



DEVELOPMENT AND CHARACTERIZATION OF FAST DISINTEGRATING TABLETS OF GLIBENCLAMIDE

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Abstract: Diabetes mellitus is an important public health concern that affects more than 170 million individuals worldwide. It is expected that the number of people suffering from diabetes in the globe will reach approximately 5 million, or almost 10% of the population, by 2025 and it is one of the leading causes of death worldwide. Diabetes is a multi-organ disease independent of age, race and gender. The condition caused by a lesion in the beta cells of the pancreas. Type 2 diabetes is a long term metabolic disorder that characterized by high blood sugar, insulin resistance, and relative lack of insulin/ The prepared tablets were adequately hard to withstand pressure the hardness ranged from. The friability from the tablets was less which represent less loss of free particles. The weight variation and wetting were within limits. The dissolution of prepared tablets was relatively fast.

Keywords: *Diabetes mellitus*, Glibenclamide, fast disintegrating tablets

Introduction: *Diabetes mellitus* is an important public health concern that affects more than 170 million individuals worldwide. It is expected that the number of people suffering from diabetes in the globe will reach approximately 5 million, or almost 10% of the population, by 2025 and it is one of the leading causes of death worldwide. Diabetes is a multi-organ disease

independent of age, race and gender. A number of pathogenic actions are involved in the progress of diabetes, including destruction of the beta cells of the pancreas, which leads to insulin deficiency. Some of the processes can cause resistance to insulin, leading to increased plasma glucose levels and abnormalities of carbohydrate, fat and protein metabolism^[1]. Diabetes is classified into four groups: type 1, type 2, gestational and maturity onset diabetes of the young (MODY). Type 2 diabetes is a group of progressive disorders characterised by high blood glucose levels caused by a lack of insulin activity which can arise from a combination of impaired insulin secretion and

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impaired response to insulin in key tissues and organs, known as insulin resistance^[2]. Diabetes mellitus is known as blood-sugar disease. The pancreas fails to perform its appropriate function to stimulate insulin production in diabetic patients. The prevalence of type 2 diabetes mellitus (T2DM) has increased dramatically during recent decades and now it is a serious global health burden. According to the International Diabetes Federation 2015 report, the ratio of diabetic patients in the world is one out of eleven adults. Diabetes mellitus and its related complications are major causes of death in various countries. Diabetes mellitus (DM) is a metabolic disorder characterised by hyperglycaemia and interruption of the metabolism of protein, carbohydrate and fat. It may be associated with distinctive symptoms, such as polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger)^[3]. One consequence is that gluconeogenesis in the liver is no longer inhibited by insulin, and thus increases. Insulin resistance means that the body is unable to use insulin efficiently, because target tissues become unresponsive to insulin. Type 2 diabetes develops most often in middle-aged and older adults, but increasingly is appearing in children, teenagers and young adults^[4]. It accounts for about 90% of cases of diabetes. Patients with this type of diabetes may not require insulin to survive. Type 2 diabetes is often a result of excess body weight and physical inactivity in genetically predisposed individuals and is the most common type^[5]. Glibenclamide, a second-generation sulfonylurea, is used with diet to lower blood glucose in patients with diabetes mellitus type II. The primary mode of action of Glibenclamide in experimental animals appears to be the stimulation of insulin secretion from the beta cells of pancreatic islet tissue and is thus dependent on functioning beta cells in the pancreatic islets. Fasting insulin levels are not elevated even on long-term Glibenclamide administration, but the postprandial insulin

response continues to be enhanced after at least 6 months of treatment. Some patients fail to respond initially, or gradually lose their responsiveness to sulfonylurea drugs, including Glibenclamide. In humans Glibenclamide appears to lower the blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. In man, stimulation of insulin secretion by Glibenclamide in response to a meal is undoubtedly of major importance. For use as an adjunct to diet for the control of hyperglycemia^[6-9] and its associated symptomatology in patients with non-insulin-dependent diabetes mellitus. The aim of this work is to formulate and evaluate fast dissolving tablets of Glibenclamide.

Materials and Methods

Drug and Chemicals: Glibenclamide was received as a gift sample from IPCA Laboratories Ltd, Ratlam and other excipients such as talc, sodium starch glycolate, and lactose were obtained from the CDH, Mumbai.

Method of Preparation: Glibenclamide was mixed with sodium starch glycolate and lactose, talc was added. The blend was mixed properly and sieved (Table 1 and 2). The blend was compressed to prepare tablets.

