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Comparative Analysis of Different Brands of Metformin and Sitagliptin Combination

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1 Data analysis and/or interpretation.
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ABSTRACT

Objective: To compare physicochemical parameters of different brands of metformin and sitagliptin combinations and check that whether the brands meet the standard criteria mentioned in monographs.

Methods: Five different brands of metformin and sitagliptin combination were purchased from the local market and evaluated for their physicochemical studies. The brands were checked for different physicochemical tests like hardness, thickness, disintegration, and dissolution. The results were observed and concluded for their comparative studies.

Results: The results showed that all brands have weights ranging from 600-900mg per tablet. Brand 1 has a higher weight as compared to other brands, whereas, Brand 2 and 5 have almost very closer weights, similarly Brand 3 and 4 weights are very close to each other. All the brands had a hardness of less than 4 kg which is within an acceptable limit for conventional tablets. The friability test showed that all the brands lie under the limit which is NMT 1%. The disintegration time of film-coated tablets of each brand was found to be within the range of 2-13 minutes. While the dissolution test of all brands meet the standard (NLT 85%) release within 45 minutes.

Conclusion: Comparative analysis of different brands of Metformin and Sitagliptin concluded that all brands meet the standard criteria for conventional tablets.

Keywords: *Metformin, Sitagliptin, weight variation, hardness, Dissolution.*

INTRODUCTION

Metformin, is a dimethyl-biguanide which is an orally administered hypoglycemic drug for the treatment of non-insulin-dependent diabetic Mellitus (NIDDM). It reduces the blood glucose concentration predominantly by enhancing peripheral as well as hepatic sensitivity to insulin but does not affect the secretion of this hormone [1]. The drug was introduced as a medicine in France in 1957 and in 1995 in the US. This drug is included in the world Health Organization's List of Essential Medicines. The anti-hyperglycemic effect of metformin is similar to sulfonylurea as both give the same efficacy for management of diabetes but have different modes of action. It is observed that metformin is generally used as the initial treatment for diabetes and also administered in combination with sulfonylurea as an additional drug because sulfonylurea alone is inadequate [2]. The absorption of metformin is reduced by food, as demonstrated by about 40% lower mean peak plasma concentration (Cmax), 25% lower area under the plasma concentration versus

time curve (AUC), and 35-minute increase in time to peak plasma concentration (Tmax) after ingestion of an 850 mg tablet of metformin taken with food, compared to the same dose administered during fasting [3] . Though the extent of metformin absorption (measured by the area under the curve - AUC) from the metformin extended-release tablet is increased by about 50% when given with food, no effect of food on Cmax and Tmax of metformin is observed. High and low-fat meals exert similar effects on the pharmacokinetics of extended-release metformin [4, 5].

Metformin is an associated antihyperglycemic agent that improves aldohexose tolerance in patients with sort a pair of diabetes, lowering each basal and postprandial plasma aldohexose. Its medical specialty mechanisms of action are totally different from different categories of oral antihyperglycemic agents. the antidiabetic drug decreases viscous glucose production, decreases enteral absorption of aldohexose, and improves hormone sensitivity by increasing peripheral aldohexose uptake and utilization [6].

Intravenous studies using a single dose of metformin in normal subjects show that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion [7]. Renal clearance of metformin is about 3.5 times higher than creatinine clearance, which shows that renal tubular secretion is the major route of metformin elimination. After oral administration, about 90% of absorbed metformin is eliminated by the kidneys within the first 24 hours post-ingestion [8]. The most common adverse effect of the anti-diabetic drug is GI irritation, cramps, nausea, vomiting, and exaggerated flatulence [9]. The potential side effect of metformin is lactic acidosis; this complication is extremely rare, and therefore the overwhelming majority of those cases appear to be associated with comorbid conditions like impaired liver or urinary organ performance, instead of the anti-diabetic drug itself [10].

Sitagliptin is a dipeptidyl peptidase-4 inhibitor and is used for the management of Diabetes Mellitus II. Sitagliptin is well tolerated as monotherapy as well as combination therapy which enhanced glycemic control in highly designed clinical testing for diabetic Mellitus II patients [11]. It is taken orally and available in combination with metformin. Sitagliptin was approved by the U.S. Food and Drug Administration in April 2007, the Food Associate in Nursing Drug Administration FDA approved an oral combination of sitagliptin and antidiabetic marketed within the USA as Janumet. Chemically Sitagliptinis is (3R)-3-amino-1-[3-(trifluoromethyl)-5H,6H,7H,8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-4-(2,4,5-tri-fluorophenyl)butane-1-one. It is tri-azole-pyrazine that exhibits hypoglycemic activity [12].

