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RESEARCH ARTICLE

FORMULATION DEVELOPMENT AND EVALUATION OF ANTI-DIABETIC DRUGS

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ABSTRACT

The purpose of this research is to prepare metformin HCL500mg and vildagliptin 50mg immediate release tablets by wet granulation method. In order to obtain the best optimized product six different formulation were developed. disintegrants and lubricants using crosscarmellose sodium as super disintegrating agent . thickness, hardness, friability, disintegration time, in-vitro drug release and pharmaceutical assay were studied as response variable. the formulation F6 was selected as optimized formulation . the dissolution profile and the stability study of the formulated product also complies with ICH guidelines in the initial two months, optimization has proven an effective tool in product development.

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INTRODUCTION

India is deemed to be the world capital of diabetes. Being one of the countries in the South East Asian Region, India has72.9million of diabetic population inIndiain2017, it is close to reach the alarming mark of 69.9 million by 2025 and 80 million by 2030 (The International Diabetes Federation (IDF)). The CPR (Crude prevalence rate) is 9 percent in urban areas,3 percent in rural areas, the prevalence is approximately of the total population in India (Aris, 2015). Indian Heart Association says nearly 1 million Indians were died due to diabetes mellitus every year (Cavan, 2015).It is reported in IDF that diabetes occupies 12% of global health expenditure, corresponding to approximately USD 673 billion in 2015, and it is expected to reach USD 802 billion in 2040 (Cavan, 2015). As the primary clinical finding in diabetes, chronic hyperglycemia poses a high potential in incurring long-term malfunction or failure inorgans such aseyes, heart, kidneys, nerves and blood vessels (Sattley, 2015). Diabetes can be classified into different types depending on the pathogenesis and clinical manifestations at the time of diagnosis.

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Type 1 diabetes mellitus (T1DM) /insulin-dependent diabetes mellitus/ idiopathic diabetes is attributed to the destruction of insulin producing beta cells in the islets of Langerhans , leading to absolute deficiency of insulin (Lakhtakia, 2013). Type 2 diabetes mellitus (T2DM)/non-insulin dependent diabetes mellitus is attributed to the irregular conformations of receptors/ destructions or insufficient receptors for insulin (Association, 2014). Therisk of microvascular and macrovascular complications in T2DM is more than T1DM.T1DM requiresadequate insulin supply through insulin injections daily, while T2DM is treated with anti-hyperglycemic agents with first line drugs (Perumal, 2013). Non-Insulin Dependent Diabetes Mellitus(NIDDM) is a chronic disease that needs a combination of anti-hyperglycemic agents to achieve glycaemia goals by different mechanisms of action (Li Ching, 2020). The wide spectra drugs such as metformin and sulphonyl urea (SU) fails to effectiveglycaemic control alone. It lend a way to find an effective third anti-hyperglycaemicagent. Metformin (class of biguanides), the first-line drug used for the treatment of type 2 diabetes mellitus. Metformin works by reducing the amount of glucose (sugar) made by your liver, decreasing the amount of glucose your body absorbs and increasing the effect of insulin on your body. Insulin is a hormone that helps your body remove extra sugar from your blood.

This lowers your blood sugar levels. In some cases, Metformin oral tablets can cause mild or serious side effects (Metformin, 2018). The some of the key side effects that may occurs are unusual muscle pain, trouble breathing, diarrhea, dizziness, nausea, stomach pain, heart burn, irregular heart rate, lactic acidosis and or hypoglycemia. Hypoglycemia (low blood sugar), symptoms can include weakness, confusion, shaking or feeling jittery, drowsiness, dizziness, irritability, sweating, hunger, fast heart rate (Metformin, 2018). Yan-Ling He *et al*. Article in Current Medical Research and Opinion· May 2009, studied the Metformin as first-line therapy in type 2 patients. It is unable to maintain adequate glycemic control with metformin alone. Then he combined Vildagliptin, selective dipeptidyl peptidase IV (DPP-4) inhibitor, which improved glycemic control in combination with metformin. This small, open-label trial suggests that vildagliptin could be coadministered with metformin without any dose adjustment for either agent (Yan-Ling, 2009).