Table No.1: Composition of Glibenclamide fast dissolving tablet Ingredients

Excipients	F1	F2	F3	F4	F5
Glibenclamide	5	5	5	5	5
Croscarmellose	2	5	2	5	0
Sodium starch glycolate	3	3	6	6	0
Lactose	60	60	60	60	60
MCC	30	30	30	30	30
Magnesium stearate	5	5	5	5	5
Talc	3	3	3	3	3

Evaluation of Formulated Tablets

Micromeritics

- **Angle of Repose:** Angle of repose was determined using fixed funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose (θ) was calculated^[10] using the formula.

$$\theta = \tan^{-1} (h / r)$$

- **Bulk Density:** Bulk density was determined by pouring the blend into a graduated cylinder. The bulk volume (V) and weight of the powder (M) was determined. The bulk density^[10] was calculated by using the below mentioned formula,

$$\text{Bulk density} = \frac{\text{Mass of Granules}}{\text{Volume}}$$

- **Tapped Density:** The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density^[10] was calculated using the following formula

$$\text{Tapped density} = \frac{\text{Weight of Blend}}{\text{Volume occupied in cylinder}}$$

- **Compressibility Index:** The simplest way for measurement of free flow of powder is compressibility, a indication of the ease with which a material can be induced to flow is given by compressibility index (I)^[11] which is calculated as follows,

$$I = \frac{V_o - V_t}{V_b \times}$$

Here, V_o is bulk volume and V_t is tapped volume. The value below 15% indicates a powder with usually give rise to good flow characteristics, whereas above 25% indicate poor flow ability.

- **Hausner's Ratio:** Hausner's ratio is an indirect index of ease of powder flow^[11]. It is calculated by the following formula,

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25).

- **Thickness:** Thickness of tablet was determined by using vernier calliper (Mitutoya, Model CD-6 CS, Japan).

- **Hardness:** The crushing strength of the tablets was measured using a Monsanto hardness tester (Sheetal Scientific Industries, Mumbai, India). Three tablets from each formulation batch were tested randomly^[12] and the average reading noted.

- **Friability:** Twenty tablets were weighed and placed in a Roche friabilator (Electrolab, India). Twenty reweighed tablets were rotated at 25 rpm for 4 min. The tablets were then dedusted and reweighed and the percentage of weight loss was calculated. The percentage friability of the tablets were measured^[12] as per the following formula,

$$\text{Percentage friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

- **Weight Variation:** Randomly, twenty tablets were selected after compression and the mean weight was determined^[12]. None of the tablets deviated from the average weight by more than $\pm 7.5\%$.

- **Wetting Time:** A piece of circular tissue paper (8cm) folded twice was placed in a Petri dish (Internal Diameter = 9cm) containing 10 ml of buffer solution simulating saliva pH 6.8. A tablet was placed on the paper and the time taken for complete wetting was noted. Three tablets from each formulation were randomly selected and the average wetting time was noted^[13]. The results are tabulated in Table 2.

- **In Vitro Dispersion Time:** *In vitro* dispersion time of prepared tablet was done by dropping the tablet in 10 ml measuring cylinder containing 6 ml of simulated salivary fluid (pH 6.8). Time required for complete dispersion of tablet was measured^[14].

- **Dissolution Study:** In vitro release of Glibenclamide from tablets was monitored by using 900 ml of simulated intestinal fluid,

SIF (USP phosphate buffer solution, pH 7.4) at 37±0.5°C and 50 rpm using programmable dissolution tester [Paddle type, model TDT-08L, Electrolab, (USP), India]. 5 ml Aliquots were withdrawn at one minute time intervals and were replenished immediately with the same volume of fresh buffer medium. Aliquots, following suitable dilutions, were assayed spectrophotometrically (UV-1700, Shimadzu, Japan) at 378 nm.

▪ **Assessment of Therapeutic Efficacy:**

Therapeutic efficacy assessment was conducted on streptozotocin-induced diabetic rats, whereby the decrease in blood glucose level (BGL) was taken as a pharmacodynamic parameter for evaluating the bioavailability of the drug. Male Wistar rats weighing 200–250 g were kept on standard diet and maintained under controlled conditions of humidity (30-70%) and temperature (24±2°C). The animals were fasted overnight and then intraperitoneally injected with 50 mg/kg streptozotocin 34, 35 10–14 days prior to the study for inducing diabetes. Fasting blood glucose level was assessed using Fast Take glucometer SmartScan®36. Rats having moderate diabetes, with fasting BGL in the range of 200-300 mg/dl, were selected for the study. The animals were divided into 5 groups each comprising 12 rats. The first group was given the drug orally in a dose of 10 mg/kg body weight. Second group received marketed formulation. The third group was subjected prepared tablets. The blood glucose level (BGL) after oral drug administration and after transdermal application of the investigated films was measured at different time intervals, up to 48 h. Each animal served as its own control and hence, the hypoglycemic response was evaluated as percentage decrease in blood glucose level calculated as follows:

$$\% \text{ Decrease in BGL} = \frac{\text{BGL at } t=0 - \text{BGL at } t}{\text{BGL at } t} \%$$