Sitagliptin works to competitively inhibit the protein dipeptidyl enzyme four (DPP-4). This protein breaks down the incretins GLP-1 and GIP(GI hormones) in response to a meal. By preventing the breakdown of GLP-1 and GIP, they're ready to increase the secretion of hypoglycemic agents and suppress the discharge of internal secretion by the alpha cells of the exocrine gland. This drives glucose levels towards normal [13]. It doesn't cause weight gain and has less hypoglycemia compared to sulfonylureas. Sitagliptin is suggested as a second-line agent when other anti-diabetic fails [14].

Food administration does not affect the pharmacokinetics of Sitagliptin. Sitagliptin reaches most plasma concentrations in two hours [15].

Minor metabolic pathways are mediated primarily by haemoproteinp450 (CYP) 3A4 and to a lesser extent by CYP2C8 [11] . Approximately 79% of sitagliptin is excreted in the urine as the unchanged parent compound. 87% of the dose is eliminated in the urine and 13% in the feces. Sitagliptin is contraindicated in patients with an identified sitagliptin hypersensitivity reactions like urticaria, angioedema, exfoliative eczema, or alternative serious skin conditions (serious rash), together with Stevens-Johnson syndrome [16].

METHODOLOGY

Five different brands of metformin and sitagliptin combination were purchased from the local market. These brands were evaluated for their physicochemical parameters. These brands were coded as Brands 1, 2, 3, 4, and 5 to avoid any biases.

Weight Variation:

20 Tablets for each brand were randomly taken and individually weighed by using Analytical balance. The average weight and the percentage deviation from mean values were calculated.

Hardness Test:

Twenty tablets were randomly taken from each brand, and hardness was measured using the Monsanto

Hardness tester. A compressing spring in the barrel helps to move the pointer along the gauze, at which the tablet fractures and shows the hardness of the tablets. The pressure required to break the tablet was recorded. Average values and Standard deviation were calculated and compared.

Thickness Test:

Twenty tablets of each brand of metformin and sitagliptin combination were taken and their degree of compaction was evaluated by determining the thickness and diameter of the sample tablets by using Vernier caliper. Mean and standard deviation was calculated.

Disintegration Test:

The disintegration test was performed by the Basket Rack Assembly apparatus of 6 tablets for each brand. One tablet was placed in each basket in a 1L beaker containing buffer solution. In the basket assembly, the standard motor device was set to move the baskets with the tablets up and down 5.3 to 5.7 cm at a frequency of about 29 to 32cycles per minute. The disintegration time was recorded. Mean values and standard deviation were determined.

Dissolution Method

The dissolution test was performed for different brands in USP paddle type apparatus. 900ml of 0.1M hydrochloric acid was used as dissolution medium. The dissolution apparatus was operated at 75 rpm for 45 minutes. The temperature was maintained at 37_+0.5'C. Samples (5 mL) were withdrawn through syringe at 45 minutes and filtered. Absorbance was measured at 230nm using Shimadzu UV visible spectrophotometer. Drug release of the different brands of tablets were noted and checked according to the criteria (not less than 85% (Q) of the labeled content within 45 minutes).

RESULTS

The results obtained from subjecting brands to a number of quality control tests in order to access their physicochemical studies were as follows:

Weight Variation:

The weight variation test for different brands was found to be within the range of 600mg-900mg with standard deviation ±0.00479-0.018117. One way ANOVA revealed that significant difference was observed in the weight variation of different brands ($p < 0.05$). Post hoc analysis further revealed that brand 1 significantly varied with all the other brands with a mean difference of 0.339 mg, 0.242 mg, 0.259 mg and 0.297 mg with brand 2, brand 3, brand 4 and brand 5 respectively.

Hardness Test:

The hardness for all brands was found to be within the range of 2.48-4Kg, all the brands meet the standard criteria of hardness which is NMT than 4 kg.

One way ANOVA revealed that significant difference was observed in the hardness of different brands ($p < 0.05$).

