 10 mL was transferred to another volumetric flask made up to 100 mL with same phosphate buffer. The resulted

solution has the concentration of 100µg/mL which was labeled as secondary stock solution. From this secondary stock solution 2 mL, 4 mL, 6 mL, 8 mL, 10 mL was taken separately and transferred into a 100 mL volumetric flask and volume was made up to 100 mL with the phosphate buffer pH 6.8 to produce 2µg/mL, 4 µg/mL, 6 µg/mL, 8 µg/mL, 10 µg/mL concentrations. The absorbance of different concentrations was recorded at λ_{max} of the drug using double beam UV-Visible spectrophotometer. Calibration curve was plotted between the concentrations on X-axis and absorbance on Y-axis.

Granule preparation of sustained release layer of Metformin Hydrochloride

The dose of Metformin HCI for sustained release was fixed as 500 mg. The sustained release layer of Metformin HCl was prepared by wet granulation technique. Metformin HCI,

Microcrystalline cellulose, HPMC K100M were sifted through Sieve no. 40#. The above sifted materials were mixed in mortar and pestle for 5 min. PVP K-30 was dissolved in mixture of IPA. Then above mixture with binder PVP K-30 solution was granulated and kneading for 2 min. The granules were dried in tray dryer at 65ºC. The granules were passed through mesh no. 20# in oscillating granulator. Finally mixture was lubricated with talc andmagnesiumstearatefor2min.

Blend preparation of immediate release layer of Glimepiride

The dose for immediate release was fixed as 1 mg. immediate release layer of Glimepiride were prepared by direct compression technique. Glimepiride and other excipients were passed through sieve no. 40# and thoroughly mixed in a blender approximately for 5 min, the color Quinoline yellow was passed through the sieve no. 100# and add to above mixer. The whole blend was lubricated for 2 min with Magnesium stearate which was already passedthroughsieveno.60#.Crosscarmellosesodiumwasusedassuperdisintegrant.

Extended release granules of Metformin Hydrochloride were compressed as first layer followed by immediate release granules of Glimepiride as second layer.

***In-vitro* drug release studies**

Dissolution test of the tablets were performed using USP dissolution apparatus II(paddle) at 50 rpm and 37±0.5°C temperature. Test sample(5 mL)was withdrawn at particular time interval and replaced with fresh dissolution media maintained at the same temperature and the concentration of dissolved drug was determined using UV-Visible spectrophotometer at 233 nm for Metformin Hydrochloride and 226 nm for Glimepiride. The media used was 0.1NHCl at a pH 2.0 and a volume of 750 mL for the first 2 hours after which 250 mL of 0.2 M sodium phosphatetri basic, was added to give a final Ph of 6.8and maintained at 37+0.5^{o}C.

Kinetic analysis of dissolution data

In order to describe the kinetics of the release process of drug in different formulations, models were fitted to the dissolution data of optimized formulation using line regression analysis.

Results &Discussion

Calibration curve of Glimepiride in 0.1 NHCl pH 1.2

The absorbance of standard solutions of Glimepiride in 0.1N HCl pH 1.2 was determined at 226 nm.The

standard calibration curve for pure drug was found to be linear in the range of 2-12µg/mL. The correlation coefficient obtained was 0.999.

Calibration curve of Metformin HCl in phosphate buffer pH 6.8

The absorbance of standard solutions of Metformin HCl in phosphate buffer pH 6.8was determined at 233 nm. The standard calibration curve for pure drug was found to be linear in the range of 2-10µg/mL.The correlation coefficient obtained was 0.998.

Drug-Excipients compatibility studies FT-IR Spectroscopy

The functional group present in the both the drug were identified. The FT-IR of Metformin HCl showed in tense bands at 3372 cm^{-1},1448.81cm^{-1}and1039.77.94cm^{-1}corresponding to the functional groups NH, $CH_3$and CN bending respectively. The FT-IR of Glimepiride showed intense bands at 3372 cm^{-1}, 1448.81 cm^{-1} and 1039.77.94 cm^{-1} corresponding to thefunctional groups NH, CH_3 and CN bending respectively. The wave numbers of individual drugs were compared with final formulated product IR spectrum. The results revealed that there was no significant disturbance in the principle peaks of pure drugs of Metformin HCl and Glimepiride. From the interpretation it was understood that there was no major shifting in the frequencies of Metformin HCl and Glimepiride which indicated that there is no chemical interaction in the formulations.Thisfurtherconfirmstheintegrityofpuredrugandcompatibilityof them with excipients.

