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Development of extended-release metformin core tablet and synergistic coating of sitagliptin for the treatment of type-II diabetes mellitus - A comparative drug release evaluation with reference product

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Abstract: Diabetes is getting a common disease and is spreading rapidly, affecting 6.6 percent world's population. Metformin HCl is an effective pharmacological treatment for type 2 diabetic patients because of its lowering blood glucose level ability, better weight-neutral effects and reduced risk of hypoglycemia. Nevertheless, gastrointestinal (GI) sensitivities are a concern in many patients using its immediate-release formulations. This study aimed to develop extended-release (ER) formulations to control the release into the body and minimize the dosage-related side effects of metformin and to develop an effective method of coating Sitagliptin immediate-release (IR) formulation over the core tablet. This study evaluated different formulations of Metformin HCl ER tablet using hydrophilic polymers. Different concentrations of Sitagliptin were used to develop immediate release coating. The dissolution profile of the designed formulation was compared with the reference 50/500mg tablet. In-vitro dissolution of Metformin HCl (MT5), containing Methocel K4M and Methocel K100 polymer, showed 37.62% release at 1hr, 53.46% at 2hr, 84.75% at 6hr and 94.81% at 10hr. The Sitagliptin (ST8) with 10% excess released 103.64% in 30min. Similarity factor values suggested that developed Metformin ER and Sitagliptin IR formulation were like the reference product.

Keywords: Diabetes mellitus type 2 (DM2), gastrointestinal (G.I.), extended-release polymer, similarity factor.

INTRODUCTION

Diabetes is one of the most widespread and advancing diseases and has affected 6.6% of the world population (Pujari *et al.*, 2016). Metformin, a biguanide, is mostly used as an anti-diabetic drug that efficiently reduces blood glucose and possesses good weight-neutral effects for diabetic patients. However, some patients suffered from gastrointestinal (G.I.) sensitivity for high metformin dose (Jabbour and Ziring, 2011). The sensitivity was found related to the immediate-release (IR) formulation of metformin HCl (Jabbour and Ziring, 2011; Pujari *et al.*, 2016). A genius solution to the G.I. side effect was the extended release (ER) metformin tablets. The tablets were developed to slowly release metformin over an extended time. The success of ER tablets included reduced total dose and improved tolerance towards G.I. sensitivity. However, it was more expensive than conventional IR metformin tablets (Kumar *et al.*, 2012; Maringanti and Nalagonda, 2013; Schwartz *et al.*, 2006).

Several studies reported the combination of metformin ER core with other antidiabetic drugs. Metformin and gliclazide combination for diabetic type 2 patients used solid dispersion of gliclazide in a bilayer tablet (Gangane *et al.*, 2018; Gottwald-Hostalek *et al.*, 2016). The glimepiride and metformin ER double-layer tablet reported a 16hr metformin dissolution profile (Sandhya and Begum, 2014). The pioglitazone IR and Metformin ER combination developed by direct compression released 99.97% pioglitazone in 2hr and 98.81% metformin HCl in 10hr. (Chowdary *et al.*, 2014). Metformin combination with empagliflozin and linagliptin are also reported (Chinta and Rohini, 2021; Gupta *et al.*, 2017; Hu *et al.*, 2016; Lingvay *et al.*, 2020). The sitagliptin and metformin HCl combination showed antidiabetic activities. It reduces the chance of low blood sugar, weight enhancement and does not cause an antagonistic impact. Both drugs have a complementary and additive effect on glycemic management and glycosylated hemoglobin levels (Maringanti and Nalagonda, 2013).

Bio-equivalency studies comprises comparing the safety and efficacy profiles for the combination tablet and the co-administered individual tablets Several studies confirmed the bio-equivalency of dual-layer Sitagliptin and metformin combination tablet versus their separate tablets (Hashem *et al.*, 2019; Hayes *et al.*, 2016).

