DESIGN, DEVELOPMENT AND EVALUATION OF ALOGLIPTIN AND METFORMIN HYDROCHLORIDE BILAYER TABLET

ABSTRACT

The objective of the present work was to formulate and evaluate bilayer tablets of alogliptin and metformin HCl. Combining alogliptin with metformin HCL gives additional benefits in comparison with either drug alone and could be considered for patients whose quality of life is impaired by diabetes mellitus. The study was performed to design bilayer tablets of alogliptin immediate release layer and metformin HCl sustained release layer by wet granulation method. The immediate release layer comprised Crospovidone superdisintegrant and sustained release layer comprised HPMC K4M as rate release controlling polymers and PVPK30 was used as binder for both layers. The *in vitro* release of drug from the formulations was studied in 0.1N HCl acidic buffer and pH 6.8 phosphate buffer, and it was found that the prepared sustained release layer tablets were able to sustain the release of the drug up to 12 h and *in vitro* studies of alogliptin shown more than 80% of drug was released within 30 min. As per ICH guidelines, accelerated stability studies were carried out and results were found within the range. The release of alogliptin follows a zero order release model and the release of metformin HCl follows Higuchi model release.

Keywords: Alogliptin, metformin HCL, HPMC K4M, Crospovidone, PVP K30, wet granulation method, Bilayer tablet

INTRODUCTION

The bilayer tablet is usually introduced to improve patient compliance, eliminate frequent dosing and fluctuation in plasma drug concentrations. The dual therapy is mainly used to achieve the rapid and extended release of drugs from the formulation. The immediate release layer contains the loading dose and the second layer provides the maintenance dose[1-4].

Alogliptin inhibits dipeptidyl peptidase 4 (DPP-4), which normally degrades the incretins glucose-dependent insulinotropic polypeptide (GIP) and glucagon like peptide 1 (GLP-1). Metformin improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose[5,6]. The present paper gives emphasis on immediate release alogliptin layer having half-life of 21 h and sustained release metformin hydrochloride layer, whose half-life is 6.2 h.

MATERIALS AND METHODS

Materials

Alogliptin and metformin HCl were obtained as gift samples. All ingredients used were of analytical grade.

METHODS

Manufacturing process using wet granulation method[7]

Weighed quantities of drug and polymers were sifted through sieve # 44 (Table I). Binder solution was prepared by dissolving PVP K30 in isopropyl alcohol. Granules were prepared by adding binder solution to dry blend and made into a wet dough and passed through sieve #18. The produced granules were dried in hot air oven at 50°C for 15 to 30 min. Dried granules were passed through sieve #22. Magnesium stearate and talc were sifted through sieve #44 and added to dried granules and mixed for 2 minutes. The granules were compressed in a rotary tablet compression machine using capsule shape punches at the required pressure.

RESULTS AND DISCUSSION

Evaluation of alogliptin granules

It was observed that for the batches AF1 to AF9, the parameter bulk density ranged from 0.170 to 0.178 (g mL^{-1}), tapped density ranged from 0.190 to 0.223 (g mL^{-1}). Hausner's ratio ranged from 1.09 to 1.27, Carr's index ranged from 8.85 % to 21.52 % and angle of repose ranged from 18.26° to 33.42°.

Evaluation of metformin HCL granules

It was observed that for the batches MF1 to MF9, the parameter bulk density ranged from 0.092 to 0.102 (g m L^{-1}), tapped density ranged from 0.104 to 0.136 (g mL^{-1}), Hausner's ratio ranged from 1.13 to 1.33, Carr's index ranged from 11.53 % to 25.18 % and angle of repose was ranged from 21.80° to 33.42°.

Evaluation of tablets[8, 9, 10]

The results showing the % drug content, disintegration time and % drug release are summarized in (Table II).

Table I: Formulation of alogliptin and metformin HCl release layer

Ingredients (mg tablet^{-1})	Alogliptin immediate release layer (AF1-AF9) Batches								
	AF1	AF2	AF3	AF4	AF5	AF6	AF7	AF8	AF9
Alogliptin	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25
Microcrystalline cellulose	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25
Crospovidone	2	4	6	2	4	6	2	4	6
PVP K30	1	1	1	2	2	2	3	3	3
Isopropyl alcohol	QS	QS	QS	QS	QS	QS	QS	QS	QS
Lactose	108	106	104	107	105	103	106	104	102
Magnesium stearate	2	2	2	2	2	2	2	2	2

Ingredients (mg tablet^{-1})	Metformin HCL Sustained release layer (MF1-MF9) Batches								
	MF1	MF2	MF3	MF4	MF5	MF6	MF7	MF8	MF9
Metformin HCL	500	500	500	500	500	500	500	500	500
Na carboxy methyl cellulose	200	200	200	200	200	200	200	200	200
HPMC K4M	10	35	60	10	35	60	10	35	60
PVP K30	6	6	6	12	12	12	18	18	18
Isopropyl alcohol	QS	QS	QS	QS	QS	QS	QS	QS	QS
Dicalcium phosphate	87	62	37	81	56	31	75	50	25
Aerosil	5	5	5	5	5	5	5	5	5
Talc	8	8	8	8	8	8	8	8	8
Magnesium stearate	9	9	9	9	9	9	9	9	9

Table II: Evaluation parameters of alogliptin layer and metformin layer

Alogliptin Layer			
Batch	Drug content (%)	Disintegration time (min)	Drug release (%)
AF1	98.4	5.00	99.20
AF2	97.2	1.30	98.39
AF3	98.0	3.20	96.89
AF4	96.2	5.20	98.34
AF5	98.2	3.00	98.26
AF6	95.2	1.20	97.86
AF7	98.2	2.20	98.30
AF8	98.4	3.05	98.01
AF9	95.4	2.45	98.27

Metformin Layer			
Batch	Drug content (%)	Disintegration time (min)	Drug release (%)
MF1	99	-	99.10
MF2	99.17	-	98.35
MF3	99.17	-	98.14
MF4	98.51	-	99.34
MF5	99.29	-	99.10
MF6	99.17	-	98.16
MF7	96.86	-	98.67
MF8	98.18	-	98.18
MF9	98.35	-	97.90

Optimization

The 3D plot of immediate release layer shows that as Crospovidone concentration increases, % drug release was found to decrease. It was concluded from the 3D plot that this factor has significant effect on the drug release while the sustained release layer shows that as HPMC K4M concentration increases,% drug release was found to decrease.

DISCUSSION

The physical parameters were within pharmacopoeial limit. The present work involves bilayer tablet for immediate and sustained release of alogliptin and metformin, respectively, using Crospovidone as superdisintegrants in immediate release and HPMC K4M as rate controlling polymer for sustained release. The UV scan of alogliptin show the maximum absorption at 222nm in 0.1N HCl, while metformin HCl shows maximum absorption at 227nm. The drug release of optimized batch shows up to 99.20% for alogliptin layer and 99.34% for metformin HCl layer. Hence, the formulated bilayer tablet can be used for effective and prolonged management of diabetes.

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