EFFECT OF SYNTHETIC SUPERDISINTEGRANTS ON DRUG RELEASE OF GLIBENCLAMIDE

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Abstract : An oral solid dosage form should ideally disperse into the primary particles from which it was prepared. Tablets and capsules which need rapid disintegration, the inclusion of the right disintegrant is a prerequisite for optimal bioavailability. Superdisintegrants are used to improve the efficacy of solid dosage forms. This is achieved by decreasing the disintegration time which in turn enhances drug dissolution rate. The present study comprises the effect of superdisintegrants which are being used in the formulation to provide the safer, effective drug delivery with patient's compliance. Glibenclamide, a sulphonyl urea is a poorly water soluble orally active hypoglycemic agent, with problems of bioavailability indicating extensive first pass metabolism in liver. In view of substantial first pass effect and shorter elimination half-life, this work investigated the possibility of developing Glibenclamide tablets allowing fast and complete drug dissolution by using three superdisintegrants namely Crosspovidone, Crosscarmellose and Sodium starch glycolate in different concentrations. Tablets were prepared by direct compression method and evaluated for weight variation, hardness, friability, disintegration time and dissolution rate and results were found to be within standard limits. Among all the six formulations, F6 was found to be fast dissolving formulation on the basis of %drug release, disintegration time & wetting time.

KeyWords **– Hypoglycemic agent, cross carmellose, sodium starch glycolate, crosspovidone.**

INTRODUCTION

Superdisintegrants:

Superdisintegrants are the agents added to the tablet and some encapsulated formulations to promote the breakup of tablet and capsules “slugs” into smaller fragments in an aqueous environment thereby increasing the available surface area and promoting a more rapid release of the drug substance

(OR)

Superdisintegrants, are those substances, which facilitate the faster disintegration with smaller quantity in contrast to disintegrants.

Ideal Properties Of Superdisintegrant:

Since superdisintegrant is used as an excipient in the tablet formulation, it has to meet certain criteria other than its swelling properties. The requirement placed on the tablet disintegrant should be clearly defined. The ideal disintegrant should have

- Poor solubility
- Poor gel formation
- Good hydration capacity
- Good mouth feel
- Good moulding and flow properties

AIM AND OBJECTIVES

Aim:
To formulate and evaluate orally disintegrating tablets of Glibenclamide

Objectives:

- To prepare various formulations by direct compression method using different concentrations of sodium starch glycolate (F1,F2) and crosscarmellose(F3,F4) and crosspovidone(F5,F6) in concentration range of 2% and 6% respectively.
- Formulations must be evaluated for precompressional and postcompressional parameters like uniformity of weight, thickness, hardness, friability, drug content, wetting time, water absorption ratio, *in vitro* disintegration time and *in vitro* dissolution study to select a promising formulation.
- To achieve its dissolution rate.
- To achieve its bioavailability.

MATERIALS AND EQUIPMENT

Materials:

S.no	Ingredients	Manufacturer
1	Glibenclamide	Dr. Reddy's laboratories Pvt. Ltd
2	Sodium starch glycolate	S.d. fine chemicals, Hyderabad.
3	Crosscarmellose	S.d. fine chemicals, Hyderabad
4	Crosspovidone	Accord laboratories, Hyderabad.
5	PVP K30	Vijaya lakshmi chemicals,Hyderabad.
6	Mannitol	Vijaya lakshmi chemicals,Hyderabad.
7	Lactose	Virat laboratories ,Hyderabad.
8	Micro crystalline cellulose	S.d. fine chemicals,Hyderabad
9	Talc	Accord laboratories,Hyderabad
10	Magnesium stearate	Accord laboratories,Hyderabad

Table No.1: Materials used in formulation of Glibenclamide tablets

Equipmemts:

