FORMULATION AND EVALUATION OF ANTI-DIABETIC TABLET OF VILDAGLIPTIN AND EFFECT OF DISINTEGRANTS CONCENTRATION ON DRUG RELEASE

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ABSTRACT

From past few decades, the demand for dosage forms with higher patient compliance has increased devastatingly. As a result, the demand for novel technologies has been increasing annually. Since the development cost of a new chemical entity is very high, the pharmaceutical companies are focusing on the development of new drug delivery systems for existing drug with an improved efficacy and bioavailability together with reduced dosing frequency to minimize side effects. Sometimes, it may be difficult to swallow conventional dosage form due to medical conditions or non-availability of water. To avert the problems, the development of a novel type of solid oral dosage form called fast disintegrating tablets has become necessary. Vildagliptin is oral antidiabetic drug for type 2 diabetic patients; it is blocking the dipeptidyl peptidase 4 (DPP-IV). Vildagliptin 50mg twice daily is generally safe in patient with diabetic disorder. Due to these effects, vildagliptin help in controlling blood sugar levels in diabetes patient. In the present investigation, Chitosan as natural superdisintegrant and crospovidone as synthetic disintegrants in varied concentration were studied for the preparation of Fast dissolving tablets of Vildagliptin. The results indicated that formulations containing Vildagliptin 50 mg and 4% crospovidone are the most effective approach in formulating fast release tablets of vildagliptin. These tablets were found to be biocompatible, safe, with optimum drug release and high patient compliance.

Keywords: *Fast Dissolving tablets, Chitosan, Crospovidone, Vildagliptin, Anti-Diabetic drugs, Drug release.*

INTRODUCTION

With vast pharmaceutical development in R&D, the oral route of administration such as tablets and capsules still continue to be the most preferred route due to its manifold advantages including patient compliance, ingestion ease and no pain as with parenteral drug delivery system. However, oral dosage forms have one main drawback that has to be avoided for its suitability which is difficulty in swallowing also known as Dysphasia. The problem in swallowing tablets/capsules is faced by more than 35% of the general population which includes paediatric and geriatric patients along with institutionalized patients and patients with nausea, vomiting, and motion sickness complications. This disorder is also associated with number of medical conditions including stroke, Parkinson's disease, AIDS, head and neck radiation therapy and other neurological disorders including cerebral palsy (1).

USFDA defines FDT as 'A solid dosage form containing medicinal substance or active pharmaceutical ingredient (API) which disintegrates and dissolves rapidly usually within a matter of seconds when placed upon the tongue' the disintegration time ranging from several seconds to about a minute (2-4). In recent years, plant derived polymers have pharmaceutical applications such as diluents, binder, disintegrants in tablets, thickeners, suspensions, gelling agents in gels and bases in suppository. The polymers such as natural gums and mucilage have several advantages that include biocompatibility, cost effectiveness, low toxicity, soothing action, non-irritant nature and ease of availability and hence, the natural polymers are preferred over synthetic and semi-synthetic polymers for the preparation of fast disintegrating tablets.

Diabetes mellitus

Diabetes mellitus is the most common chronic endocrine disorder that affects more than 100 million people worldwide. The world health organization projects that the number of diabetics may exceed 350 million by 2030 (5). Diabetes mellitus is syndrome of disordered metabolism, usually due to a combination of hereditary and environmental causes, resulting in abnormally high blood sugar levels (hyperglycemia) (6). Blood glucose levels are controlled by a complex interaction of multiple chemicals and hormones in the body. Diabetes and its treatments can cause many complications. Acute complications such as hypoglycemia, ketoacidosis and serious long term complications include cardiovascular disease, chronic renal failure, retinal damage, nerve damage, poor healing of wounds etc. All forms of diabetes have been treatable since insulin became available medically in 1921, but there is no cure which is the basic treatment for Type I diabetes. Type II is managed with a combination of dietary treatment, exercise, medications and insulin supplementation.