The drug-excipient-incompatibility study is essential for any drug formulation. The impurities present in the excipients may react with the API and form mutagenic and genotoxic products. Shantikumar *et al*. studied compatibility of sitagliptin with several pharmaceutical excipients and reported that it is compatible with microcrystalline cellulose, croscarmellose and pregelatinized starch. Some excipients like magnesium stearate, ascorbic acid and citric acid showed interaction with Sitagliptin (Gupta *et al*., 2019; Shantikumar *et al*., 2014).

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The objective of the present study was to develop Metformin ER tablet with an IR coating of Sitagliptin phosphate that reduces gastrointestinal adverse effects and frequency of high dose of Metformin HCl. The study also focused on the drug-excipient compatibility study of the developed products. *In vivo - In vitro* Correlation (IVIVC) and kinetics of drug release were studied using similarity factor and model-dependent methods (Zero-order, first-order, Higuchi, Korsmeyer-Peppas and Hixson-Crowell model). The study also included 6 months real-time (30±2C°, 65±5% RH) and accelerated (40±2C°, 75±5 % RH) stability study as per ICH guidelines.

MATERIALS AND METHODS

The source of metformin HCl and sitagliptin phosphate monohydrate were Aarti Drug Limited India and Zhejiang Yongtai Pharmaceutical China, respectively. The excipients used in the study were microcrystalline cellulose 101, colloidal silicon dioxide, sodium stearyl fumarate, aerosil, hydroxypropyl methylcellulose, polyethylene glycol 6000, Kaolin, propyl gallate, methocel K4M Premium, methocel K 100 Premium LV, Tylopur 4000SR, Tylopur 100SR, Tylopur 10000SR and Opadry II Blue 85G205004. The study comprised several formulations trials of immediate Sitagliptin coating over metformin extended release (ER). The formation design in two-stage. In 1st stage, metformin ER core formulated by wet granulation method. Sitagliptin IR layer developed and coated over metformin ER core in 2nd stage using API spray coating method. Finally, the film layer is coated in final stage. HPLC equipped with a UV detector used to analyze developed formulation samples. The mixture of pH 7.0 potassium phosphate buffer and acetonitrile (70:30 v/v) was used as a mobile phase at a flow rate of 1.0ml/min. The HPLC column was C18, 250×4.6mm, 5µm and wavelength was selected at 215nm. The retention time range for metformin was 2.5-3.5 min, whereas the range for Sitagliptin was 7.5-8.5 min Fig. 1.

Stage 1: Metformin HCl ER core

Metformin ER core 500mg, were prepared by wet granulation process using sustain release (SR) polymers. All the ingredients were accurately weighed as per the respective formulation for 500 tablets. The formation of metformin core tablets started with the preparation of clear povidone solution in purified water and transfer into super granulator mixer (Model#HLSG10) containing metformin HCl, microcrystalline cellulose and polymers. All materials were mixed for two min. The wet granules were milled using an oscillating granulator, passed through mesh # 8 and transferred to a fluidized bed dryer (Model# F.G. 5). The granules dried at 60°C±5°C until the moisture content reached 1.00-2.00 %w/w and transferred to multi-directional mixer (Model#HD-15), where remaining excipients i.e., Aerosil 200 and Sodium stearyl fumarate were added and mixed for two minutes. Finally, blended granules were compressed on a compression machine at 15-20rpm.

Stage 2: Sitagliptin spray coating

The Sitagliptin immediate-release layer was coated using the direct spray coating method. The spray solution was prepared by dissolving sitagliptin and kaolin in purified water. The solution was set on stirring while HPMC, PEG and propyl gallate were added to the solution. The mixture was stirred to an obtained 500mL of homogeneous solution.

The metformin ER core tablets are loaded into a dust-free coating machine (Model#BGB5) and start rotation at 3-7rpm with exhaust temperature 40°C. Sitagliptin solution sprays through nozzle gun 1.0mm at flow rate 58-126ml/min. distance of spray gun maintains at 10-15 inches from tablet bed.