Thickness and Diameter:

The values for thickness of all brands range from 2.35mm-3.76mm. Whereas the diameter of different brands ranges from 6.07mm-7.57mm. The values were found to be varied significantly between different brands ($p < 0.05$).

Friability:

In friability test, all the brands lie under the limit which is NMT 1%, i.e., ranged within the 0.01-0.11%.

Table 1. Parameters and their Comparisons.

Parameters	Brand 1	Brand 2	Brand 3	Brand 4	Brand 5	p-value
Weight Variation (n=20)	0.96 ± 0.01 *	0.62 ± 0.14	0.72 ± 0.01	0.70± 0.004	0.66 ± 0.008	0.000
Hardness (n=20)	3.39 ± 0.12	3.96 ±.013	3.95 ±.006	3.08 ±.032	3.66 ±0.18	0.000
Thickness (n=20)	2.55 ±.037	3.08 ±.065	3.54 ±.024	3.59 ±.019	3.56 ± 0.023	0.000
Diameter (n=20)	7.44 ±.0.60	7.39 ±.0.53	6.70 ±.0.22	7.49 ±.0.28	7.05 ± 0.21	0.000

*p < 0.05 Post Hoc Tukey Test, one way ANOVA.

Table 2. Friability Test.

Serial number	Friability (%)	Official Limit	Remarks
Brand 1	0.04%	NMT 1%	Pass
Brand 2	0.02%	NMT 1%	Pass
Brand 3	0.05%	NMT 1%	Pass
Brand 4	0.01%	NMT 1%	Pass
Brand 5	0.11%	NMT 1%	Pass

NMT: Not More Than

Table 3. Disintegration Test.

Serial Number	Disintegration Time (min)	Official Limit	Remarks
Brand 1	2.06	NMT 30min	Pass
Brand 2	13.22	NMT 30min	Pass
Brand 3	8.21	NMT 30min	Pass
Brand 4	6.08	NMT 30min	Pass
Brand 5	6.4	NMT 30min	Pass

NMT: Not more than

Table 4. Dissolution Test.

Serial Number	(%) Dissolution At 45 Minute Metformin	(%) Dissolution At 45 Minute Sitagliptin	Official Limit.	Remarks
Brand 1	90%	92%	NLT 85%	Pass
Brand 2	85%	88%	NLT 85%	Pass
Brand 3	92%	91%	NLT 85%	pass
Brand 4	87%	90%	NLT 85%+	Pass
Brand 5	88%	85.80%	NLT 85%	Pass

NLT: Not less than

DisintegrationTest:

In disintegration test, our drug is film-coated tablet so the disintegration time should be within 30 minutes.All the brands disintegrate ranges within 2-13 minutes.

DissolutionTest:

Dissolution for all tablets ranges within 85-92%. All brands meet the standard criteria.

DISCUSSION

The outcome of weight variation, hardness, thickness, disintegrations time, friability, diameter, and dissolution test of various brands of metformin and Sitagliptin combination are presented in Table **1**, 2,3,4, 5, 6, and 7. In the weight variation test of tablets, brand 1 has higher weight reading than brand 2. This may be due to the number of active ingredients in both of the brand's tablets. The difference in the hardness of tablets among the brands may happen due to the various properties of the excipients that are used in the formulation of the medicine. Although, hardness is the measurement of the tablets crushing strength and can affect the rate of disintegrations and drug release of the drug. But in the test of hardness, all the brands meet the standard criteria of hardness which is NMT than 4 kg which shows that the properties of the excipients that are used in all brands are the same. While the thickness and Diameter test of all brands give almost the same result - as all the brands have the same thickness brand 3 is the smallest among all. The friability test was also done to analyze the capacity of the brands to withstand abrasion at the time of handling, packaging, and transportation. The friability test

showed that all the brands lie under the limit which is NMT 1%. All the tablets that were used in this study are film-coated; therefore, the disintegration time of the tablets of each brand was within 30 minutes. The results showed that all the brands disintegrate within 2-13 minutes. While the dissolution test of all brands meets the standard criteria of drug release of 85% within 45 minutes.

CONCLUSIONS

The comparative analysis of different brands of Metformin and Sitagliptin concluded that all Brands meet the standard criteria for Conventional tablets.

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