Vildagliptin ((S)-1-(N-(3-hydroxy-1-adamantyl) glycyl) pyrrolidine-2-carbonitrile) is an oral anti-diabetic drug of the class dipeptidyl peptidase-4 (DPP4) inhibitor (Vildagliptin, 2018). By such inhibition of DPP-4 enzyme it prevents the glucose-dependent insulinotropic polypeptide (GIP) and Glucogen-like peptide-1 (GLP-1), the incretic hormone degradations. It improve the pancreatic α- and β-cell functions and enhance the glycaemic control. It can be determined by the levels of fasting plasma glucose (FPG) and glycated haemoglobin(HbA1c)(Ganesh Kumar, 2015).

Priyanka Shrestha, Shiva Kumar Bhandari, (Article in Research Journal of Pharmaceutical, Biological and Chemical Sciences July 2014) formulated the immediate release tablets of Vildagliptin and it possesses of 95-100% of release profile within 45 minutes without any chemical interaction (Priyanka Shrestha, 2014; Perves). MD Perves Khan*et al*. International Journal Of Pharmacy & Technology (2014) formulated and evaluated vildagliptin and metformin Hclbilayered tablets for treating type 2 diabetes (Perves, 2014). NishitGohel1*et al*., Int. J. Pharm. Sci. Rev. Res., 2017 formulated the bilayer tablet of Vildagliptin(VLD) immediate release layer MetforminHydrochloride(MET) sustained releaselayer (VLD) (Sujan banik *et al*., 2015).

By dual oral therapy of metformin hydrochloride in combination with vildagliptin, in patients with insufficient glycemic control despite maximal tolerated dose of monotherapy with metformin may have additional reduction of HbA_{1c} levels and more effective. And vildagliptin is well tolerated and reduce a risk of hypoglycaemia. However, the addition of vildagliptin with metforminhydrochloride may improve the range of treatments available and enhance the potential for the management of non-insulin dependent diabetic populationwhich is inadequately maintainedby monotherapy. Both the drugs are not altered with pharmacokinetic properties with each one another. In one way it helps to enhance the glycaemic control by vildagliptin and in another way by MET it makes better utilization of insulin in the body. Hence, we attempted to formulate the Metformin HCL and vildagliptin oral tablets in combined form to enhance thedrugs bioavailability, reduce the dosing frequency, patient complianceand to reduce the other sideeffects of Metformin HCL and Vildagliptin alone. The method used to formulate the Metformin HCl and Vildagliptin is wet granulation method.The stability studies Revealed no significant changes in physical and chemical properties of optimized formulation.

AIM: The aim of this work is to develop a formulation with fixed dose combination of Metformin 500 mg and vildagliptin 50mg in tablet dosage form.

MATERIALS

Metformin HCL and vildagliptin were purchased from Kimia biosciences ltd, Haryana. Starch from Angel starch products (India) ltd, Croscarmellose from Heerpharma private ltd, microcrystalline cellulose from RanQ Remedies Mumbai, Pvpk-30 from Basf Germany, Magnesium sterate from Amshi Drug and Chemicals Gujarat,Potassium dihydrogen phosphate AR, Sodium hydroxide AR and Hydrochloric acid AR fromRankem New Delhi, Acetonitrile HPLC from Merck Canada and Whatman filter paper from Sartourious 292A, North America. And instruments such as Electronic weighing balance from Shimadzu corporation Japan, pH Meter fromMettler Toledo India, Tap Density apparatus, ETD-1020, Friability Test Apparatus, ET-2, Dissolution Apparatus, TDT-08L from Electro lab India, Hardness tester from Monsanto India, FT-IR Spectrophotometer 8300, UV-Visible Spectrophotometer (UV-1601) and HPLC with PDA detector from Shimadzu corporation Japan.

