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Research Article

Formulation and in-vitro evaluation of metformin-glipizide sustained release matrix tablets

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ABSTRACT

Sustained release formulation of Metformin-Glipizide presents significant challenges due to its poor inherent compressibility, high dose and high water solubility. Sustained release matrix tablets of Metformin-Glipizide were formulated using different concentration of Guar gum, Xanthan gum, and Chitosan polymers. The formulated powder blends were evaluated for angle of repose, bulk density, true density, compressibility index and total % porosity. The tablets were subjected to hardness, friability, % weight variation and % drug content. *In vitro* release studies were carried out at pH 1.2 and pH 7.2 using the dissolution test apparatus USP. The formulated powder blends and tablets showed satisfactory results from selected formulation.

Keywords: Metformin-Glipizide, Guar gum, Xanthangum, and Chitosan, Sustained release, Direct compression method.

INTRODUCTION

Metformin-Glipizide, an anti-diabetic drug lowers both basal and postprandial-elevated blood glucose in patients with non-insulin-dependent diabetes mellitus (NIDDM or type-II diabetes) whose hyperglycemia cannot be satisfactorily managed by diet alone. Some high incidence of concomitant GI symptoms, such as abdominal discomfort, nausea and diarrhea, many occur during the treatment. Administration of a extended release, once-a-day Metformin hydrochloride dosage form could reduce the dosing frequency and improve patient compliance.

Numerous studies have been reported in literature investigating the HPMC matrices to control the release of variety of drug from matrices .Several authors have reported the use of ethyl cellulose matrices to control the release a variety of drugs. Therefore, in this study, the hydrophobic (EC) and hydrophilic polymer (HPMC) alone/ in combination have been used as matrix material in order to get the required release profile of Metformin-Glipizide.

Preparation of Metformin-Glipizide Sustained release matrix tablets

Different tablet formulations (MGF_1 to MGF_9) were prepared by direct compression technique. Ingredients required per tablet are given in Table no: 1 and tabulated as follows.

Composition of tablet formulations F_1 to F_9

Ingredients (mg/tab)	MGF1	MGF2	MGF3	MGF4	MGF5	MGF6	MGF7	MGF8	MGF9
Metformin Hydrochloride	500	500	500	500	500	500	500	500	500
Glipizide	10	10	10	10	10	10	10	10	10
Guar gum	30	60	90	-	-	-	-	-	-
Xanthan gum	-	-	-	30	60	90	-	-	-
Chitosan	-	-	-	-	-	-	30	60	90
F1+F2+F3(1:1:1)	-	-	-	-	-	-	-	-	-
Lactose	74	44	14	74	44	14	74	44	14
Polyvinylpyrolidone	14	14	14	14	14	14	14	14	14
Methyl paraben	6	6	6	6	6	6	6	6	6
Talc	10	10	10	10	10	10	10	10	10
Magnesium Stearate	6	6	6	6	6	6	6	6	6
Total weight	650	650	650	650	650	650	650	650	650

The Metformin-Glipizide, Guar gum, Xanthangum, and Chitosan and Lactose, Polyvinylpyrolidone and Talc were separately passed through mesh No.44. The powders were uniformly mixed in a double cone blender for 5 mins. Then the dried powders were lubricated with magnesium stearate by mixing in a rapid mixer at slow speed for 5 mins, separately and compressed using 16/32 inch flat punches in cadmach tablet compression machine to get tablets.

Evaluation of powder blends

The formulated powder blends were evaluated for compatibility, angle of repose, bulk density, true density, percentage compressibility index and total percentage porosity.

Evaluation of tablets

The compressed tablets (formulations MGF_1 to MGF_9) were tested for hardness, percentage friability, percentage weight variations and the percentage drug content.

In-vitro Release Studies

In-vitro dissolution studies were carried out using six stage dissolution rate test apparatus USP at 50 rpm. The dissolution medium consisted of simulated gastric fluid (pH 1.2 - acid buffer) (for first 2 h) and followed by in simulated intestinal fluid (pH 7.2 - Phosphate buffer) from 2 to 12 hours (900 ml), maintained at 37°±0.5°C. Samples were withdrawn at predetermined time intervals and drug content was analyzed by UV visible spectrophotometer at 227.5 and 286nm respectively compared with blank. The same procedure was

followed to study the *in-vitro* release of Metformin-Glipizide sustained release tablet.

RESULTS AND DISCUSSION

Metformin-Glipizide is a highly water soluble drug. Its poor inherent compressibility coupled with high dose (500mg), and Glipizide (10mg) dose posses a significance challenge for developing an sustained release dosage form.

Compatibility study of Metformin hydrochloride by DSC

DSC thermograms of pure sustained, blend of polymer/polymers mixture with drug were determined. The different in the peak areas in the thermograms of blends of drug in the polymer from that of pure drug is due to less quantum of drug in the blend. Absence of any new endothermic peak are disappearance of no shift of endothermic peak confirms that peak in thermo grams of pure drug and the blends of drug in the polymer confirms that there is no any interaction and hence the polymers are compatible with drug.

Evaluation of physical and chemical parameters of formulated powder blends

Physical parameters such as specific surface area, shape, hardness, surface characteristics and size can be significantly affect the rate of dissolution of drugs contained in a complex system. The formulated powder blends of different formulations (MGF1 to MGF9) were evaluated for angle of repose, true density, bulk density, compressibility index and total percentage porosity.

