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Original Article

Preparation and *in vitro* studies of fixed-dose tablet combination of repaglinide and metformin

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ABSTRACT

Background and Aims: The study aimed to design a Fixed-dose tablet formulation of Metformine and Repaglinide.
Methods: Wet granulation method was used to prepare tablet formulations. Characterization studies and dissolution studies were performed.
Results: A stable formulation was developed according to the requirements of the pharmacopoeia criteria. This new formulsation dissolution results showed that Repaglinide and Metformin HCl dissolved more than 85% from film tablets at 15 minutes.
Conclusion: Thus, an alternative product to the market product was developed.

Keywords: Fixed-Dose Tablet, Metformin, Repaglinide

INTRODUCTION

Life expectancy is an average statistical data that indicates how long a newborn will live, assuming that death rates remain constant from the moment it is born. It is rapidly increasing worldwide thanks to factors such as the advancement of technology, development in new and effective treatment methods, improving the quality of care services, and facilitating individuals' access to care services. Since individuals' daily lives are directly affected by the socioeconomic status of the society they live in and the living standards offered by that country, life expectancy is calculated specifically for each country. The life expectancy of western countries is higher all around the world. As life expectancy increases, the prevalence of non-communicable chronic diseases (NCDs) such as cardiovascular, metabolic, and respiratory diseases may increase. Also, the changes in eating habits and the spread of fast-food-style nutrition throughout the world and the widespread of a sedentary lifestyle have a negative effect on individuals' metabolism. Thus, the diseases that are expected to be seen in the elderly population can be encountered at a younger age, even in the adolescent period.

Diabetes Mellitus (DM) is a metabolic disorder that causes hyperglycemia with impaired insulin production and/or function (Maffi & Secchi, 2017; Spampinato, Caruso, De Pasquale, Sortino, & Merlo, 2020). The American Diabetes Association (ADA) classified DM into two primary classes, types 1 and 2 (American Diabetes Association, 2015). In type1 diabetes, insulin insufficiency occurs due to the destruction of the β-cells of the pancreas, where insulin is secreted. Type 2 diabetes is characterized by insulin resistance due to progressive insulin secretion defects. Type 2 DM usually occurs concerning age (Longo et al., 2019). A rapid

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increase in its prevalence was observed with prolonged life expectancy. The World Health Organization (WHO) reported that more than 425 million people worldwide live with diabetes, and more than 1.6 million deaths are directly related to diabetes (Rachdaoui, 2020; World Health Organization, 2020). Also, contrary to popular belief, Type 2 DM can be seen during childhood and adolescence (American Diabetes Association, 2000). Obesity, mainly due to changes in dietary and lifestyle habits, increased the prevalence of type 2 DM among children as well as adults. DM may destroy the vascular and neurological system due to hyperglycemia (Malone, 2016). Thus, different cases of NCDs are also seen in DM patients who cannot be treated efficiently. Problems in controlling the DM and accompanying other diseases seriously reduce the quality of life of the patient and his/her family and increase the costs of hospitalization (Riddle & Herman, 2018; Young-Hyman et al., 2016). One of the approaches developed in the treatment of Type 2 DM is to combine drugs to eliminate all the problems (Massi-Benedetti & Orsini-Federici, 2008).

Combine drug therapy is the combined usage of active pharmaceutical ingredient (API) that has successful results with different action mechanisms in the treatment of a single disease. If a more effective and/or faster treatment process is desired, combined therapy can be preferred. Studies have shown that combined therapy with additional APIs in the treatment of chronic diseases is five times effective than increasing the dose of the drug used in single therapy by two times (Tsioufis & Thomopoulos, 2017). In cases where hyperglycemia can not be controlled in type 2 DM patients with a single treatment agent, combined therapy is started (Massi-Benedetti & Orsini-Federici, 2008). Considering the damage caused by hyperglycemia on the vascular and neural system, the combined treatment approach seems to be a clinical requirement rather than an option. Despite these significant advantages, combine treatment has two main disadvantages. One of these disadvantages is since the increasing number of drugs that the patient will take in one time, the patient's compliance may decrease. Increasing health care costs is the other one. To overcome this situation, fixed-dose combinations (FDCs) have been developed. FDCs are pharmaceutical dosage forms prepared by combining two or more APIs in a single formulation (Gautam & Saha, 2008; Godman, McCabe, & D Leong, 2020; Tangalos & Zarowitz, 2005). Owing to FDCs, patient compliance may increase as it will use fewer drugs at one time and achieve a more therapeutic effect. Also, since the therapeutic effect will be increased, the dose of each APIs can be reduced. Thus systemic side effects can be reduced.