METHODS

- Preformulation study:
- Physical observation of metformin HCL and vildagliptin.
- Drug –Excipient compatibility studies.
- Formulation and evaluation oftablets:
- Formulation of Immediate-release of vildagliptin and metformin HCL.
- Evaluation of Immediate-release ofvildagliptin and metformin HCL.
- In vitro dissolution study for different formulations.
- Stability study for selected formulation.

PREFORMULATION STUDIES: Preformulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first step in the rational development of dosage forms (table 2).

Determination of Bulk Density and Tapped Density: An accurately weighed quantity of the blend (W), was carefully poured into the graduated cylinder and the volume (V_0) was measured. Then the graduated cylinder with lid, set into the density determination apparatus (Tapped Density Apparatus, Electro lab, Mumbai). The density apparatus was set for 250 taps/min. and after that the volume (V_f) was measured and continued operation till the two consecutive readings were equal. The bulk density and tapped density were calculated by using the following formulas.

Bulk Density = W/ V_0
Tapped Density = W/ V_f

Compressibility Index (CI): It was obtained from bulk and tapped densities. It was calculated by using the following formula

$$CI = \frac{100 \times (V_o - V_f)}{V_o}$$

Hausner Ratio: It indicates the flow properties of a powder. It is measured by ratio of tapped density to bulk density.

Hausner Ratio = Tapped density / Bulk density

Sieve Analysis: The A series of sieves were arranged in order of decreasing of pore diameter (Increasing in Sieve no.) i.e. sieve numbers #20, #40, #60, #80, #100. 100 grams of blend were weight accurately and transferred to sieve # 20, which was kept on the top. The sieves were shaken in an electromagnetic sieve shaker for 10 minutes at power 16. Then the drug retain on each sieve were taken, weighed separately and expressed in terms of percentage (%)(table 3).

Loss on Drying (LOD): It was measured by Electronic LOD measurement apparatus (Sartorius, Germany). Above 500 mg of blend was taken on aluminum plate of the apparatus. The blend was kept at 105°C for 5 minutes. After that the displayed result was noted in terms of % w/w.

Drug and Drug Excipients Compatibility Studies: The drug metformin HCL and vildagliptin was taken in the ratio 1:1 and the mixtures were taken 2 ml glass vials and sealed. These glass vials were kept at 40celcius/75RH and 60celcium/ 90% RH for about one month. At the interval of 2 weeks and 4weeks, the samples were withdrawn and analyzed for any color change(table 4).

FORMULATION AND EVALUATION OF TABLETS

Description: For checking appearance of tablets take about 100 tablets from a representative sample.

Dimensions: Check the dimensions of tablets using a venire caliper. Take randomly 10 tablets from the representative sample and check individual tablet dimensions.

Hardness: Clean the hardness tester and put the tablet between the sliding plates of the schleuniger tester (Table 5).

Friability: Weight accurately 20 tablets; put he tablets in the friability test apparatus. Adjust the timer to 4 minutes. Operate the apparatus and observe the tablet while rotating. No tablets should stick to the walls of the apparatus. If so, brush the walls with talcum powders. Take the tablets out and observe. No capping should be there. Weight the tablets (Table 5).

% Friability = $(W_1 - W_2) \times 100 / W_1$
Where,
W_1 = Initial weight of the 20 tablets
W_2 = Weight of the 20 tablets after testing

Drug content (assay)(Wael abu dayyih, 2018; Sujan banik, 2015**):**

Assay (by hplc) vildagliptin and metformin HCL:

Chromatographic conditions
Column :c18 (25cm×4.6)
Flow rate :1.0 ml/min
Detection :210 nm
Injection volume :5 ul
Column temperature: ambient
Mobile phase: 6.8g of potassium dihydragen phosphate in to 1000ml of water adjust ph to 6.0 with (NaoH)orthophosphoric acid.
Preparation of mobile phase buffer:
Dissolve about 70ml buffer : 30ml of acetrontrile.
Preparation of diluent:
80 : 20 , aceteronitrile : water

Calculations for vildagliptin:

$$ASSAY = \frac{\text{area of sample}}{\text{Area of std}} \times \frac{\text{wt of std}}{\text{wt of sample}} \times \frac{\text{100-std wc}}{\text{100-wc}}$$

