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FORMULATION AND EVALUATION OF FAST DISINTEGRATING TABLET OF GLIMEPIRIDE

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ABSTRACT

Objective: Glimepiride is the third generation sulphonylurea agent, used for the treatment of type II diabetes mellitus. Glimepiride is given once daily in doses from 1-4 mg. The objective of the present study was to formulate and evaluate the fast disintegrating tablets of Glimepiride. **Method:** The fast dissolving tablets of glimepiride were prepared by direct compression method by using different disintegrating agents. The drug and the excipients were evaluated for angle of repose, bulk density, tapped density, carr's index and hausner's ratio for the determination of flow property of the powder. The formulated tablets were evaluated for thickness, hardness, friability, wetting time, water absorption ratio, and dissolution and disintegration time. **Result:** Fast disintegrating tablets were successfully prepared by direct compression method. The disintegration time was less than 1 minute which is acceptable. The obtained results clearly indicated that the prepared tablets of glimepiride were fast disintegrating. **Conclusion:** The fast disintegrating tablets of glimepiride are prepared with disintegrating time less than 1 minute, this will help in future for further improvement of dosage and formulation and will help to control immediately the rise glucose level of chronic diabetic patients.

Key words: Glimepiride, Fast disintegrating tablet (FDTs), Direct compression method, Super disintegrants.

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INTRODUCTION

Glimepiride is long acting, third generation sulfonylurea with hypoglycemic activity. The duration of action of glimepiride is 12-14 hours. Glimepiride acts either by stimulating the release of insulin from the pancreatic beta cells or it binds to ATP-sensitive potassium channel receptors on the pancreatic cell surface, reducing the potassium conductance and causing depolarization of the membrane. It is 99.5% bound to plasma proteins. Its dose is 1 mg, 2 mg and 4 mg according to the need of the patient. It is used for type 2 diabetes mellitus, which account for 95% of the total cases of diabetes mellitus **[1, 2].**

Fast disintegrating tablets (FDT's) are also known as fast disintegrating, fast dispersing, rapid dissolving, and rapid melting and or orodisperse tablets **[3].** It is defined as 'the solid dosage form that can be disintegrated, dissolved or suspended by saliva in the mouth resulting in easy swallowing, and it disintegrates instantly when placed on the tongue **[4].** FDT's disintegrate by any of the mechanisms including capillary action, swelling, due to repulsive forces, deformation and release of gases **[5].**

The fast disintegrating tablets are prepared by new technology and are far better than other conventional dosage forms. Fast disintegrating tablets were selected to be prepared as there is an ease of administration for patients who are mentally ill, disabled and uncooperative. It requires no water and has quick disintegration and dissolution time. It allows high drug loading, bioavailability and rapid onset of action is achieved. Rapid absorption through pregastric absorption of drugs from mouth, pharynx, and esophagus as saliva passes down.

In manufacturing procedure, there are many methods like wet granulation and dry granulation but here tablets were prepared by direct compression method. The FDTs are hard tablets with decreased disintegration time and ensures formulation to meet dissolution requirements **[6].**

Fast disintegrating tablets were prepared by changing the quantity of super disintegrants as super disintegrants are essential in its formulation because it disintegrates the tablets within seconds. By different trials and by increasing the quantity of croscarmellose sodium that is superdisintegrant, disintegration time was checked and then FDTs of glimepiride were prepared.

MATERIAL AND METHOD

All the ingredients were weighed separately and accurately on the electrical weighing balance, sieved all the ingredients separately from sieve no. 30. Then all the ingredients were mixed in the pestle and mortar except lubricant (magnesium stearate). After that all the ingredients were mixed in the double cone blender, in order to obtain homogenous mixing. Then lubricant was added in the mixer and the process of mixing was continued for 5 more minutes. The powder mixture was filled into the die, so that the powder can be compressed to form the tablets of 150 mg each containing 4 mg of glimepiride (**Table 1, Fig. 1**).

Table 1: Formulation composition of fast disintegration tablets batch.

Ingredients	**(mg)**
Glimepiride	600
MCC	4500
Croscarmellose sodium	1800
Magnesium stearate	750
Lactose	9000
Talc	450

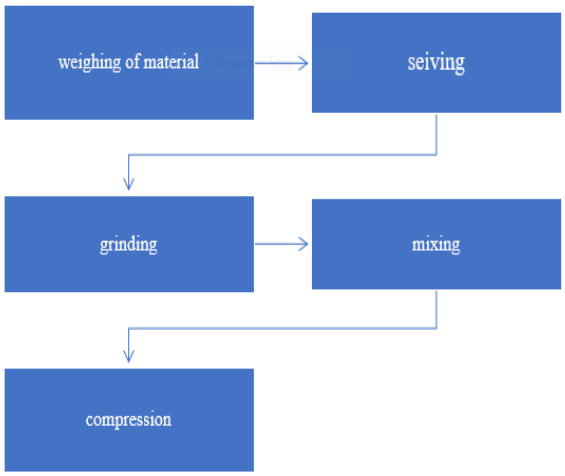

Figure 1: Schematic diagram of direct compression method fast disintegration tablets.