Vildagliptin

Vildagliptin is a potent, selective, and orally active dipeptidyl peptidase-4 (DPP-4) inhibitor, which prevents inactivation of incretion hormones by inhibiting DPP-4. A lower dose of sulphonylurea, reduce the risk of hypoglycaemia. Vildagliptin is used for type 2 or non-insulin dependent diabetes. It can trigger the amount of insulin in the body it may also decrease the amount of glucagon in the body. It has been shown to be an effective and safe option for better glycemic control in a wide range of T2DM patients and has demonstrated

HbA1C lowering potential when given as monotherapy or in combination with other OADs, without weight gain. Drugs like sulfonylureas, meglitinides, and insulin are associated with weight gain and hypoglycemia; thiazolidinediones (TZDs) cause weight gain and possibly peripheral edema. Metformin and a- glucosidase inhibitors are associated with gut-related side effects. Additionally, the impact of different drugs, even within a single class, on the risk of long-term vascular complications has recently come under scrutiny (5).

In context of above principle, the research was attempted to improve the disintegration of tablets of vildagliptin by using super disintegrants. The different concentration of disintegrants is used in order to determine the release of the drug from the tablets. The disintegrants are used to make the tablet fast disintegrating for rapid onset of action in the body. The 50mg of vildagliptin is highly effective in maintaining the blood glucose level in patients with diabetes mellitus. Fast dissolving tablet of anti-diabetic drugs are designed for rapid and complete absorption in the body and for achieve therapeutic success. The research work involves the formulation and evaluation of fast disintegrating tablets of vildagliptin using natural and synthetic super disintegrants. The formulation is further evaluated for tablet characteristics, drug content, *in vitro* disintegration, *in vitro* dissolution study and wetting time etc. The fast disintegration enhances the bioavailability of drug and thereby improved therapeutic efficacy in T2DM. Therefore, development of Vildagliptin fast release dosage forms is desirable to achieve a more effective therapy with rapid onset of action. Chitosan is selected as natural super disintegrant for its high swelling index.

MATERIAL AND METHODS

Materials

Vildagliptin was received as gift sample from Kimia Bioscience Ltd. Other excipients like Crospovidone, Chitosan, MCC, Sodium saccharine, magnesium stearate etc. were obtained from college laboratory.

Experimental Methods

Formulation of Fast Disintegrating Tablets of Vildagliptin

Fast disintegrating tablets of Vildagliptin were prepared by Direct Compression Method. All the ingredients except granular directly compressible excipients were passed through 60mesh separately. Then, the ingredients were weighed and mixed in geometrical order and compressed into tablets of 100mg by using 8mm flat face round tooling on 10 station rotary tablet compression machine. A batch of 20 tablets was prepared for all designed formulations (7-10). The formulation designs have been shown in (Table I).

Ingredients (mg/tablet)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
Vildagliptin	50	50	50	50	50	50	50	50	50	50
Chitosan	1	2	3	4	5	-	-	-	-	-
Crospovidone	-	-	-	-	-	1	2	3	4	5
MCC	Qs	qs	Qs	qs	Qs	Qs	qs	qs	qs	qs
Sodium saccharine	3	3	3	3	3	3	3	3	3	3
Magnesium Stearate	3	3	3	3	3	3	3	3	3	3

Table I: Compositions of various FDTs with different superdisintegrants

Pre-compression Characterization

Irregular flow of powder from the hopper produces non-uniform weight tablets and capsules. Flow property depends on particle size, shape, porosity and density of the powder. The prepared powder was characterised on several parameters such as Angle of repose, Bulk Density, Tapped density, Carr's index and Hausner's ratio (11).

Characterization of Fast Disintegrating Tablets

Drug Content

For the determination of drug contents, ten tablets were accurately weighed. It was crushed and finely powdered. An amount of the powder equivalent to 50 mg of drug was taken in volumetric flask. It was completely dissolved in 100 ml volumetric flask containing phosphate buffer solution of pH 7.4. It was passed and filtered through filter paper. Filtered solution was further diluted with solvent. It was analyzed for drug contents study at wavelength of 243 nm by using UV-visible spectrophotometer (12).

Tablets hardness

Hardness of the FDTs was measured by using Monsanto tablet hardness tester apparatus. Hardness of the tablets can be defined as the force which required crushing the tablets. It is measured as hardness and in kg/cm^2.

Thickness

The thickness of tablet can vary without any change in weight. This is generally due to the differences of density of granules, pressure applied for compression and the speed of compression. It was measured by Vernier Caliper (13).

Weight variation

To carry out the weight variation study, twenty tablets were accurately weighed individually. Weighing was carried out by using digital weighing balance. After accurately weighing of twenty tablets, their average weight was determined. The weight of an individual tablet weight was compared with average weight (14).