Sl. No.	Equipment	Model/ Source
1.	UV-spectrophotometer	1700 Pharmascope, Shimadzu
2.	Digital Balance	BL-220H, Shimadzu
3.	Digital pH meter	Systronic Electronics, Mumbai
4.	Dissolution apparatus	TDT-06 N, Electrolab, Mumbai
5.	Hot air oven	Tempo Instruments & Equipments, Mumbai
6.	Hardness tester	.Pfizer Hardness Tester

7.	Friability test apparatus	Riche Rich Pharma, Mumbai
8.	Tablet punching machine	Clit, Ahmedabad
9.	Stability chamber	Osworld JRIC-11, Mumbai

Table no- 2 : Instruments used

METHEDOLOGY

Preperation Of Buffers And Reagents:

Potassium dihydrogen phosphate(0.2M): Dissolve 27.218gms of potassium dihydrogen phosphate in water and dilute with water upto 1000ml.

Sodium hydroxide(0.2M): Dissolve 8gms of sodium hydroxide pellets in water and make upto 1000ml with distilled water.

pH 7.4 Phosphate buffer: Place 50ml of 0.2M potassium dihydrogen phosphate in a 200ml volumetric flask, add 39.1 volume of 0.2M NaOH and then add water to makeup the volume.

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Spectroscopic studies:

Detection of analytical wavelength λ_{max} :

A 100µg/ml solution was prepared by dissolving 10 mg in dissolution media (pH 7.4 phosphate buffer) in a 100 ml volumetric flask. The solution was sonicated and solution was made upto 100 ml and scanned between 400-200 nm (UV range).

Preparation Of Calibration Curve:

Preparation of standard calibration curve in pH 7.4 phosphate buffer:

100mg of Glibenclamide is dissolved in 100 ml phosphate buffer. From the solution pipette out 10ml and make upto 100ml. From this solution 1ml, 2ml, 3ml, 4ml, 5ml were taken and made upto 10 ml with pH7.4 phosphate buffer The correlation coefficient was calculated.

PREFORMULATION STUDIES

Characterization Of Powder Mixture

The powder blend was evaluated for bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose.

1. **Bulk density (D_b):** It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and the initial volume was noted. This initial volume is called the bulk volume. From this, the bulk density is calculated according to the formula mentioned below. It is expressed in g/cc and is given by:

$$D_b = \frac{M}{V_0}$$

Where,

M is the mass of powder,

V_0 is the bulk volume of the powder.

2. **Tapped density (D_t):** It is the ratio of total mass of powder to the tapped volume of powder. The volume was measured by tapping the powder for 500 times. Then the tapping was done for 750 times and the tapped volume was noted (the difference between these two volumes should be less than 2 %). If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. It is expressed in g/cc and is given by:

$$D_t = \frac{M}{V_1}$$

Where,

M is the mass of powder,

V_t is the tapped volume of the powder .

3. **Carr's index (%):** The bulk density is the measurement of weight to the volume of the sample. Tapped density is determined as the measurement of weight of the sample to the volume after tapping the measuring cylinder for 500 times from a height of 2 inches. The percentage compressibility (Carr's index) was calculated as 100 times the ratio of the difference between tapped density and bulk density to the tapped density.

$$\text{Carr's index} = 100 \times \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}}$$

4. **Hausner's ratio:** Hausner's ratio is the ratio of tapped density to bulk density. Lower the value of Hausner's ratio better is the flow property. The powder with Hausner's ratio less than 1.18, 1.19-1.25, 1.3-1.5 and greater than 1.5 indicates excellent, good, passable and very poor flow properties, respectively.

$$\text{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

5. **Angle of repose (θ):** It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane.