Metformin, a biguanide drug, is a first option in the treatment of type 2 DM patients who cannot be controlled with lifestyle changes (Lefèbvre & Scheen, 1992; Sanchez-Rangel & Inzucchi, 2017). It is used safely in Europe since 1957 and in America since 1995 (Pernicova & Korbonits, 2014). It increases the effect of insulin in the liver and decreases hepatic glucose production (Natali & Ferrannini, 2006). Although it has little impact on the absorption of glucose in the gastrointestinal tract, it can delay the absorption of glucose (Czyzyk, Tawecki, Sadowski, Ponikowska, & Szczepanik, 1968; Pernicova & Korbonits, 2014). The most significant advantage of metformin is that it does not cause hypoglycemia while reducing the blood glucose level (Nasri & Rafieian-Kopaei, 2014). As a medicine that has been used for years, the therapeutic safety is quite high. It is indicated for use in gestational diabetes, polycystic ovarian syndrome, metabolic syndrome or prediabetes period, as well as type 2 DM (Cicero, Tartagni, & Ertek, 2012; Hostalek, Gwilt, & Hildemann, 2015). Metformin is used single or combined with other antidiabetes agents in the treatment of type 2 DM (Sanchez-Rangel & Inzucchi, 2017).

Repaglinide, a derivative of carbamoylbenzoic acid, enhances insulin secretion from pancreatic β-cells by closing ATP-sensitive potassium (KATP) channels in the plasma membrane (Johansen & Birkeland, 2007; Scott, 2012). It has a short duration of action (Abbink, van der Wal, Sweep, Smits, & Tack, 2004). It can be used primarily in type 2 DM patients with renal insufficiency since the kidneys do not perform its metabolism and elimination (Hasslacher, 2003). There are also studies showing that pharmacokinetic data in individuals with renal impairment can be safely used by kidney patients, although some studies have demonstrated minor differences to healthy individuals (Marbury, 2000; Schumacher et al., 2001; Scott, 2012).

The combined therapy of type 2 DM with repaglinide and metformin was approved in the USA in 1997 and in Europe in 1998. Since repaglinide, which provides insulin secretion, has a short-term effect, when used with metformin, the secreted insulin has the highest possible effect. Also, the fact that this combination does not have a negative effect on hepatic β-cells provides safe control of hyperglycemia for a long time (Kawamori et al., 2014).

In this study, stable fixed-dose combinations of Repaglinide and Metformin HCl with rapid drug release profiles were developed.

MATERIALS AND METHODS

Materials

Repaglinide (Polpharma, Poland), Metformin HCl (Aarti Drugs Limited, India), Povidone (PVP K25) (BASF), Microcrystalline Cellulose Types 101 and 102 (Vivapur 101 and Vivapur 102) (JRS Pharma), Sorbitol (Roquette), Polyethylene Glycol 6000 (Magrogol 6000) (Clariant), Poloxamer 188 (BASF), Meglumin (Merck), Polacriline potassium (Amberlite IRP88) (DOW), Ethanol (JT Baker), Magnesium stearate (FACI SpA), Opadry Pink 03B240027 (Colorcon). All other chemicals were analytical grade.

Methods

Active ingredients and excipients compatibility studies

Excipients that are included in the composition of repaglinide / metformin HCl 2 mg / 500 mg film tablet are defined in international pharmacopoeias. Also, in the literature for the reference product PrandiMet (repaglinide/metformin HCl) Tablet 2 mg / 500 mg, the excipients found in the content of the product were identified and mostly the same excipients were used in the developed formulation. To decide the

appropriate excipients compatibility tests were performed. The samples were stored for 30 days at different ratios and in different environments (2-8°C, 25°C±2°C; 60%±5% RH and 40°C±2°C; 75%±5% RH) and their compatibilities were examined after 30 days. DSC thermal analysis methodology was used to evaluate the compatibility. The tests were performed by using approximately 5 mg sample in a hermetic aluminum sample holder and heated from 35°C to 350°C at a heating rate of 10°C/min, an empty pan was used as the reference, the details of the studies are given in Table 1.