Where

AT2&AS2 are the area of standard and the sample preparation. WS2 is the weight of the vildagliptn working standard (WS) in g, P2 is the percent purity of the vildagliptin (WS) & AV is the average weight of tablet in g.

$$\% \text{ of labeled amount} = \frac{\text{Content of drug (mg/tab)}}{\text{Label claim (mg/tab)}} \times 100$$

Potency:
Content = 49.624mg
% = 99.25

Calculations for metformin HCL:

$$ASSAY = \frac{\text{area of sample}}{\text{Area of std}} \times \frac{\text{wt of std}}{\text{wt of sample}} \times \frac{\text{100-std wc}}{\text{100-wc}}$$

Where

AT2&AS2 are the area of standard and the sample preparation. WS2 is the weight of the metformin HCLworking standard (WS) in g, P2 is the percent purity of the metformin HCL (WS) & AV is the average weight of tablet in g.

$$\% \text{ of labeled amount} = \frac{\text{Content of drug (mg/tab)}}{\text{Label claim (mg/tab)}} \times 100$$

Potency:
Content = 499mg
% = 99.8

In-vitro drug release (dissolution) (Indian Pharmacopoeia, Manish, 2017**):**

Potency determination of Metformin HCL and Vildagliptin tablets

Medium: pH 6.8 buffer
Volume: 900ml
Apparatus: paddle
Wavelength: 233nm
RPM: 100 speed
Time : 45 mins

Table 1. Immediate release formulation of Metformin HCL and Vildagliptin

Sl.no	Ingredients	F1	F2	F3	F4	F5	F6
1.	Metformin HCL	5500g0g	500g	50g	500g	500g	500g
2.	Vildagliptin	50g	50g	50g	50g	50g	50g
3.	Starch	34g	34g	30g	28g	26g	26g
4.	Cross carmellose sodium	20g	20g	20g	20g	20g	20g
5.	Mccp	38g	38g	38g	38g	38g	40g
6.	Pvpk-30	34g	32g	30g	28g	27g	28g
7.	Magnesium sterate	8g	8g	8g	8g	8g	8g
8.	Aerosil	2g	2g	2g	2g	2g	2g
9.	Cross carmellose sodium	10g	12g	14g	16g0g	18g	20g
10.	Talc	6g	6g	6g	6g	6g	6g

Table 2. Preformulation studies of Metformin HCL and Vildagliptin

Sl.no	Parameters	F-01	F-02	F-03	F-04	F-05	F-06
1	Loss on drying or water content % w/w	4.37	4.19	4.23	4.35	4.28	4.35
2	Bulk density gm/ml	0.563	0.437	0.437	0.437	0.437	0.625
3	Tapped density gm/ml	0.667	0.537	0.537	0.537	0.537	0.837
4	Compressibility Index %	20.93	23.75	23.75	23.75	23.75	25.32
5	Hausner's Ratio	1.20	1.31	1.31	1.31	1.31	1.31

Table no.3. Pre-compression parameter sieve analysis study

S. No	Sieve No.	% Blend Retained					
		F-01	F-02	F-03	F-04	F-05	F-06
1	Sieve No.20	3	4	4	3	3	2
2	Sieve No.40	20	18	16	14	12	10
3	Sieve No.60	20	22	24	26	28	30
4	Sieve No.80	40	42	44	46	48	50
5	Sieve No.100	64	66	68	70	75	80
6	Receiver	100	100	100	100	100	100

Table no.4. Drug and Drug Excipients Compatability Studies:

S.No	Drugs + Excipients	Parameter	Initial value of parameter	Conditions RT 40 C/75% RH	
				2 weeks	4 weeks
1.	Metformin HCL+ vidalgliptin	Any colour change	No colour change	No colour change	No colour change
2.	Drugs + Starch	Any colour change	No colour change	No colour change	No colour change
3.	Drugs + croscarmellose sodium	Any colour change	No colour change	No colour change	No colour change
4.	Drugs + MCCP	Any colour change	No colour change	No colour change	No colour change
5.	Drugs + PVP K-30	Any colour change	No colour change	No colour change	No colour change

Table 5. Evaluation studies of metformin HCL and vildagliptin.