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

Where, θ is the angle of repose

h is the height in cms

r is the radius in cms

Method: The powder mixture was allowed to flow through the funnel with its tip fixed to stand at a definite height (h) from a graph paper placed on a horizontal surface. The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. A value for angle of repose ≥ 40° suggests a poorly flowing material

PREPARATION OF MOUTH DISSOLVING GLIBENCLAMIDE TABLETS BY DIRECT COMPRESSION METHOD USING SUPERDISINTEGRANTS

Direct Compression Method: Glibenclamide and all the ingredients were weighed accurately and passed through sieve # 44. The drug and sifted materials were mixed thoroughly in a polythene bag. Finally accurately weighed talc, magnesium stearate were added to the above blend and powder was blended thoroughly, and then compressed the tablets using 10mm round shape concave punches

Formulation/ Ingredients	F1(mg)	F2(mg)	F3(mg)	F4(mg)	F5(mg)	F6(mg)
Glibenclamide	10	10	10	10	10	10
Sodium starch glycolate	8	24	-	-	-	-
Croscarmellose sodium	-	-	8	24	-	-
Crosspovidone	-	-	-	-	8	24
Mannitol	50	50	50	50	50	50
Microcrystalline cellulose	266	250	266	250	266	250
PVP K30	10	10	10	10	10	10
Magnesium stearate	4	4	4	4	4	4
Talc	2	2	2	2	2	2

Table No.3: Composition of glibenclamide tablets prepared by direct compression (for 1 tablet)

EVALUATION OF TABLETS:

Weight variation: Twenty tablets were selected at random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with an average weight. The results were tabulated.

Content uniformity test

Ten tablets were weighed and powdered, a quantity of powder equivalent to 10 mg of glibenclamide was transferred to a 25 ml volumetric flask and 15 ml pH7.4 phosphate buffer is added. The drug is extracted in water by vigorously shaking the stoppered flask for 15 minutes. Then the volume is adjusted to the mark with distilled water and the liquid is filtered. The glibenclamide content was determined by measuring the absorbance at 300 nm after appropriate dilution. The drug content was calculated using the standard calibration curve. The mean percent drug content was calculated as an average of three determinations.

***In vitro* dispersion time**

Tablet was added to 10 ml of pH7.4 phosphate buffer solution at 37 ± 0.5° C. Time required for complete dispersion of a tablet was measured. The results were tabulated.

Hardness

A significant strength of ODT is difficult, to achieve, due to, the specialized processes, and ingredients used in the manufacturing. The limit, of hardness for the ODT is usually kept in a, lower range to facilitate early disintegration in the mouth. The hardness of the tablet may be, measured using conventional hardness test.

Friability

To achieve % friability within limits for an ODT is a challenge for a formulator since all methods of manufacturing of ODT are, responsible for increasing the % friability values., Thus, it is necessary that this parameter should be evaluated and the results are within bound, limits (0.1-0.9%).

Wetting time and water absorption ratio

Wetting time of dosage form is related to the contact angle. Wetting time of the ODT is another important parameter, which needs to be assessed to give an insight into the disintegration properties of the tablet. Lower wetting time, implies a quicker disintegration of the tablet. The wetting time of the tablets can be measured, by using the simple procedure. Five circular, tissue papers of 10cm diameter are placed in a petridish. Ten milliliters of water soluble dye, solution is added to Petridish. A tablet is, carefully placed on the surface of the tissue paper. The time required for water to reach, upper surface of the tablet is noted as the, wetting time. For measuring water absorption ratio, the weight of the tablet before keeping in the petridish is noted (Wb). The wetted tablet from the Petridis is taken and reweighed (Wa). The, water absorption ratio, *R* can be the determined, according to the following equation.,

$$R = 100\ (Wa-Wb) / Wb$$

Where,

Wa = weight of tablet after wetting

Wb = weight of tablet before wetting

Disintegration test

The time for disintegration of ODTs is generally <1min and actual the disintegration time that patients can experience ranges from 5 to 30s. The standard procedure of performing disintegration test for these dosage forms has several limitations and they do not suffice the measurement of very short disintegration times. The disintegration test for ODT should mimic disintegration in mouth with in salivary contents.