Pre-Compression Parameters

Melting Point

Reduce the substance to a very fine powder and unless otherwise directed, render it anhydrous when it contains water of hydration by drying it to a specified temperature. Charge a capillary glass tube, one end of which is sealed, with the sufficient quantity of powder to form a column in the bottom of the tube 2.5 to 3.5 mm. Heat the bath until the temperature is about 30˚C below the expected

melting point. Remove the thermometer, and quickly attach the capillary tube to the thermometer by wetting bath with a drop of the liquid of the bath or otherwise and adjust its height so that material in the capillary level with the thermometer bulb. When temperature is about 3˚C below the lower limit of the expected range, reduce the heating so that the temperature rises at a rate of about 1 to 2 degrees per minute Continue the heating until melting is complete and note the melting point **[7].**

Bulk Density

Bulk density of the powder was determined by pouring gently some amount of sample through a glass funnel into a graduated cylinder. The volume occupied by the sample was recorded. Bulk density was calculated by applying the following equation **[7, 8].**

Bulk Density = Wt of sample / Vol of sample

Tapped Density

Tapped density of the powder was measured by pouring gently some amount of sample through a glass funnel into a graduated cylinder. The cylinder was tapped from height of 2 inches until a constant volume was obtained (100 taps). Volume occupied by the sample after tapping was recorded and tapped density was calculated.

Angle of Repose

The angle of repose of the powder was determined by fixed funnel method. The powder was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap I was measured. It is expressed in gm/ml. By applying following formula, angle of repose was calculated **[9, 10]**.

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

Carr's Index

% compressibility was determined by the Carr's compressibility index **[11].**

Carr's Index = (TD - BD / TD) X 100

Hausner's Ratio

Hausner's ratio was calculated by making use of BD and TBD **[12].**

Hausner's Ratio = Tapped Density / Bulk Density

Post-Compression Parameters

Weight Variation

Twenty tablets were randomly selected and weighed individually using an electronic digital balance. Mean of tablet weights was calculated. Results are presented as mean±SD. Formulated tablets comply with the test if not more than two of the individual tablet deviate from the average weight by more than percentage and none deviate more than the twice percentage specified **[7].**

Hardness Test

Ten tablets were randomly selected and then by placing the tablet one by one in between jaws of Monsanto Hardness Tester, the hardness was measured. Then the average value of all tablets was calculated **[12].**

Thickness Variation

Ten tablets were taken randomly, and their thickness was measured with a digital vernier caliper. The mean standard deviation values were calculated. It should be not more than ±5 % variation of standard value **[14].**

Friability test: Ten tablets were randomly selected and weighed them. Friability was measured using Roche friabilator. Pre-weighed tablets were placed in a plastic chambered friabilator attached to a motor revolving at a speed of 25 rpm for 4 min. The tablets were then de-dusted, accurately reweighed, and

percentage loss in weight (friability) was calculated [**14**].

Content Uniformity

The tablets were kept in 100ml volumetric flask containing phosphate buffer pH 4.4 for 24hrs.When the tablets were completely dissolved the solution was centrifuged. After centrifugation the supernatant was dissolved. Absorbance was measured spectrophotometrically at 228 nm. Dilution was made using phosphate buffer (pH 7.8) as per requirement [**12**].

Wetting Time and Water Absorption Ratio

It is related with each other and performed in the same manner. The tissue papers were placed in a petri dish by folding it into five circular form in a 10 cm diameter. Petri dish containing ten milliliters of water with 0.5 % nigrosine, a water-soluble dye, was added to the petri dish. The dye solution was used to identify complete wetting of the tablet surface. The Tablet was carefully placed on the surface of the tissue paper in the center of the petri dish at 25 ℃. The time required for water to reach the upper surface of the tablets and to completely wet them was noted as the wetting time. It was carried out in six times. Wetting time was recorded using a stopwatch and presented as mean standard deviation [**11**].

Dissolution Test

The *invitro* drug release study was performed using USP dissolution apparatus (Paddle Apparatus) Dissolution study was carried out for 12 hours. Phosphate buffer having pH 7.8; 900ml was used as dissolution media. Samples of each 5ml were withdrawn after everyone hour for a period of 12h.Volume in dissolution vessel was kept constant by equal replacement with fresh media. The samples were collected in test tubes after filtration through filter paper. The amount of the drug in the aliquots was quantified by taking absorbance of the sample at 288 nm spectrophotometrically, using phosphate buffer pH 7.8 (dissolution media) as the blank [**7**].