Preformulation studies

Preformulation studies were carried out to determine the quantitative composition of the formulation of the film tablets to be prepared. As a result of these studies, the physical parameters of the core tablets (hardness, disintegration, friability) were evaluated and film coating of the formulations closest to the physical parameters of the reference product was prepared, and the dissolution tests of this formulations were performed and compared with the reference product.

Table 1. Active ingredients and excipients compatibility studies details.

No	Mixture	Mixture ratio	2-8°C 30 day	25°C±2°C, 60%±5% RH 30 day		40°C±2°C, 75%±5% RH 30 day	
			*P	*P	**UP	*P	**UP
1	Metformin HCl	-	+	+	+	+	+
2	Repaglinide	-	+	+	+	+	+
3	Metformin HCl+ Repaglinide	20:1	+	+	+	+	+
4	(Metformin HCl+ Repaglinide)***+ PVP K25	10:1	+	+	+	+	+
5	(Metformin HCl+ Repaglinide)***+Poloxamer 188	20:1	+	+	+	+	+
6	(Metformin HCl+ Repaglinide)***+ Meglumin	20:1	+	+	+	+	+
7	(Metformin HCl+ Repaglinide)***+ MCC tip 101	5:1	+	+	+	+	+
8	(Metformin HCl+ Repaglinide)***+ Sorbitol	10:1	+	+	+	+	+
9	(Metformin HCl+ Repaglinide)***+ Magrogol 6000	20:1	+	+	+	+	+
10	(Metformin HCl+ Repaglinide)***+ Polakrilin potasyum (Amberlite IRP88)	10:1	+	+	+	+	+
11	(Metformin HCl+ Repaglinide)***+ Akdisol	10:1	+	+	+	+	+
12	(Metformin HCl+ Repaglinide)***+ Starch 1500	10:1	+	+	+	+	+
13	(Metformin HCl+ Repaglinide)***+ Magnezyum stearat	20:1	+	+	+	+	+
14	(Metformin HCl+ Repaglinide)***+ Opadry II 85F240049 Pink	20:1	+	+	+	+	+
15	(Metformin HCl+ Repaglinide)***+ Opadry II 85F220124 Yellow	20:1	+	+	+	+	+
16	(Metformin HCl+ Repaglinide)***+ Opadry 03B240027 Pink	20:1	+	+	+	+	+
17	(Metformin HCl+ Repaglinid)***+ Opadry 03B220042 Yellow	20:1	+	+	+	+	+

*Packaged; **Unpackaged; ***The Metformin HCl + Repaglinide mixture was prepared in a 20:1 ratio.

Pilot scale batch production

Pilot productions were prepared by using the wet granulation method. Firstly, Repaglinide granule mixture and Metformin HCl granule mixture were prepared and dried in the oven at 50°C until to obtain well-dried granules to a loss of drying value is less than 2%. Dried granules were blended with external granular phase excipients. Three series of pilot production was carried out by using the unit formula and the production method determined based on the results of the *in vitro* dissolution test performed at zero time and after waiting for one month at 40ºC±2ºC; 75%±5% RH of the pre-formulation studies.

The tablet serial size prepared for pilot production was 100,000 and serial numbers were P001, P002 and P0003, respectively.

Physicochemical properties and dissolution tests

Physical tests (weight variation, hardness, diameter, thickness, water content), assay, content uniformity and dissolution tests were performed on the tablets prepared in the preformulation studies on the tablets in the pilot product series.

Tablet weight variation tests were performed according to the EP 6 section 2.9.5. Uniformity of Mass of Single-Dose (European Pharmacopeia, 2008). Tweenty tablets were taken and weighed individually using digital analytical balance (Sartorius BP 3105, Germany). The results were recorded.

Tablet hardness test was performed by using Erweka hardness test equipment (D63150, Germany). 10 tablets were tested and the avarage hardness value (N) was recorded.

Disintegration test was performed according to USP <701> Disintegration test (2019). 6 tablets were checked (Erweka ZT304, Germany) and their disinteration times (min.) were recorded.

Friability % test was performed using Erweka TAR 220 (Germany) friability tester in accordance with USP <1216> Tablet Friability (2019). Weight loss % was calculated.

The analysis of Metformin HCl and Repaglinide were performed by using different system. To analyse Metformin HCl, HPLC system was used and the system was operated at 40°C at a flow rate of 1 mL/min and 240 nm. The injection volume was 10 µL. To analyse Repaglinide, UPLC system was used and the system was operated at 25°C at a flow rate of 0.3 mL/min and 240 nm. The injection volume was 10 µL.