Stage 3: Film coating

Opadry Blue solution of 0.15g/ml concentration ware prepared in 500ml water as coating solution. The Sitagliptin-coated tablets were loaded in a dust-free coating machine and coated with the coating solution. The tablet appeared blue after film coating.

Physical characterization of blend and tablet

The physical characterization of metformin ER granules comprises the angle of repose, bulk density, tapped density, compressibility index, Hausner's ratio and other pre-compression parameters. Average weight, weight variation, length, width, thickness, hardness, surface area and friability were also studied after compression.

Kinetic analysis of drug release data

The mechanism of controlled drug release was investigated and evaluated utilizing model-independent methods (similarity factory), model-dependent methods (Zero order, First order, Higuchi, Korsmeyer-Peppar and Hixson-Crowell models) and statistical analysis.

In-vivo-In-vitro correlation (IVIVC) study

The in-vivo in-vitro correlation of the developed product against reference product was established using statistical analysis of comparative dissolution profile (CDP) data. The CDP of metformin was performed in 900ml phosphate buffer pH 6.8 medium up to 12 hours using apparatus USP I at 100rpm maintaining the temperature at 37±0.5°C. The sample was collected at 1, 2, 3, 4, 5, 6, 8, 10 and 12hours, while the dissolution profile for Sitagliptin was obtained in three different media i.e. 0.1N HCl, Acetate buffer pH 4.5 and Phosphate buffer pH 6.8. The sample was collected at 10, 15, 20 and 30min for sitagliptin and analyzed using HPLC. The percentage drug release for both active ingredients was compared with the reference tablet.

Model-dependent kinetic analysis

To study the drug release mechanism of the developed metformin ER tablet, the dissolution profile was analyzed on different kinetic models such as Zero order, First Order, Higuchi, Hixson-Crowell and Korsmeyer-Peppar model.

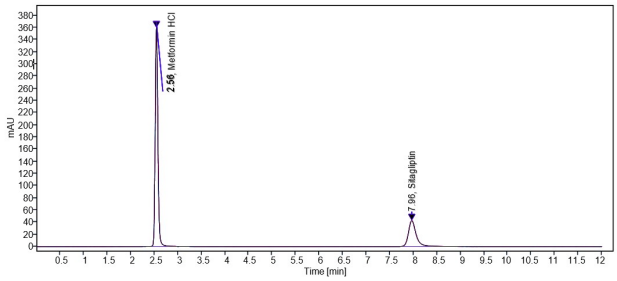


Fig. 1: Chromatogram of Metformin HCl and Sitagliptin Standard Solutions.

The time taken to release 25% (t_{25}), 50% (t_{50}), 75% (t_{75}), 80% (t_{80}) and 90% (t_{90}) of drug from different formulation was evaluated.

Statistical evaluation of drug product

The data were subjected to f-test and t-test for analyzing the statistical difference using Minitab software 19 and in all the cases, $P<0.05$ was considered as significant.

Stability studies

The stability studies performed at accelerated (40°C at 75% relative humidity) and real-time conditions (30°C at 65% relative humidity) for six months and assessed the physical parameters, drug content and *In Vitro* drug release at specified time points.

Drug-Excipient compatibility

The Drug-excipient compatibility study investigated the existence of interactions between active ingredients and the excipients and the subsequent impact of those interactions on the chemical and physical stability and the bioavailability of the product. Drug and excipient are mixed in ratio 1:1 and blend sample kept at accelerated conditions of 40±2°C, 75±5% relative humidity for one month. The physical and chemical analyses of the blend sample were studied using HPLC method.

STATISTICAL ANALYSIS

The drug release data for the developed formulations and the reference product was compared statistically using Minitab, LLC, software, version 19. The F-test evaluated the precision of data and then t-test was used to compare the two means. The data was evaluated at P=0.05.