S.No	Hardness test(N)	Thickness (mm)	Friability(% W/W)	Disintegration time
				Core tablets
1	5.0 kg/cm2	4.00mm to4.30mm	3.00	7.30
2	5.0to6.0kg/cm2	4.7mm to4.90mm	4.00	8.50
3	6.0to 65kg/cm2	4.40mm to 4.60mm	4.30	6.00
4	6.0 to7.0kg/cm2	5.0mm to5.3mm	4.50	5.30
5	8.5to9.0kg/cm2	5.8mm to5.9mm	5	5.00
6	7.0 to8.0kg/cm2	5.8mm to6.0mm	5	4.50

Table 6. Dissolution studies of metformin HCL and Vildagliptin

Mean of % dissolved	Formulations					
	F1	F2	F3	F4	F5	F6
Metformin HCL	65	75	78	85	87	102
Vildagliptin	58	68	70	76	79	86

Table 7. Cumulative % drug release

Formulations	Immediate release of Drugs	Time(mins)	Limit	Amount of drug release	Cumulative%drug release
F1	MET	45 mins	NLT 80%	325mg	65%
	VIL	45 mins	NLT 70%	29mg	58%
F2	MET	45 mins	NLT 80%	375mg	75%
	VIL	45 mins	NLT 70%	34mg	68%
F3	MET	45 mins	NLT 80%	390mg	78%
	VIL	45 mins	NLT 70%	35mg	70%
F4	MET	45 mins	NLT 80%	425mg	85%
	VIL	45 mins	NLT 70%	38mg	76%
F5	MET	45 mins	NLT 80%	439mg	87%
	VIL	45 mins	NLT 70%	39.5mg	79%
F6	MET	45 mins	NLT 80%	513mg	102%
	VIL	45 mins	NLT 70%	43mg	86%

1.	Description	Complies	White to off white colored ,oblong shape tablets
2.	Identifications	Complies	The retention time of major peaks in the chromatogram of the assay preparation corresponds to that in the chromatogram of the std preparation as obtained in the assay.
3.	Average weight	688 mg	686 to 691 mg
4.	Thickness	5.9mm	5.8 mm to 6.0mm
5.	Hardness	7.6 kg/cm2	7.0 to 8.0 kg/cm2
6.	Disintegration time	4 min 50 sec	NMT 10 min
7.	Dissolution:		
	MetforminHCL	100%	90 % to 110 % of the average value
	Vildagliptin	85.6%	80% to 100% of the average value
8.	Assay :		
	MetforminHCL	490mg	480 mg to 500 mg
	Vildagliptin	40mg	40 mg to 50 mg