The Repaglinide/Metformine HCl tablet dissolution test method was performed according to the FDA dissolution method (FDA, 2009). USP apparatus II with the paddle method was used at 37°C±0.5 at 50 rpm and the medium was pH 5.0 citric acid/phosphate buffer. The samples were taken from the dissolution medium at the determined time intervals 5, 10, 15, 20, 30, 45 and 60 minutes.

The dissolution rate test was performed on the film tablets obtained as a result of pilot productions and the reference tablet (PrandiMet Tablets 2 mg / 500 mg) in the pH 5.0 citric acid/phosphate buffer. *In vitro* dissolution tests were performed to the pilot production series and to the reference product at three different pHs (1.2, 4.5 and 6.8) of the gastrointestinal tract recommended by the EMA guidelines and f2 similarity factors were calculated. An f2 value greater than 50 to be taken here shows the similarity between the two formulations (EMA, 2010).

Stability studies

The prepared tablets were put in the final packing and kept for stability studies. The stability studies were carried out in accordance with the storage conditions specified in the ICH Q1A (R2) guide of the three pilot production series produced. According to the ICH Q1A (R2) (2003) guidelines (ICH, 2003), long-term stability operating conditions are 25°C±2°C / 60%±5% RH and accelerated stability conditions are 40°C±2°C / 75%±5% RH. During stability, at different time intervals, the tablets were tested for its physicochemical parameters which include appearance, weight average, hardness, assay, dissolution and impurities.

RESULTS AND DISCUSSION

Active ingredients and excipients compatibility test results

It was seen that all the samples in different storage conditions (2-8°C, 25°C±2°C; 60%±5% RH and 40°C±2°C / 75%±5% RH) of the mixtures prepared with all excipients were found suitable. There was any inconsistency in the graphics of the studies. The DSC graphic showing 10:1 active ingredients (Metformin HCl and Repaglinide) / Starch 1500 mixtures is given in Figure 1.

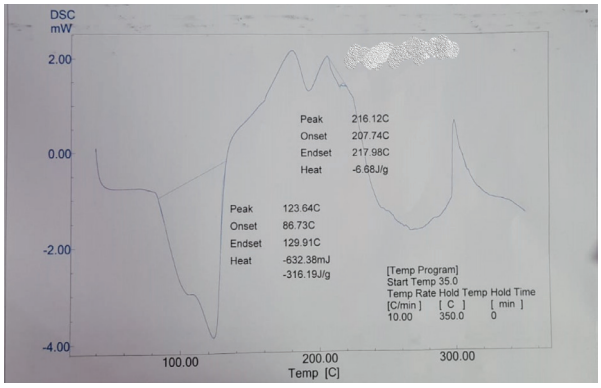

Figure 1. Active ingredients (Metformin HCl and Repaglinide):Starch 1500 mixture (10:1) DSC graphic under 25°C±2°C / 60%±5% RH condition after 30 days.

Preformulation studies

Preformulation studies were performed, the Components of D001 and D002 formulations and the detected quantitative amounts are given in Tables 2 and 3.

The unit formula of the optimum formula determined as a result of the tests made on the tablets obtained by the preformulation studies is given in Table 4.

Physicochemical properties and dissolution tests

Physicochemical test results of the formulations D001 and D002 prepared in the preformulation studies are given in the

Table 2. Unit formula of Repaglinide / Metformin HCl 2 mg / 500 mg film tablets coded D001.

Active Ingredient and excipients	Unit formula (mg/tablet)
Repaglinide Granule	
Repaglinide	2.00
Povidone (PVP K25)	0.572
Poloksamer 188	0.572
Meglumine	1.00
Microcrystalline cellulose 101 (Vivapur 101)	44.00
Deionized water	qs.
Metformin HCl Granule	
Metformin HCl	500.00
Povidone (PVP K25)	20.00
Sorbitol	10.00
Polyethylene glycol (Magrogol 6000)	5.00
Deionized water	qs.
External Phase	
Microcrystalline cellulose 112 (Vivapur 112)	20.00
Polacrilin potassium (Amberlite IRP88)	18.76
Magnesium stearate	3.10
Core tablet weight	625.00
Opadry 3B240027 Pink	15.00
Deionized water	135.00
Film tablet weight	640.00

Table 3. Unit formula of Repaglinide / Metformin HCl 2 mg / 500 mg film tablets coded D002.