RESULTS

The formulations developed for metformin ER blend are shown in table 1, whereas table 2 summarized the formulations developed for sitagliptin coating on the core tablet.

Evaluation of blend

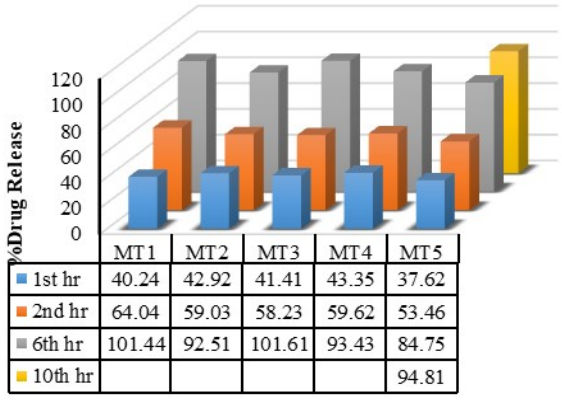
Six replicates were used to determine the physicochemical characteristics of the samples of the metformin ER blend and the results are shown in
Table .

Evaluation of core tablet

Ten replicates were used to evaluate the physical characteristics of Metformin ER core and the findings are reported in
Table ***4***.

Model-dependent kinetic analysis

Different sustained release polymers were used in the development of Metformin ER core trials. Dissolution profile of each trial was evaluated in phosphate media with a pH of 6.8 and the percentage of drug release for all trial formulations summarize in Fig. 2.



	MT1	MT2	MT3	MT4	MT5
1st hr	40.24	42.92	41.41	43.35	37.62
2nd hr	64.04	59.03	58.23	59.62	53.46
6th hr	101.44	92.51	101.61	93.43	84.75
10th hr					94.81

Fig. 2: % Drug release of Metformin HCl ER tablet formulated at different time points.

Development and dissolution profile of sitagliptin

Sitagliptin was coated over Metformin ER core (MT05) formulation by using different concentrations of Sitagliptin as well as increasing coating weight (ST1-ST9). *In Vitro* release was evaluated and summarized in Fig. 3.

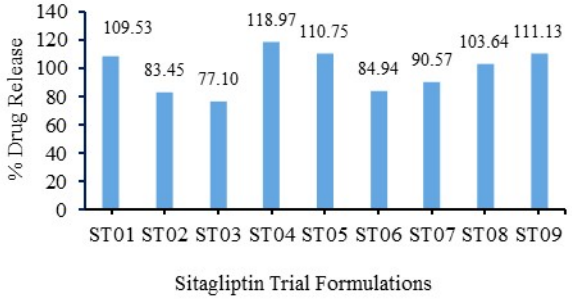


Fig. 3: % drug release of Sitagliptin Trial formulations

In-Vivo-In-Vitro-correlation (IVIVC)

The comparative dissolution profile (CDP) study was used to established in-vivo-in-vitro correlation (IVIVC). Similarity factor (F2) was calculated for both drugs against reference 50/500mg tablet

For metformin HCl

The comparative dissolution profile of Metformin HCl was studied in phosphate buffer pH 6.8 and average % drug release of reference product and test product at different time intervals were used to determine the similarity factor (f2). Results shown in Fig. 4 demonstrate how similar the produced product's release profile is to the reference product.

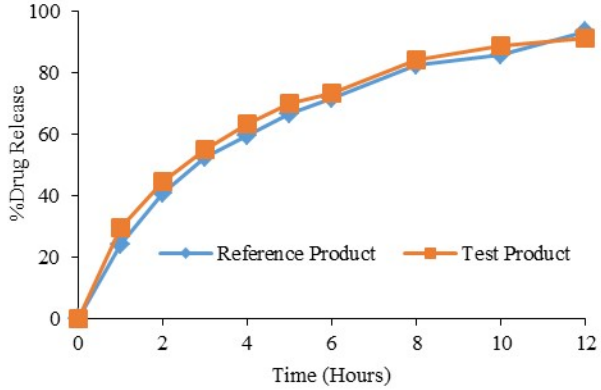


Fig. 4: Comparative dissolution profile of Metformin HCl in phosphate buffer pH 6.8.