Friability

Friability of the FDTs was determined by using Roche Friabilator. Tablets were subjected to the combined effect of shock and abrasions in a plastic chamber which revolves at the speed of 25 rpm. Tablets were dropped at the height of 6 inches in every revolution. To carry out the friability test, pre-weighed sample of tablets were placed in the friabilator. It was subjected to 100 revolutions. Tablets were dedusted by using soft muslin cloth and reweighed (14).

***In- vitro* disintegration test**

The *in-vitro* disintegration test of the prepared tablets was measured by using disintegrating apparatus. To carry out the disintegration test, one tablet was positioned in each tube of the basket. The basket is having the bottom surface made of a stainless-steel screen with mesh size no. 10. It was immersed in water bath at temperature of 37 ± 2°C. The time required for complete disintegration of the tablet in each tube was determined using a stop watch. It was

further complied with the given Pharmacopoeia standards. As per pharmacopoeia given standards “dispersible or disintegrating tablets must disintegrate within 3 mins” (15).

Wetting time

Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipient. The water penetration rate into the powder bed is proportional to the pore radius and is affected by the hydrophilicity of the powders. It is obvious that pores size becomes smaller and wetting time increases with an increase in compression force or a decrease in porosity. A linear relationship exists between wetting time and disintegration time. Thus wetting is the important step for integration process to take place. A piece of tissue paper folded double was placed in a petri dish (internal diameter is 6.5 cm) containing 6ml of water. The tablet was placed on the paper, and the time for complete wetting of the tablet was measured in seconds. The method was slightly modified by maintaining water at 37^{o}C. Wetting-time corresponds to the time taken for the tablet to disintegrate when kept motionless on the tongue (16, 17).

Dissolution Studies

The release rate of FDTs was determined using USP dissolution testing apparatus II. The dissolution testing was performed using 900ml of phosphate buffer pH 6.8 at 37±0.5°C temperature and speed 50 rpm. Sample of 5ml was withdrawn at 2 minutes interval of time upto 20 minutes and replaced with fresh medium to maintain sink condition and the percentage of drug release was determined using UV spectrophotometer (18-19).

RESULT AND DISCUSSION

Preparation of FDTs

Fast disintegrating tablets of Vildagliptin were prepared by Direct Compression Method. All the ingredients except granular directly compressible excipients were passed through 60mesh separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 50mg by using 8mm flat face round tooling on 10 station rotary tablet compression machine. A batch of 20 tablets was prepared for all designed formulations.

Pre-compression Characterization

The pre-compression characterization parameters such as Angle of repose, Bulk Density, Tapped Density, Carr’s index and Hausner’s ratio depicted that the prepared granules have good flow properties and the results of pre-compression parameters are displayed in Table II.

Batch	Angle of repose (θ)	Bulk density	Tapped density	Carr’s index	Hausner’s Ratio
F1	25.7±0.12	0.564 ± 0.02	0.532 ± 0.018	9.91 ± 0.33	1.11 ± 0.014
F2	25.5±0.22	0.565 ± 0.03	0.540 ± 0.022	10.80 ± 0.42	1.12 ± 0.012
F3	25.6±0.58	0.554 ± 0.02	0.575 ± 0.014	12.12 ± 0.44	1.13 ± 0.015
F4	26.5±0.41	0.564 ± 0.08	0.564 ± 0.017	12.01 ± 0.38	1.14 ± 0.012

F5	27.5±0.02	0.574 ± 0.01	0.568 ± 0.089	12.41 ± 0.44	1.12 ± 0.011
F6	25.0±0.07	0.561 ± 0.80	0.531 ± 0.182	9.081 ± 0.80	1.13 ± 0.12
F7	26.5±0.17	0.572 ± 0.08	0.522 ± 0.251	10.12 ± 0.012	1.14 ± 0.64
F8	28.8±0.23	0.581 ± 0.12	0.531 ± 0.93	11.32 ± 0.02	1.25 ± 0.097
F9	27.4±0.68	0.589 ± 0.18	0.562 ± 0.11	12.18 ± 0.018	1.14 ± 0.109
F10	28.0±0.18	0.59 ± 0.08	0.52 ± 0.05	12.28 ± 0.87	1.14 ± 0.180

Table II. Characterization of Vildagliptin granules (mean± sd., n=3)

Characterization of FDTs

Drug content

The drug content of FDTs indicated uniform distribution of drug in formulation. The results are depicted in Table III.