Active Ingredient and excipients	Unit formula (mg/tablet)
Internal Phase	
Repaglinide	2.00
Metformin HCl	500.00
Poloksamer 188	0.572
Meglumine	1.00
Microcrystalline cellulose 101 (Vivapur 101)	44.00
Povidone (PVP K25)	20.572
Sorbitol	10.00
Polyethylene glycol (Magrogol 6000)	5.00
Ethanol	qs.
Deionized water	qs.
External Phase	
Microcrystalline cellulose 102 (Vivapur 112)	20.00
Polacrilin potassium (Amberlite IRP88)	18.76
Magnesium stearate	3.10
Core tablet weight	625.00
Opadry 3B240027 Pink	15.00
Deionized water	135.00
Film tablet weight	**640.00**

Table 4. Unit formula of the optimised formulation.

Active Ingredient and excipients	Unit formula (mg/tablet)
Internal Phase	
Repaglinide	2.00
Metformin HCl	500.00
Poloksamer 188	0.572
Meglumine	1.00
Microcrystalline cellulose 101 (Vivapur 101)	44.00
Povidone (PVP K25)	20.572
Sorbitol	10.00
Polyethylene glycol (Magrogol 6000)	5.00
Ethanol	qs.
Deionized water	qs.
External Phase	
Microcrystalline cellulose 102 (Vivapur 112)	20.00
Polacrilin potassium (Amberlite IRP88)	18.76
Magnesium stearate	3.10
Core tablet weight	625.00
Opadry 3B240027 Pink	15.00
Deionized water	135.00
Film tablet weight	**640.00**

Table 5. Physicochemical test results of formulations D001 and D002.

Tests	D001	D002
Appearance	White or whitish oblong, biconvex tablet White or whitish oblong, biconvex tablet	White or whitish oblong, biconvex tablet White or whitish oblong, biconvex tablet
Average tablet weight (mg)	623.5	624.2
Hardness (N)	130	120
Disintegration time (min.)	4	2
Friability (%)	0.1	0.2
Loss of Water Content (%)	2.28	2.11

Table 5. There was no significant difference in the test results obtained from the D001 and D002 formulations.

Consequently, the calibration curves used to analyze the concentration of Metformin HCl and Repaglinide showed good linear relationship over the concentration range 139,71 -399,385 µg/mL and 1,80 – 8,03 µg/mL. The correlation coefficient values were above then >0,99 and precise (intra- and inter-day variation <2%) and accurate (mean recovery>98 %).

The LOD and LOQ values of Metformin HCl were 18,67 µg/mL and 56.58 µg/mL, respectively. And, The LOD and LOQ values of Repaglinide were 0,80 and 1,68 µg/mL, respectively.

The findings of the dissolution study of pilot production tablets and commercial product in pH 5.0 environment are given in Figure 2. At the end of 15 minutes, it was observed that both repaglinide and metformin dissolved above 85% in all formulations.

The dissolution data's of pilot production series (P001 and P002) and commercial product in different pH's 1.2, 4.5 and 6.8 are given in Figures 3, 4 and 5, respectively. As a result of dissolution studies conducted in different environments, it was observed that the active substances dissolved above 85% after 15 minutes.

When *in vitro* dissolution rate test data were examined, it was determined that the amount of active substances released from

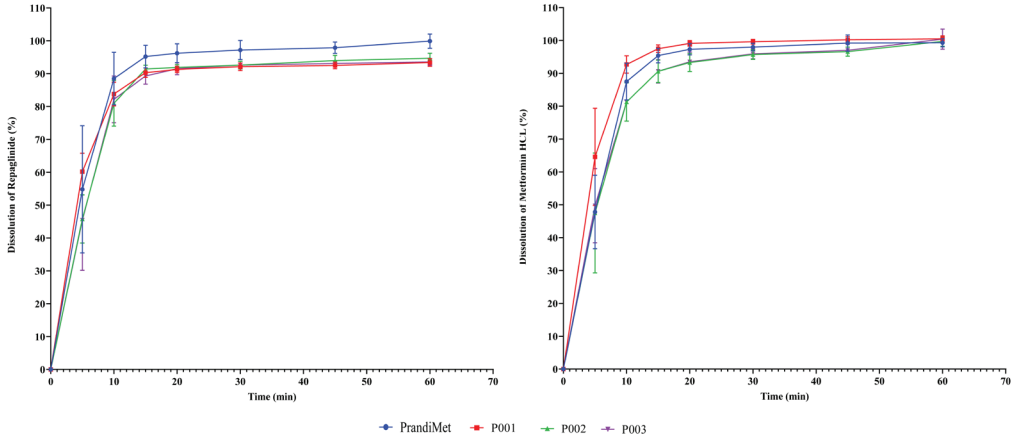

Figure 2. Pilot production formulations and the commercial product dissolution study results in pH 5.0.