For sitagliptin

For Sitagliptin similarity profile, average percentages drug release of reference and test product were evaluated at 10 minutes, 15 minutes, 20 minutes and 30 minutes in three different dissolution mediums i.e., 0.1N HCl pH 1.2, Acetate buffer pH 4.5 and Phosphate buffer pH 6.8. Results are listed in Fig. 5

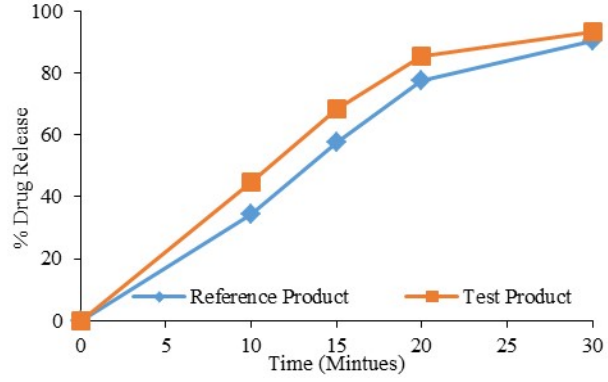


Fig. 5: Comparative dissolution profile for Sitagliptin in phosphate buffer pH 6.8.

Model-dependent kinetic analysis

To characterize the kinetics of drug release from the tablet matrix, release data were examined using several kinetics models and the regression coefficient values for the optimized formulation and the reference product are shown in tables 6 and 7.

Evaluation of stability study

Stability studied on finalize formulation i.e., MT5-ST8 were performed at the accelerated (40°C±2°C, 75%±5%RH) and real-time condition (30°C±2°C, 65%±5%RH) for 6 months. Physical parameters, drug content and in-vitro drug release were evaluated every 3 months. The data were shown in table 7.

Drug excipients compatibility study

Drug excipient performed at accelerated condition (40°C±2°C, 75%±5%RH) storage for one month for evaluation of physical and chemical properties of drug product. The results are summarized in table 8.

DISCUSSION

For the metformin ER core tablet, five formulations (MT1-MT5) were developed and physical and chemical characteristics were evaluated.

Different concentrations of Sitagliptin were coated over the optimal metformin ER core in nine design formulations (ST1-ST9).

Evaluation of blend

The angle of repose ranging between 25.2-28.7, Hausner ratio 1.09-1.18 and compressibility index 8.64-15.29 indicate a good flow of Metformin granules.

Evaluation of core tablet

The average weight of the tablet was 1020mg and weight variation of the compressed tablet were found less than 5% variation as per pharmacopeia guidelines. Thickness and hardness were found in the range of 6.432-6.490mm and 18.35-19.120kPa respectively. Friability obtained at 100 revolutions lied between 0.38-0.84% and complies with the Pharmacopeia limit of F<1%.

Metformin HCl dissolution profile

The % drug release of all trial formulations are summarized in Fig. 2. In the first trial formulation (MT1), Methocel K4M and Methocel K100 were used as SR polymers and obtained slightly higher release at the first hour, whereas second-hour release was within the proposed limit. However, at the 6thhour drug was released completely. Based on MT1 results, the quantity of SR polymers was redesigned, Methocel K4M increase 30-35%, Methocel K100 was reduced by approx. 40%, in the second trial (MT2). However, insignificant change was observed in % drug release compared to MT1.

In the 3rd trial (MT3), Tylopur 4000 SR and Tylopur 100 were used as SR polymers. The drug released 41.41% and 58.23% at 1 and 2 hours respectively while at the 6th hour, 98.66% drugs were released. As a result, combining Tylopur 4000SR with 100SR was not a good choice.