***In-vitro* drug release**

The results of *in-vitro* release of drugs Metformin HCl and Glimepiride from formulations F1-F6 along with the marketed preparation were tabulated in Tables 1-4. Graphs plotted against time vs % drug release for Metformin HCl and Glimepiride were shown in Figures 1-5. The *in-vitro* drug release characteristics were studied in 0.1 N HCl of pH 1.2 for a period of 2 hrs followed by phosphate buffer of pH 7.4 for a period up to 24 hrs using USP type I dissolution apparatus.

Mathematical models

In order to understand the kinetics and mechanism of drug release, the result of the *in-vitro* dissolution study of all formulations was fitted with various kinetic equations like zero order as cumulative percentage released vs time, first order as log percentage of drug remaining to be released vs time, and higuchi's model, cumulative percentage drug released vs square root of time. The R^2 values were calculated for the linear curves obtained by regression analysis of the above plots. The mathematical modeling of the*in-vitro* drug released for all theformulations were complied and R^2 values of all formulations were within the limits. It isevident from the R^2 values that the drug release from formulations was found to follow first order kinetics. The mechanism of drug release from the formulations was by non-ficki an diffusion as the value of nis less than 0.89 and greater than 0.45.

Summary

The aim of the present study was to develop and optimize bilayered tablets of Metformin HCl sustained release and Glimepiride immediate release.The choice of selection of Glimepiride a sulphonylure a drug and Metformin hydrochloride a biguanide drug is based on their mechanism of action; in a synergistic manner by decreasing

glucose level in blood. Various formulations were prepared and evaluated with an aim of presenting Metformin Hydrochloride as sustained release and Glimepiride as immediate release for improving the patient compliance. Six formulations of Metformin HCl were prepared with varying concentrations of the HPMC K100 polymer to attain the required release rate by wet granulation technique. Six formulations of Glimepiride were prepared by direct compression technique with varying concentrations of Cross carmellose sodium as super disintegrate. The physic chemical evaluation results for the powdered blend of all trails pass the official limits in angle of repose, compressibility index and hauser's ratio. The prepared tablets also maintained the physicochemical properties such as thickness, hardness, weight variation, friability. The optimized formulation F6 contains the average thickness of 4.44 mm, average hardness of 7.16kg/cm^2, average weight of1099 mg, friabilityof0.36%. The prepared tablets were subjected to *in-vitro* dissolution studies using 0.1N HCl for the first two hours and pH 6.8 phosphate buffer for the next 10 hours. The F6 formulation of Metformin Hydrochloride has shown a drug release of 99.87% at the end of 12 hrs. The F6 formulation of Glimepiride has shownthedrugreleaseof99.92% attheendof45min.The optimized formulation; F6 was compared with the marketed preparation and was found to show a similar release rate. With the data of kinetic analysis,F6 formulation showed best linearity in higuchi's equation plot indicating that the release of drug from bilayered tablet follows non-ficki an diffusion.

Conclusion

The present research was carried out to develop a bilayered tablet of Metformin HCl sustained release and Glimepiride immediate release using super disintegrate Cross carmellose sodium for fast release layer and combination of HPMC K100M and Avicel for sustained release layer. The tablets showed an initial burst release to provide the loading dose of drug followed by sustained release up to 12 hours. This modified release bilayered tablets also reduced dosing frequency, increase the bioavailability and provide better patient compliance. Finally bilayered tablet is improved beneficial technology to overcome the limitation of the single layered tablet. It 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 and second layer is maintenance dose. The preparation of the tablets Metformin HCl sustained release and Glimepiride immediate release in the form of bilayers used to provide system for the administration of drugs, which are incompatible and to provide controlled release tablets preparations by providing surrounding or multiples welling layer.