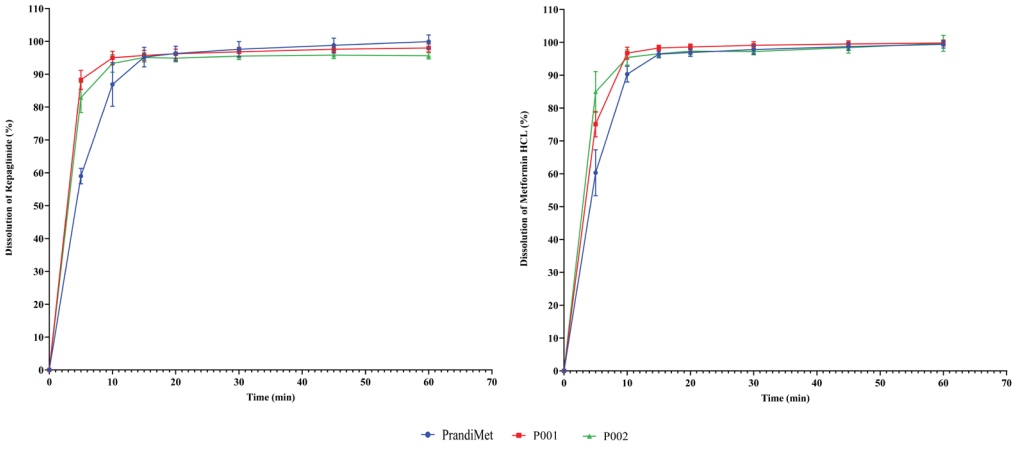

Figure 3. The dissolution profile of the commercial product and pilot production series (P001 and P002) in pH 1.2 buffer.

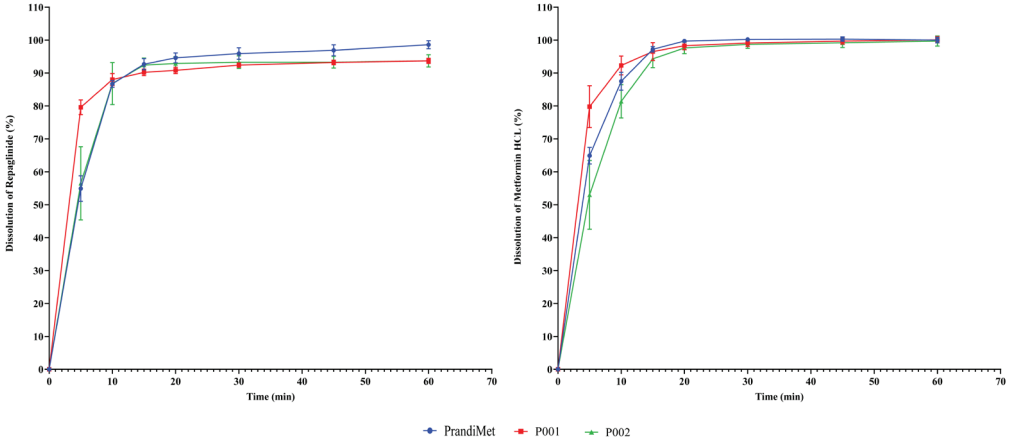

Figure 4. The dissolution profile of the commercial product and pilot production series (P001 and P002) in pH 4.5 buffer.