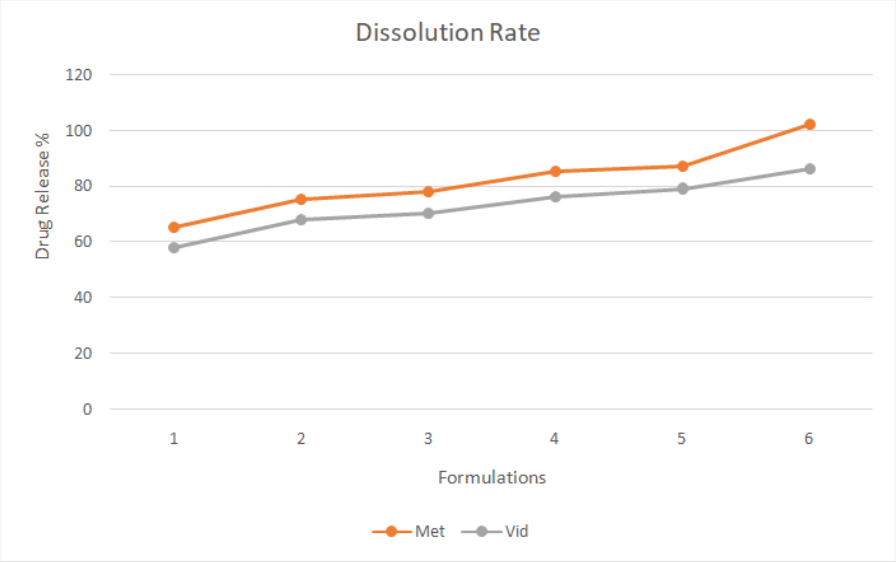

Fig. 1. Dissolution rate of Metformin HCL and Vildagliptin

Procedure: The dissolution test on metforminHCL 500mg and vildagliptin 50mg were performed using apparatus 11 at 37± 0.5ºc with rotation speed 100rpm for paddle and pH 6.8 buffer used 900ml were tested, sample withdrawn in 45mins after the sample filtered through 0.45µm membrane filter and then analysed by uv spectrophotometric method. (Table 6&7).

Formulation and evaluation of tablets

PROCEDURE: The method used to formulate the Metformin HCl and Vildagliptin is wet granulation method. Dispense all the ingredients as per the batch size. Shift metformin HCL, Vildagliptin, starch, cross carmellos , Mccp, magnesium sterate through mesh size (#) 30 separately. Mix above ingredients geometrically ratio and blend for 15mins in a Ribbon mixer add pvp k-30 binder on above mixer. The above mixer load on tray tryer for drying 1hr. Shift the above granules sieve on 20# mesh size. Finally sieve lubrications materials 30# mesh size and add above granule thoroughly mix in the cone blender. Compress the above blend using M.D.S punches. The ingredient ratios for Immediate release formulation ofMetformin HCL and Vildagliptin in Table 1.

RESULT AND DISCUSSION

The results ofphysical parameters (LOD/Water content, bulk density, tapped density,Compressibility index and hausners ratio) and potency of the prepared immediate release tablets are shown in Table 2.

Sieve analysis is shown in table 3and drug and drug excipients compatabilitystudies in table4. Evaluation studies of metformin HCL and vildagliptin such as hardness, thickness, Friability(% W/W) and disintegration time are given in table 5.And Dissolution rate of Metformin HCL and Vildagliptin is given in Fig:1. All preformulation parameters and evaluation parameters after the formulation shows the effective results as follows.

Conclusion

The study conducted on formulation development and evaluation of combination tablet of Vildagliptin and Metformin HCl for the effective management of type 2 diabetes mellitus revealed that, fixed dose combination contains Vildagliptin 50mg and Metformin HCl 500 mg as immediate release. The precompression parameters of the powder blends used for the preparation of immediate releasing were in acceptable range of pharmacopeial specification with good flow and good compressibility. Vildagliptin and metformin HCL was formulated as immediate releasing layer using Cross carmellose sodium by wet granulation method. Under the preformulation studies API (Active pharmaceutical ingredients) characterization, drug-drug, drug-excipient compatibility studies were carried out and showed satisfactory results. The compatibility studies between drug-drug and drug-excipients were shown passionate results and found to be compatible with each other. The excipients were selected based on the satisfying

results produced during drug-excipient compatibility studies to develop the final formulation. The in vitro release of Vildagliptin was rapid from tablet and showed highest drug release 86% within 45 minutes and hence, formulation F6 was selected for preparation of combination tablet. Metformin in vitro release was 102%. Formulation 6shows the highest drug release within 45mins. Hence, it was selected for preparation of combination tablet. Hence, fixed dose combination tablet of Vildagliptin and Metformin HCl immediate release could be used to improve patient compliance towards the effective management of type 2 diabetes mellitus with improved dosing frequency and bioavailability. The physicochemical properties of the finished product complies with the in-house specifications of good man pharmaceuticals limited. The dissolution profile and the stability studies of the formulated product also complies with ICH guidelines in the initial two months of study and further studies is in progress. After the success of the stability studies, bioequilancestudies should be carried out. If the results are positive, the developed product can be introduced in the market.

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