The pharmacodynamic parameters taken into consideration were maximum percentage decrease in blood glucose level, time for maximum response (t_{\max}), time at which half peak percentage decrease in BGL prevails ($t_{1/2p}$) and area under percentage decrease in BGL versus time curve ($\text{AUC}_{0-48 \text{ h}}$) which was calculated adopting the trapezoidal rule 38.

▪ **Study Approval:** All Animal studies were conducted according to the protocol approved by the Institutional Animal Ethics Committee, College of Pharmacy, Sri Satya Sai University of Technology & Medical University, Sehore, Madhya Pradesh, India.

▪ **Statistical Analysis:** Statistical analysis of the results was performed using one-way analysis of variance (ANOVA), followed by the least-significant difference test (LSD). This statistical analysis was computed using the SPSS® software.

Results & Discussion: Five formulations of Glibenclamide were prepared with different concentration of the four individual Superdisintegrants: Croscarmellose and Sodium starch glycolate. For each formulation, blend of drug and excipients were prepared and evaluated for various parameters as explained earlier. The powder blend was compressed using direct compression technique. Bulk density was found in the range of 0.45 – 0.43 g/cm³ and the tapped density between 0.35 – 0.38 g/cm³. By using these two density data, Hausner's ratio and compressibility index was calculated. The compressibility index was found between 13.27 and 20.32 and the compressibility correlation data indicated a fairly good flowability of the powder blend. The good flowability of the powder blend was also evidenced with angle of repose (range of 20.12 –25.97), which is below 40° indicating good flowability. Micromeretic results of the all batches were shown in Table 2.

Table 2: Characterization of Glibenclamide Tablets

Parameters	F1	F2	F3	F4	F5
Hardness (kg/cm ²)	3.21±0.13	3.25±0.84	2.87±0.47	3.26±0.48	3.57±0.76
Friability (%)	0.874± 0.023	0.742±0.012	0.654±0.023	0.698±0.075	0.575±0.024
Weight variation (mg)	101±4	100±3	99±2	100±4	102±3
Thickness (mm)	3.25±0.075	3.37±0.066	3.52±0.012	3.92±0.031	3.97±0.074
Wetting time (s)	16.23±2.45	15.23±1.12	13.45±2.02	14.54±2.13	14.21±1.45
In-vitro dispersion time (s)	30.55±2.21	28.57±1.56	26.23±2.43	25.54±3.33	24.41±2.23

Results are expressed as mean±SD (n=3)

The prepared tablets were adequately hard to withstand pressure the hardness ranged from (2.91-3.67). The friability from the tablets was

less which represent less loss of free particles. The weight variation and wetting were within limits (Table 3).

Table 3: Micromeretics of Glibenclamide Blend

Formulation Code	Bulk density (gm/ml)	Tapped density (gm/ml)	Angle of repose (θ)	Percentage compressibility	Hausner's Ratio
F 1	0.47	0.42	27.23	21.35	1.32
F 2	0.47	0.40	26.75	19.75	1.35
F 3	0.46	0.39	27.12	17.62	1.37
F 4	0.45	0.38	24.63	15.35	1.38
F 5	0.45	0.37	22.76	14.31	1.45

Results are expressed as mean±SD (n=3)

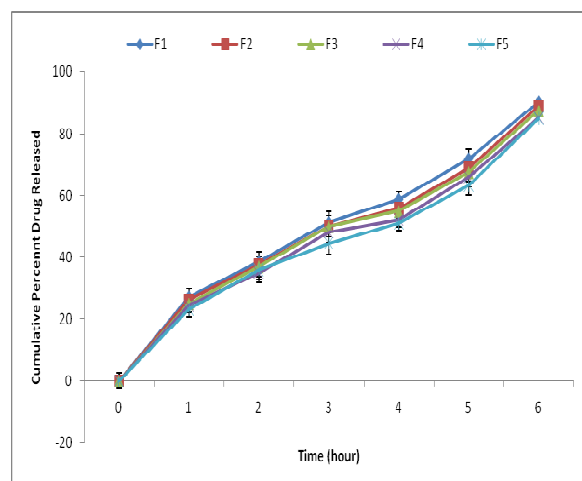


Figure 1: Dissolution studies of prepared tablets (n=3)

The dissolution of prepared tablets was relatively fast (Figure 1). These results indicated that dissolution parameter values of croscarmellose sodium and sodium starch glycolate^[15] containing tablets are in consistent with the disintegration time values observed.