Tablet Hardness and Thickness

The hardness test depicted good mechanical strength and optimum formulation of tablets. The results are depicted in Table III.

Weight Variation

The weight variations of all the tablets were found to be uniform with low values of standard deviation and within the prescribed IP limits (Table III). It is related to tooling of the compression machine, head pressure, machine speed and flow properties of the powder. Inconsistent powder or granulate density and particle sizedistribution are common sources of weight variation during compression.

Friability

The friability values less than 1% indicated optimum formulation with good mechanical resistance (Table III). It is designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping.

Batch	Drug Content (%)	Hardness (kg/cm^2)	Thickness (mm)	Weight Variation (mg)	Friability
F1	98.3 ± 0.14	4.2 ± 0.12	3.28 ± 0.4	199 ± 0.21	0.59
F2	98.72 ± 0.5	4.2 ± 0.05	3.46±0.02	198±05	0.56
F3	98.45 ± 0.1	4.4 ± 0.18	3.73±0.3	200 ± 0.5	0.49
F4	99.5 ± 0.22	4.3 ± 0.22	4.00±0.03	201 ± 0.03	0.34
F5	98.7 ± 0.78	4.2 ± 0.78	3.43±0.03	198 ± 0.05	0.48
F6	99.75± 0.06	4.3 ± 0.06	3.69±0.1	199 ± 0.03	0.39
F7	100.25± 0.1	4.3 ± 0.12	3.44±0.04	201 ± 0.36	0.36
F8	97.2 ± 0.14	4.5 ± 0.14	3.38±0.05	198 ± 0.34	0.55
F9	98.8 ± 0.03	4.5 ± 0.03	3.71±0.04	201 ± 0.78	0.56
F10	97.5 ± 0.45	4.4 ± 0.45	3.48±0.08	200 ± 0.9	0.51

Table III. Post Compression characterization of Vildagliptin FDTs: Drug content, Hardness,Thickness, weight variation and Friability (mean± sd., n=3)

***In- vitro* disintegration test**

The FDTs showed rapid disintegration which is due to the penetration of saliva into the pores of the tablet, which lead to swelling of superdisintegrants to create enough hydrodynamic pressure for quick and complete disintegration of the tablets (Table IV).

It was concluded that the disintegration time increases with the increase in concentration of chitosan in the tablets, which was related to the disintegration mechanism of chitosan, which act by swelling on contact with the aqueous medium. As swelling is reported to be accompanied by gelling this could possibly occlude the pore in the tablet preventing further penetration of water into tablet matrix hence delay in disintegration time as the concentration increases. It indicates that increase in the concentration of chitosan has a negative effect on the disintegration of tablets.

In case of tablets containing crosspovidone, increasing concentration of crosspovidone from 2% to 5%, the disintegration times of tablets was affected significantly, indicating positive effect on the disintegration time, which may be due to the higher capillary action and little tendency of the crosspovidone to form viscous gel. Based on the disintegration results, the investigated superdisintegrants can be ranked according to their ability to swell in water as crosspovidone, Chitosan. On the basis of the results obtained in the preliminary screening studies, the batch containing crosspovidone showed the fastest disintegration.

Wetting Time/ *in vitro* dispersion time

The wetting time/ dispersion time decreased with increase in the concentration of superdisintegrants. It was observed that as the concentration of superdisintegrants increases water absorption ratio increases and disintegration time decreases (Table IV).

Water absorption ratio

The capacity of disintegrants to swell in presence of little amount of water was found to be in the range of 85.25 to 95.52 %. The water absorption ratio that is the up taking of water was very fast and the ratio was found higher (Table IV).