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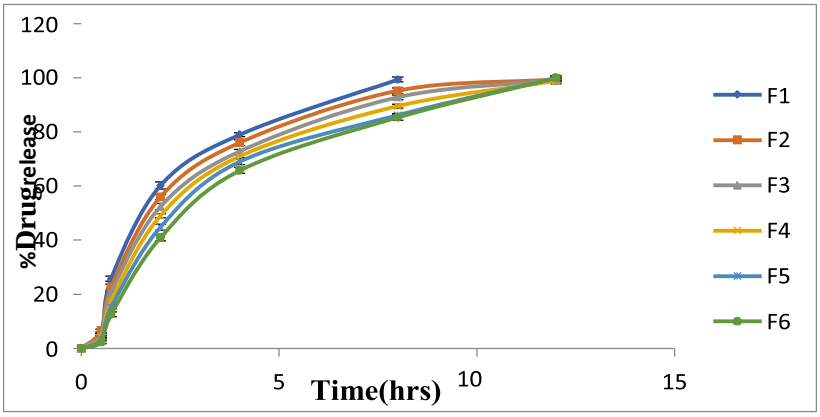

Figure1: Comparison of dissolution profile of Metformin HCl formulations F1 to F6

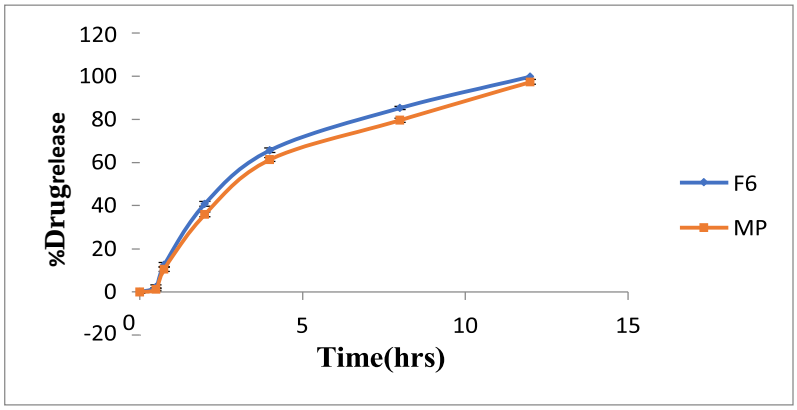

Figure2: Comparison of dissolution profile of Metformin HCl optimized formulation and marketed preparation