Disintegration Test

The disintegration of tablets was determined using a USP disintegration testing apparatus type II with pH 6.8 phosphate buffer as a disintegrating medium. The medium was maintained at 37±0.5 °C throughout the test. Six tablets were placed into an apparatus and disintegration time was recorded. Measurements were carried out in replicates of six and mean standard deviation were recorded **[7].**

RESULTS

Different tests were performed on powder material before compression of tablet.

Pre-compression Parameters

Physical appearance of the powder material was solid (amorphous). Melting point determined by capillary method was 207 ˚C. Bulk density and tapped density was found to be 0.499 and 0.898 respectively. Carr's index and Hausner's ratio was found to be 16 % and 1.16 respectively. Angle of repose was measured as 33.

Post compression Parameters

In weight variation test, the standard deviation was 7.3% which is within acceptable range.

After applying force, the hardness limit of all prepared tablets was 2.6-3.5 kg/cm^2 that is acceptable. The mean of the thickness of the tablets was±5% that is somehow acceptable for fast dissolving tablets. Friability percentage was 0.98% that is an indication of good mechanical resistance of the tablets.

Water absorption ratio and wetting time, which are important criteria for understanding the capacity of disintegrants to swell in the presence of little amount of water were found to be in the range of 64-84% and

22-94 seconds respectively. Drug content was found to be in the range of 96 to 98%, which is within acceptable limits. Disintegration time was less than 1 minute that is in acceptable limits for fast disintegrating tablets. *In-vitro* dissolution studies showed that more than 50 % of the drug was released from the formulation within 5 min.

FTIR studies did not indicate any excipient incompatibility, either during mixing or after compression.

Table 2: post-compression parameters of fast disintegrating glimepiride tablets

Parameters	Results
Weight variation	7.3%
Hardness	2.6-3.5 kg/cm^2
Friability	0.98%
Water absorption ratio	64-84 %
Wetting time	22-94 sec
Drug Content	96-98 %
Dissolution time	>50% drug release within 5min
Disintegration time	<1 min

DISCUSSION

The aim of making directly compressible fast disintegrating tablet is that it disintegrates or disperses quickly in saliva within seconds. Super disintegrants form the core on FDT formulations that are necessary for formulation of fast dissolving tablets. So by increasing quantity of super disintegrants or by using in combinations, target of fast disintegrating tablet can be achieved.

CCS is cross linked carboxymethyl cellulose sodium; its unique ability imparts excellent water-wicking properties and cross linking makes formulation more hydrophilic and highly absorbent material resulting in excellent swelling properties. Magnesium stearate and Talc are lubricants that provide anti-adherent property so that powder can't stick to the surface of the punch machine. When using talc, it should always be blended into the formulation first followed by the lubricant (i.e. magnesium stearate). Lactose is diluent that increases compressibility properties of powder in direct compression method. Microcrystalline cellulose is a binder that also imparts ability to powder to compress with each other.

Melting point obtained was 207˚C that is conforming to official compendia. Angle of Repose of powder material indicates good flow property because of the lactose that is a diluent that increases the flow and compressibility properties of the powder in direct compression. Bulk density and tapped density was found to be 0.499 and 0.898 respectively.

In post-compression parameters, weight variation was 7.3% that is in acceptable limit. Deviation occurs because of improper filling of die while compressing tablet or sometimes due to instrumental error. So the weight variation and hardness can be affected by the compression force applied by punching machine. Thus, weight variation, hardness, thickness and friability are closely linked to causing rapid disintegration.

The hardness of the tablet was 2.6-3.5kg/cm2 that is within acceptable range for FDTs because if the tablet is too hard, it cannot disintegrate immediately and if not disintegrate then there is delay in tablet dissolution. Friability percentage was 0.98% that is in acceptable limit. It can be affected by increasing or decreasing the amount of binder (Microcrystalline cellulose). Water absorption ratio and wetting time is affected by nature of superdisintegrant. The

mechanism involved in Croscarmellose sodium is when it comes into contact with water it swells to a large extent to disintegrate the tablets. Also, it has fibrous nature that allows intra-particulate as well as extra-particulate wicking of water even at low concentration levels. Disintegration time was less than 1min that is affected by nature and amount of filler, binder and lubricant. In vitro dissolution studies showed that more than 50 % of the drug was released from the formulation within 5 min. It can be affected by nature and amount of excipients. There are also some other factors in test apparatus like temperature, pH of buffer, agitation intensity, vibration , eccentricity of stirring element.

CONCLUSION

Fast disintegrating tablets of glimepiride was formulated successfully. In designing a Fast disintegrating tablets selection of superdisintegrant is extremely important. The results of the present study suggest that cross carmellose made the drug release faster from tablets. It is concluded that it is possible to prepare the fast disintegrating tablets of glimepiride by using the simple and conventional technique.

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