Table 1: Formulation of metformin hydrochloride (500mg dose) ER blend

Ingredients	Quantity (mg/tablet)					Role of ingredient
	MT1	MT2	MT3	MT4	MT5	
Metformin HCl	500	500	500	500	500	Active Substance
Povidone K-30	40	40	40	40	40	Binder
Methocel K4 M	153	200	-	-	255	SR polymer
Methocel K100 (LV)	132.6	81.5	-	-	122.4	SR polymer
Tylopur 4000 SR	-	-	205	-	-	SR polymer
Tylopur 100 SR	-	-	81.6	-	-	SR polymer
Tylopur 100000 SR	-	-		153	-	SR polymer
MCC 101	176.4	180.5	175.4	309	84.6	Diluent
Aerosil 200	10	10	10	10	10	Glidant
Sod. stearyl fumarate	8	8	8	8	8	Lubricant
Total Weight (mg)	1020	1020	1020	1020	1020	-

Table 2: Formulation of Sitagliptin (50mg dose) IR coating

Ingredients	Quantity (mg/tablet)									Role of ingredient
	ST1	ST2	ST3	ST4	ST5	ST6	ST7	ST8	ST9	
Sitagliptin	64.2	64.2	64.2	64.2	64.2	64.2	64.2	64.2	64.2	Active
Propyl Gallate	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	Antioxidant
HPMC	31.0	37.5	37.5	37.5	37.5	37.5	37.5	31.0	31.0	Coating agent
PEG 6000	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	Plasticizer
Kaolin	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	Opacifier
API Coating (mg)	130	122	122	150	140	122	128	135	140	-
% API excess	35	0	0	0	15	0	0	0	0	-
% Coat increase	0	0	0	23	0	0	5	10	15	-

Table 3: Physicochemical properties of metformin HCl ER granules (n=6)

Formulation	Bulk density (g/ml)	Tap. Density (g/ml)	Compressibility index (%)	Hausner ratio	Angle of repose (Degree)
	(Mean ± SD)	(Mean±SD)	(Mean±SD)	(Mean ± SD)	(Mean ± SD)
MT1	0.617±0.0005	0.693±0.0010	10.976±0.1151	1.123±0.0015	26.565±0.0021
MT2	0.588±0.0009	0.694±0.0017	15.294±0.3103	1.181±0.0043	25.263±0.0045
MT3	0.607±0.0006	0.682±0.0009	10.976±0.1728	1.123±0.0022	28.706±0.0042
MT4	0.628±0.0010	0.697±0.0013	10.000±0.2532	1.111±0.0031	27.096±0.0042
MT5	0.617±0.0022	0.676±0.0014	8.642±0.4133	1.095±0.0057	25.731±0.0008

Table 4: Physicochemical evaluation of metformin HCl ER tablet (n=10)

Formulation	Avg. Wt. (mg)	Length (mm)	Width (mm)	Thickness (mm)	Surface area (mm)2	Hardness (kPa)	Friability (%)
	(Mean ± SD)	(Mean ± SD)	(Mean±SD)	(Mean±SD)	(Mean ± SD)	(Mean ± SD)	
MT1	1024.38±11.91	20.336±0.025	9.932±0.031	6.472±0.035	201.977±0.696	19.120±0.868	0.50
MT2	1021.31±14.46	20.385±0.057	9.929±0.028	6.436±0.052	202.403±0.769	18.900±0.889	0.38
MT3	1018.15±10.22	20.329±0.023	9.937±0.026	6.432±0.066	202.009±0.546	18.790±0.963	0.84
MT4	1022.51±12.90	20.358±0.043	9.931±0.026	6.490±0.026	202.175±0.634	18.460±0.769	0.63
MT5	1018.99±11.20	20.339±0.029	9.920±0.023	6.487±0.034	202.763±0.519	18.350±0.778	0.58