Batch	*In vitro* disintegration time (sec)	Wetting Time (sec)	Water absorption Ratio
F1	33.8 ± 0.45	40.2 ± 0.21	74.69 ± 0.13
F2	33.46±0.02	31.08 ± 0.15	78.47 ± 0.24
F3	15.73±0.3	25.5 ± 0.54	79.56 ± 0.39
F4	24.00±0.03	22.2 ± 0.13	81.47 ± 0.37
F5	23.43±0.03	20.5 ± 0.05	85.48 ± 0.27
F6	20.69±0.1	38.9 ± 0.93	79.41 ± 0.15
F7	28.44±0.04	32.1 ± 0.63	80.54 ± 0.95
F8	29.38±0.05	21.8 ± 0.13	85.36 ± 0.35
F9	27.71±0.04	15.1 ± 0.97	87.46 ± 0.33

F10	31.48±0.08	17.10 ± 0.25	85.52 ± 0.16

Table IV Post Compression characterization of Vildagliptin FDTs: *in vitro* disintegration time, wetting time, water absorption ratio(mean± sd., n=3)

Dissolution studies

The drug release is shown in table 5.12 and Figure 5.20, 5.21. The formulation F1-F5 containing 1,2,3,4 and 5% of chitosan showed a release of 82.4% to 92.14% indicating that the increase in superdisintegrant concentration increased the release of the drug from the tablets. Similarly, for the formulations F6-F10 containing 1-5% of Crospovidone showed the drug release 85.7 to 94.7 % indicating that the increase in superdisintegrant concentration increased the release of the drug from the tablets. Resultant formulation F9 showed best results with high percentage.

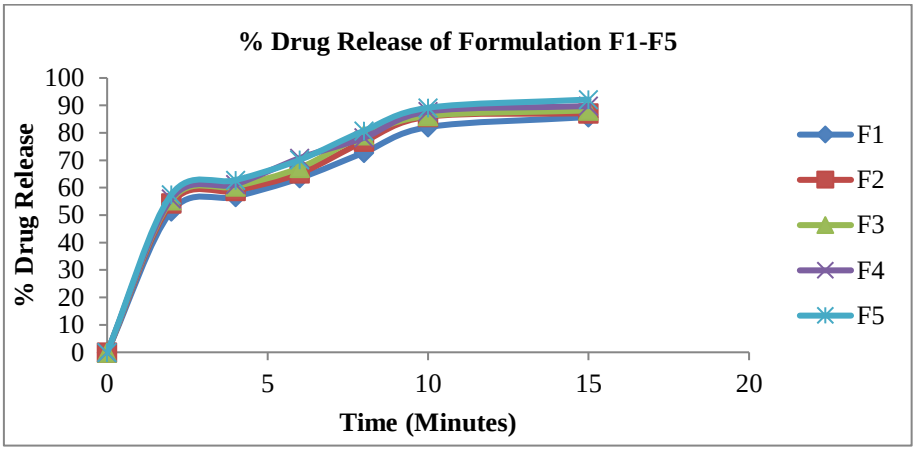

Figure I Dissolution time for Vildagliptin FDTs (F1-F5)

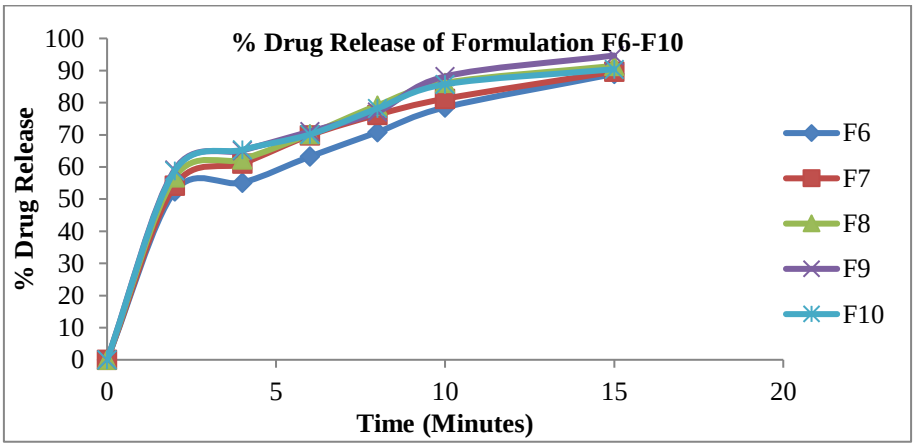

Figure II Dissolution time for Vildagliptin FDTs (F6-F10)

CONCLUSION

In conclusion, Fast disintegrating tablet formulation prepared by direct compression method using crospovidone in 4% concentration, formulation F9 emerged as the overall best formulation based in drug release characteristics (0.1N HCl) compared to other tablet formulation containing chitosan and crospovidone in varied concentration. These tablets were found to be biocompatible, safe, fast releasing and with higher patient compliance.

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