Physical and chemical parameters of formulated Metformin-Glipizide powder blends (MGF1 to MGF9)

Flow properties of powder

Formulation Code	Angle of repose (θ)*	Bulk density (gm/cm3)*	Tapped density (gm/cm3)*	Hausner ratio (HR)*	Carr's index (IC)*
MGF1	22.30±0.19	0.590±0.006	0.879±0.008	1.02±0.011	12.41±0.94
MGF2	21.99±0.28	0.793±0.010	0.686±0.011	1.13±0.02	11.99±1.07
MGF3	19.3±0.49	0.597±0.0005	0.798±0.008	1.42±0.011	13.95±1.50
MGF4	20.37±0.30	0.595±0.01	0.729±0.002	1.52±0.015	10.85±0.34
MGF5	21.11±0.24	0.584±0.009	0.736±0.01	1.14±0.001	11.92±0.68
MGF6	21.07±0.29	0.682±0.004	0.797±0.011	1.31±0.02	10.02±0.75
MGF7	22.88±0.60	0.692±0.004	0.873±0.01	1.13±0.02	13.78±1.65
MGF8	19.84±0.72	0.772±0.009	0.890±0.06	1.25±0.011	11.87±0.84
MGF9	23.15±1.00	0.883±0.005	0.744±0.05	1.15±0.02	12.44±0.71

*All the values are expressed as mean± SE, n=3.

*All values are mean ±S.D for n=3

The results of angle of repose (<30) indicated good flow properties of all the formulated powder blends except one formulation (MGF_1). The compressibility index value were recorded <15%, result in good to excellent flow properties in one formulation (MGF_3) supporting the angle of repose indicating good flow, which in rest of the formulations it can >15%. Formulated powder blends density; porosity and hardness are often interrelated properties and are likely to influence compressibility, porosity, dissolution profile and properties of tablets made from it. The percentage porosity value ranged from 24.31 to 31.25 indicating that the packaging of the powder blend may range from close to lose packaging and also confirming that the particle are not of greatly different sizes. Generally a percentage porosity value below 25% shows that the particles in the powders are of greatly different sizes and values greater than 48 % shows that particle in the powder are in the form aggregates of flocculates. All these results indicate that the formulated powder blends processed satisfactory flow properties and compressibility.

Evaluation of formulated tablets

Code	Thickness (mm)*	Weight variation test (%)	Hardness (kg/cm^2)*	Friability (%)*	Drug content (%)*
MGF1	4.2±0.24	±2.30	4.83±0.25	0.32±0.03	90.89±6.65
MGF2	3.2±0.10	±2.40	6.66±0.40	0.48±0.08	99±6.09
MGF3	3.3±0.07	±1.90	5.58±0.37	0.29±0.08	93.32±5.92
MGF4	3.2±0.07	±2.19	5.75±0.41	0.45±0.02	97.02±5.79
MGF5	3.2±0.05	±2.12	5.66±0.40	0.57±0.05	96.99±5.18
MGF6	3.1±0.054	±1.92	6.66±0.40	0.54±0.04	98.11±2.38
MGF7	3.1±0.089	±2.09	5.83±025	0.53±0.09	97.14±5.37
MGF8	3.2±0.075	±2.12	5.66±0.40	0.59±0.04	99.15±4.680
MGF9	3.1±0.075	±2.03	5.57±0.37	0.66±0.05	95.99±2.65

*All the values are expressed as mean± SE, n=3.

The tablets of different formulations (MGF_1 to MGF_{10})) were evaluated for various parameters viz., hardness, friability, percentage weight variation and percentage drug content. The results of these parameters are given in Table

In-vitro release studies

Results of the *in-vitro* release studies of various formulations designed and manufactured along with reference standard formulations of Metformin-Glipizide from MGF1 to MGF10 made with different concentration Polymers. It is found that the cumulative percentage drug release MGF9 was Observed Optimum Drug release at 11 Hrs 97.99.

Stability studies

Characteristic	Initials	1 Month	2 Month	3 Month
Hardness (kg/cm2)*	6.57±0.37	5.33±0.76	5.06±0.422	5.01±0.00
Drug content (mg/tablet)*	95.99±2.65	95.07.04±0.79	94.96.±0.13	94.17±0.70
In vitro drug release at 11 hour*	98.99±1.11	97.62±1.11	96.35±0.32	96.26±1.61

*All the values are expressed as mean± SE, n=3.

Stability studies of optimized formulation (MGF9) of sustained release Metformin-Glipizide tablet

CONCLUSION

The study was to effect of various hydrophilic polymers on in vitro release rate from sustained release tablet of Metformin-Glipizide based on a low density polymer. The sustained release drug delivery was a promising approach to achieve a prolonged therapeutic action of drug. Different types of matrix forming polymers guar gum, Xanthan gum and chitosan were studied. Formulation MGF9 containing chitosan polymer showed sustained drug release for 11 hours. When percentage drug release plotted versus time it was observed that, as increases in polymer concentration time shows that the decreases in release rate of drug. The drug release from MGF9 11 hr was found 97.99±0.04 slow as compared with all formulations. The optimized formulation MGF9 was subjected to stability studies. From the above it was concluded that formulation MG**F9** was stable in short term stability study.

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