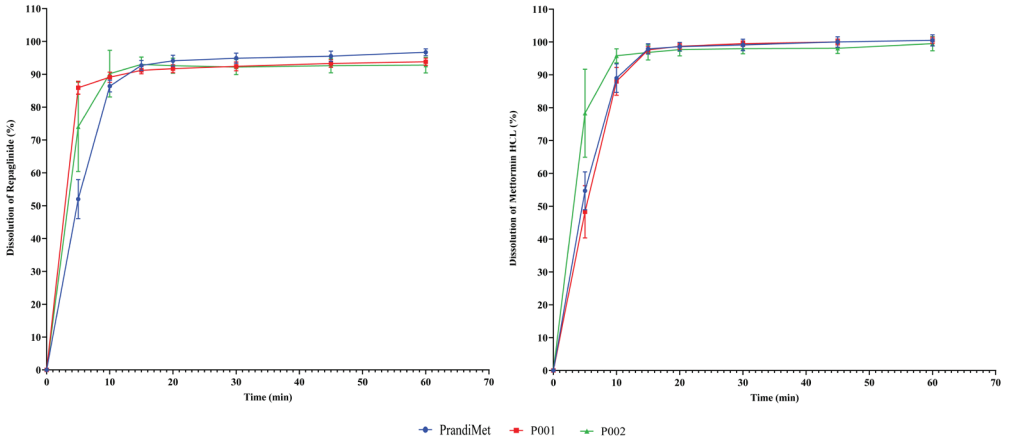

Figure 5. The dissolution profile of the commercial product and pilot production series (P001 and P002) in pH 6.8 buffer.

tablets in all 3 environments was more than 85% in 15 minutes. For this reason, it was found that they are equivalent according to EMA criteria and there is no need to perform f2 similarity test.

Stability studies

The stability studies are very important to provide the evidence about the quality of the tablet formulation that changes with time through environmental aspects. Prepared tablets were kept in stability cabines for 6 months for acceleretad stability studies (40°C±2°C / 75%±5% RH) and 24 months for long term stability studies (25°C±2°C / 60%±5% RH). The samples analyzed at the end. As a result of the findings of all physicochemical tests, assay analysis and impurity analysis, both long

Table 6. Stability test results of pilot production tablets.

Spesifications	P001		P002	
	Long Term* (24 Month)	**Accelerated** (6 Month)**	**Long Term* (24 Month)**	**Accelerated** (6 Month)**
Appereance	Suitable	Suitable	Suitable	Suitable
Average weight 640.0 mg ±% 5.0 (608.0 mg – 672.0 mg)	638.6 mg	640.5 mg	638.3 mg	644.98 mg
Hardness (for information)	169 N	158 N	167 N	102 N
Disintegration (max. 30 min.)	3 min.	3 min.	3 min.	3 min.
Water content (KF) (Max. 6 %)	2.04%	1.78%	2.01%	2.50%
Assay (HPLC)				
Metformin HCl 500.0 mg/tb (%90-%105) (450.0-525.0) mg/tb	497.9 mg/tb (99.6%)	486.3 mg/tb (97.3%)	497.3 mg/tb (99.5%)	488.4 mg/tb (97.7%)
Repaglinide 2.00 mg/tb (%90-%105) (1.80-2.10) mg/tb	1.98 mg/tb (99.0%)	1.97 mg/tb (98.5%)	1.99 mg/tb (99.5%)	1.92 mg/tb (96.0%)
Dissolution				
Metformin HCl Min 85 % (30. min) (Q=80)	98.4%	98.5%	95.9%	94.3%
Repaglinide Min 75 % (30. min) (Q=70)	92.9%	92.2%	92.7%	89.0%
Impruties				
Metformin HCl				
Unknown imp. % 0.1 max.	0.03%	0.01%	0.03%	0.03%
Repaglinide				
Unknown imp. % 0.2 max.	0.06%	0.13%	0.08%	0.04%
Related imp. A % 0.5 max.	N.D.	N.D.	N.D.	N.D.
Related imp. C % 0.5 max.	0.21%	N.D.	0.20%	0.01%
Total imp. % 1.0 max.	0.42%	0.32%	0.40%	0.14%

*Long term: **25°C±2°C; 60%±5% RH;** **Accelertated: **40°C±2°C; 75%±5% RH**; ND: Not dedected

and accelerated stability findings were found within the limit. The details of the analysis are given in Table 6.

CONCLUSION

The tablet formulation containing Fixed-Dose Metformin and Repaglinide was developed and compared to the commercial product available in the market. The characterization studies and the dissolution rate tests were carried out and compared with the commercial product. In dissolution studies at pH 1.2, 4.5 and 6.8, over 85% data were obtained in 15 minutes. It was seen that it could be an alternative product to market preparation.

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