Table 5: Kinetics parameters for selected kinetics models

Kinetics models		MT5-ST8	Ref. Tablet
Zero-order	k	10.237	9.888
	r^2	0.405	0.6
First Order	k	0.259	0.227
	r^2	0.95	0.978
Higuchi	k	29.047	27.827
	r^2	0.987	0.986
Hixson-Crowell	k	0.07	0.061
	r^2	0.863	0.92
Korsmeyer-Peppas	k	31.632	27.532
	r^2	0.992	0.979
	N	0.454	0.506

Table 6: Statistical comparison of drug release between developed formulation and reference product

Time (hr)	% Drug Release		t-Value	P-Value
	Ref	MT5-ST8		
1	24.01	29.56	7.79	0.000
2	40.64	44.48	5.82	0.000
3	52.44	55.02	2.34	0.029
4	60.05	63.17	3.41	0.002
5	66.90	69.86	2.91	0.008
6	72.18	73.24	0.45	0.654
8	82.57	84.23	1.19	0.247
10	85.84	88.55	1.47	0.155
12	91.18	93.44	-0.94	0.360

Table 7: Stability studies of MT5-ST8 for sitagliptin (STG.) and metformin (MET.) drug content and drug release

	Real-Time		Accelerated	
	3 mos.	6 mos.	3 mos.	6 mos.
% Drug Content				
STG.	100.21%	99.20%	98.11%	101.67%
MET.	101.71%	99.90%	97.48%	101.61%
% Drug Release				
STG.	99.39%	99.36%	96.42%	98.67%
MET.1hr	29.35%	28.27%	29.84%	28.39%
MET.2hr	54.46%	44.40%	52.19%	45.91%
MET.6hr	80.24%	80.09%	78.99%	81.49%
MET. 10hr	93.22%	93.97%	91.63%	94.28%

Table 8: Drug-Excipients Compatibility study for metformin HCl (MET.) and sitagliptin (STG.)

Excipients	% Drug Content	
	MET.	STG.
Povidone	100.04%	100.33%
Hypromellose	100.29%	99.94%
MCC*	98.76%	100.74%
Aerosil 200	100.72%	101.71%
SCF†	101.32%	102.20%
Propyl Gallate	99.45%	100.54%
HPMC	100.64%	100.30%
PEG 6000	100.30%	101.54%
Titanium Dioxide	98.86%	99.14%
Talc	99.73%	102.08%
Dye	99.46%	103.59%
Methocel K4M	98.68%	101.38%

*MCC Microcrystalline Cellulose, †SCF. Sodium Stearyl Fumarate

Tylopur 100000SR polymer was chosen instead of Tylopur 4000 SR and Tylopur 100 SR in the fourth (4^{th}) trial formulation (MT4). Almost similar release profiles compared to MT3 were obtained. A combination of Tylopur 4000SR and 100SR and Tylopur 100000SR alone was not a good choice for SR Metformin tablet.

In the 5^{th} trial (MT5), the amounts of the Methocel K4M increase by approx. 65% while Methocel K100 decrease around 5-7% compare to MT1. Dissolution profiles were found within the proposed limits at each time interval, therefore, MT5 formulation was considered as a comparable SR product with innovator and further study was conducted on MT5 formulation.

Sitagliptin dissolution profile

The % drug release of sitagliptin in the developed formulations is summarized in Fig. 3. In the 1^{st} Sitagliptin trial (ST1) 35% excess API was taken by considering loss in the coating process, 109.53% dissolution release

obtained. In the 2nd and 3rd Sitagliptin trial (ST2 and ST3), no excess API was taken and dissolution results were obtained between 77%-84%. Based on ST2 and ST3 formulation results, in the 4th Sitagliptin trial (ST4), 23% excess of API was coated by weight over Metformin tablet which gives unexpected results i.e 118.97%. In trial formulation (ST5) 15% of excess quantity of Sitagliptin was taken and %drug release was obtained 110%. In new formulation design (ST6 to ST9), concentration of Sitagliptin varied from 0% to 15% with 5% increment by increasing the coating weight. Average dissolution of each formulation obtained 84.94%, 90.57%, 103.64% and 111.13% in 30min for ST6, ST7, ST8 and ST9 receptivity.