Assessment of Therapeutic Efficacy: *In vivo* studies on diabetic rats revealed that BGL of the control group at different time intervals was higher than the corresponding level for the groups treated by oral or transdermal administration of the drug (Table 6). All tested formulae exhibited significant (p < 0.001) decrease in BGL). The control group didn't show any noticeable hypoglycemic effect. Prepared tablets exhibited maximum hypoglycemic effect 4-6 hours post application and the hypoglycemic effect were sustained up to 48 hours. However, oral administration of the drug showed a peak percentage decrease in BGL, which was reached within 3-4 hours post dosing; after which a marked fast decline in hypoglycemic effect was observed. The peak of percentage decrease in BGL (Table 2) for the orally administered drug was higher than that of formulation; the difference is significant (P<0.01).. This points out that the use of a combination of release enhancers led to a

significant increase in peak hypoglycaemic effect to such an extent reaching values comparable to that of the oral administration (Table 2). The values of t_{max} for the formulation

(F3) were higher than that after oral administration of the drug the difference is significant ($P < 0.01$).

Table 4: Effect of Formulations of Glibenclamide on its Pharmacodynamic Parameters in Diabetic Rats

Treatment	Pharmacodynamic Parameter			
	Max (%) decrease in BGL	t_{max} (hr.)	$t_{1/2p}$ (hr.)	AUC(0-48hr.)
Group I	34.01±1.52	3.25±0.70	8.05±1.35	399.33±29.55
Group II	25.70±1.45**	6.020±0.00**	35.05±1.26***	857.42±45.42***
Group III	30.66±1.34	5.29±0.67**	36.81±1.31***	959.51±27.44***

***Significance at $p > 0.001$

Conclusion: In the light of the results, our study indicates that Glibenclamide tablets may have good anti-diabetic activity. The immediate release effect of drug may be responsible for rapid reduction of blood glucose levels.

References

1. Alberti KGMM, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. *Diabet Med* 1998;15(7):539–53.
2. Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001;344(18):1343–50.
3. Association AD. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2010;33(Supplement 1):S62–9.
4. Ganeshpurkar A, Kohli S, Rai G. Antidiabetic potential of polysaccharides from the white oyster culinary-medicinal mushroom *Pleurotus florida* (higher Basidiomycetes). *Int J Med Mushrooms* 2014;16(3):207–17.
5. Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *N Engl J Med* 2001;345(11):790–7.
6. Ganeshpurkar, A, Saluja A. The Pharmacological Potential of Rutin. *Saudi Pharm J* 2016;
7. Ganeshpurkar A, Rai G, Jain A. Medicinal mushrooms: Towards a new horizon. *Pharmacogn Rev* 2010;4(8):127–35.
8. Bhadoriya SS, Ganeshpurkar A, Bhadoriya RPS, Sahu SK, Patel JR. Antidiabetic potential of polyphenolic-rich fraction of *Tamarindus indica* seed coat in alloxan-induced diabetic rats. *J Basic Clin Physiol Pharmacol* 2018;29(1):37–45.
9. Dubey PK, Ganeshpurkar A, Dubey S, Kakkar A. Isolation and studies on chemotherapeutic potential of aloin. *Int J Green Pharm* 2015;9(1):45–9.
10. Bagster RHDF, Crooks MJ. Flow studies on directly compressible tablet vehicles.

- Drug Dev Ind Pharm 1977;3(5):475–87.
11. Fassihi AR, Kanfer I. Effect of compressibility and powder flow properties on tablet weight variation. Drug Dev Ind Pharm 1986;12(11–13):1947–66.
 12. Seitz JA, Flessland GM. Evaluation of the physical properties of compressed tablets I: Tablet hardness and friability. J Pharm Sci 1965;54(9):1353–7.
 13. Bi Y, Sunada H, Yonezawa Y, Danjo K, Otsuka A, IIDA K. Preparation and evaluation of a compressed tablet rapidly disintegrating in the oral cavity. Chem Pharm Bull 1996;44(11):2121–7.
 14. Swamy P V, Areefulla SH, Shirs SB, Smitha G, Prashanth B. Orodispersible tablets of meloxicam using disintegrant blends for improved efficacy. Indian J Pharm Sci 2007;69(6):836.
 15. Sharma D. Formulation development and evaluation of fast disintegrating tablets of salbutamol sulphate for respiratory disorders. ISRN Pharm 2013;13:67–75.