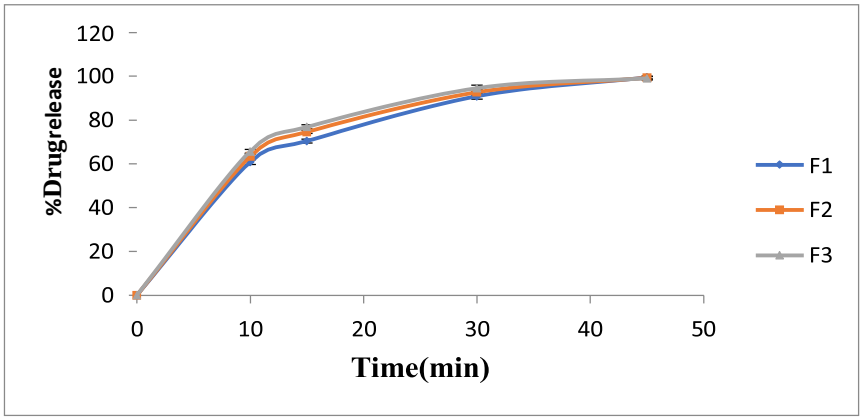

Figure3: ComparisonofdissolutionprofileofGlimepirideformulationsF1toF3

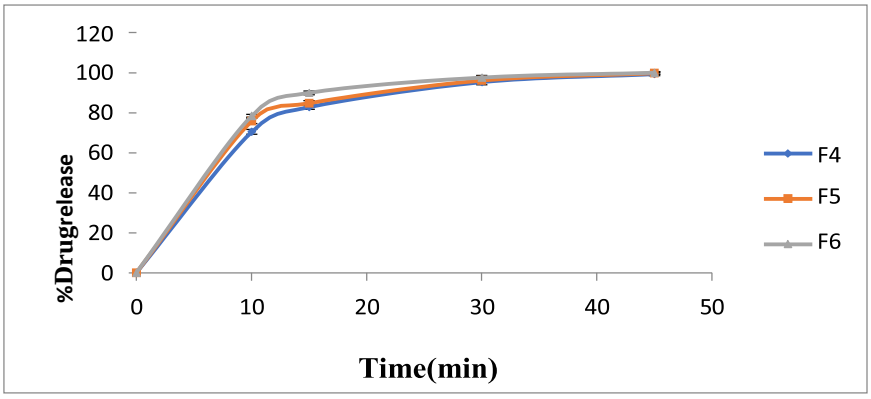

Figure4: Comparison of dissolution profile of Glimepiride formulations F4 to F6

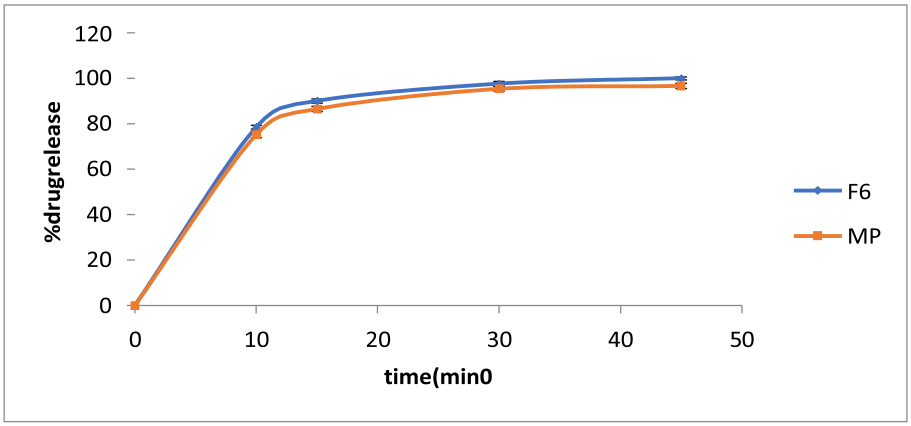

Figure5: Comparison of dissolution profile of Glimepiride optimized formulation and marketed preparation

Table1: Dissolution profile of MetforminHCl

Time(hr)	F1	F2	F3	F4	F5	F6
0	0±0	0±0	0±0	0±0	0±0	0±0
0.5	5.23±0.37	6.54±0.49	4.87±0.72	4.12±0.49	3.45±0.46	2.34±0.53
0.75	25.73±0.95	22.65±1.11	20.55±0.62	17.32±0.54	15.23±0.56	12.54±0.88
2	60.12±1.30	55.87±1.04	52.34±1.14	48.98±0.81	44.77±1.10	40.89±1.13
4	78.98±0.68	75.98±1.03	72.77±0.77	7095±0.56	68.98±1.08	65.76±1.07
8	99.34±0.83	95.12±1.07	92.76±0.90	89.44±0.70	86.18±0.61	85.32±1.06
12	-	99.43±0.66	99.13±0.72	98.76±1.03	99.9±0.77	99.87±0.77

Table2: Dissolution profile of Metformin optimized formulation and marketed preparation

Time(hr)	F6	MP
0	0±0	0±0
0.5	2.34±0.53	1.32±0.64
0.75	12.54±0.88	10.65±1.11
2	40.89±1.13	35.98±1.08
4	65.76±1.07	61.45±0.82
8	85.32±1.06	79.66±0.94
12	99.87±0.77	97.43±1.17

Table3: Dissolution profile of Glimepiride

Time(min)	F1	F2	F3	F4	F5	F6
0	0±0	0±0	0±0	0±0	0±0	0±0
10	60.87±1.07	63.87±1.17	65.72±0.84	70.45±1.18	75.87±1.28	78.44±0.79
15	70.43±0.83	74.65±0.72	76.88±0.98	82.76±1.11	84.77±1.23	89.91±0.94
30	90.87±1.33	92.77±1.26	94.55±1.38	95.33±1.24	96.13±0.90	97.55±1.05
45	99.54±0.59	99.32±0.66	99.12±0.77	99.31±0.73	99.76±0.61	99.92±0.62

Table4: Dissolution profile of Glimepiride optimized formulation and marketed preparation

Time(min)	F6	MP
0	0±0	0±0
10	78.44±0.79	75.16±1.39
15	89.91±0.94	86.45±1.16
30	97.55±1.05	95.34±0.94
45	99.92±0.62	96.55±1.15