The drug release increased with the increase in API coating. The correlation coefficient between % coating increase and % drug release is 0.9782. The 15% coating increase yielded 111.13% drug release whereas the required % drug release (i.e. more than 80% in 30 minutes) and % drug content (i.e 90%-110%) was achieved by a 10% coating increase. Hence, the % increase in the coating was set to 10% in the final formulation (ST8).

In-Vivo-In-Vitro-correlation of metformin HCl

Fig. 4 shows the comparison of *In-Vivo In-Vitro* correlation profile of MT5-ST8 formulation and the reference product. The correlations were determined by similarity factor (f2) as per WHO guideline. F2 Value obtained from data was 73.77, which confirms that the release profiles of the test product and reference product are similar

In-Vivo-In-Vitro-correlation of sitagliptin

The IVIVC profiles for sitagliptin release from MT5-ST8 and reference product are shown in Fig. 5 The similarity factor of Sitagliptin was calculated in three different media and was found to be 54.71 in 0.1N HCl pH 1.2 and 51.93 in phosphate pH 6.8, respectively, while more than 85% of the product was released in 15 minutes in acetate buffer pH 4.5, demonstrating that the profile of the test product was similar to the reference product in all three media.

Model-dependent kinetic analysis

The data on release kinetics, table 5, indicate that the formulations follow first-order kinetics, while Higuchi's model also exhibits a high degree of linearity (r^2=0.97-1.00). To confirm the diffusion mechanism, the data were fitted into Korsmeyer-Peppas equation. The formulations showed good linearity (r^2=0.97-1.00), with slope (n) between 0.385 and 0.506. The drug release from different formulations confirmed the ER behavior of the polymers.

The F-test indicate that the replicate data for the test and reference products has statistically similar variance at each time point hence can be pooled at P=0.05. Table 6 shows the comparison of average metformin release rate of the reference and test products, using t-test, revealed that the release rate was statistically different for the first 5 hours and the test formulations release rates were better than the reference product. However, for further time intervals the drug release rate was statistically similar for both products.

Evaluation of stability study

The data obtained for stability studies shown in depicted no significant changes in the physical and chemical properties of the drug product after 6 months of stability and considered as stable.

Drug excipients compatibility study

Drug excipient performed at accelerated condition (40°C±2°C, 75%±5%RH) storage for one month showed no evidence of possible interaction between the drug and the excipients. The physical appearance of the blended powder, i.e. the mixture of drug and excipient, did not change significantly, and the chemical test, i.e. Assay content did not degrade considerably.

CONCLUSION

The study developed several formulations for coating sitagliptin immediate release (IR) layer over metformin HCl extended release (ER) core and compared them with reference product 50/500mg tablet. Metformin HCl tablets were formulated utilizing a variety of polymers. Sitagliptin immediate release coating was produced using variable API proportions along with propyl Gallate as antioxidant and kaolin as suspending agent. The study concluded that the assessed parameters produced statistically similar result for the developed and the reference product. The sitagliptin coating provides the required dose rapidly, while the Metformin ER core may provide up to 12 hours of drug. The kinetics study showed that the developed product and the reference product followed first-order kinetics as well as Higuchi's model. The Korsmeyer-Peppas model suggested the anomalous diffusion mechanism-coupled diffusion and erosion might be the mechanism for the drug release. The anomalous mechanism is suggested to decrease the dose-dependent side effects associated with repeated administration of immediate release metformin HCl tablets. The study, therefore, concludes that the MT5-ST8 formulation is suitable for the treatment of diabetes and is interchangeable with the reference product.

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