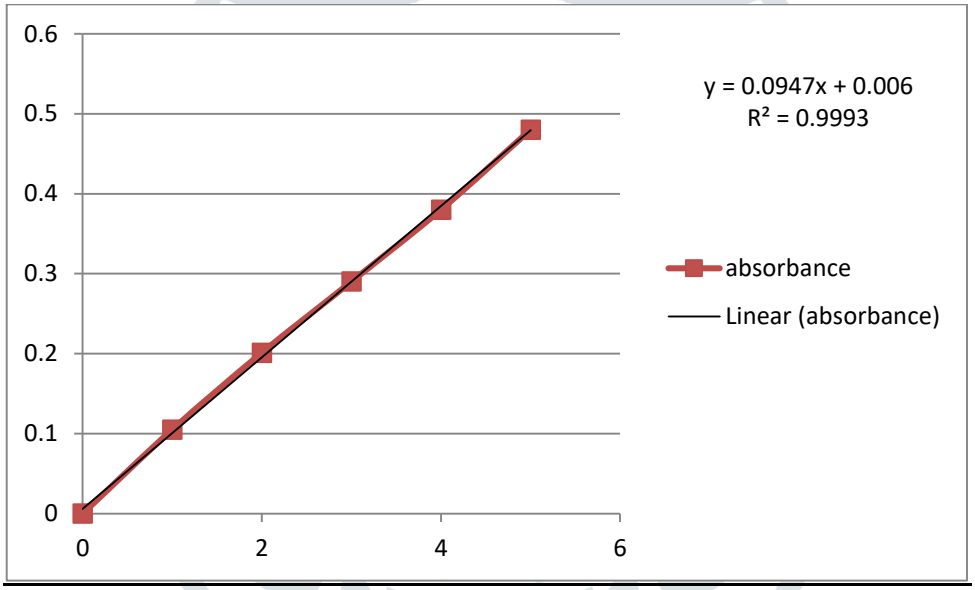
Dissolution test

The development of dissolution methods for ODT is comparable to approach taken for conventional tablets and is practically identical when ODT does not utilize taste masking. Commonly the drugs may have dissolution conditions as in USP monograph. Other media such as pH7.4 phosphate buffers should be used for evaluation of ODT in the same way as their ordinary tablet counterparts. Experience has indicated that USP 2 paddle apparatus is most suitable and common choice for dissolution test of ODT tablets, where a paddle speed of 50 rpm is commonly used. Typically the dissolution of ODTs is very fast when using USP monograph conditions. Hence slower paddle speeds may be utilized to obtain a comparative profile. Large tablets approaching or exceeding one gram and containing relatively dense particles may produce a mound in the dissolution vessel, which can be prevented by using higher paddle speeds. These two situations expand the suitable range of stirring to 25-75 rpm. The USP 1 (basket) apparatus may have certain applications for ODT but is used less frequently due to specific physical properties of tablets. Specifically tablet fragments or disintegration tablet masses may become trapped on the inside top of the basket at the spindle where little or no effective stirring occurs, yielding irreproducible results in dissolution profile.

RESULTS AND DISCUSSION

S.No	Concentration (µg/ml)	Absorbance(nm)
1.	1	0.105
2.	2	0.201
3.	3	0.290
4.	4	0.380
5.	5	0.480

Table No.4 : Standard Calibration curve results



calibration curve of glibenclamide at 300nm

Pre compressional characteristics of Glibenclamide Formulations

Formulation code	Bulk Density gm/cc	Tapped Density gm/cc	Hausners ratio	%Compressibility (%)
F1	0.376±0.06	0.399±0.02	1.061±0.03	5.764±0.05
F2	0.419±0.05	0.503±0.05	1.20±0.02	4.69±0.42
F3	0.391±0.06	0.405±0.09	1.035±0.03	3.456±0.05
F4	0.440±0.06	0.495±0.16	1.12±0.06	3.62±0.76
F5	0.398±0.09	0.407±0.14	1.19±0.02	2.211±0.32

F6	0.397±0.05	0.441±0.31	1.022±0.03	2.50±0.64

Post-compressional characteristics

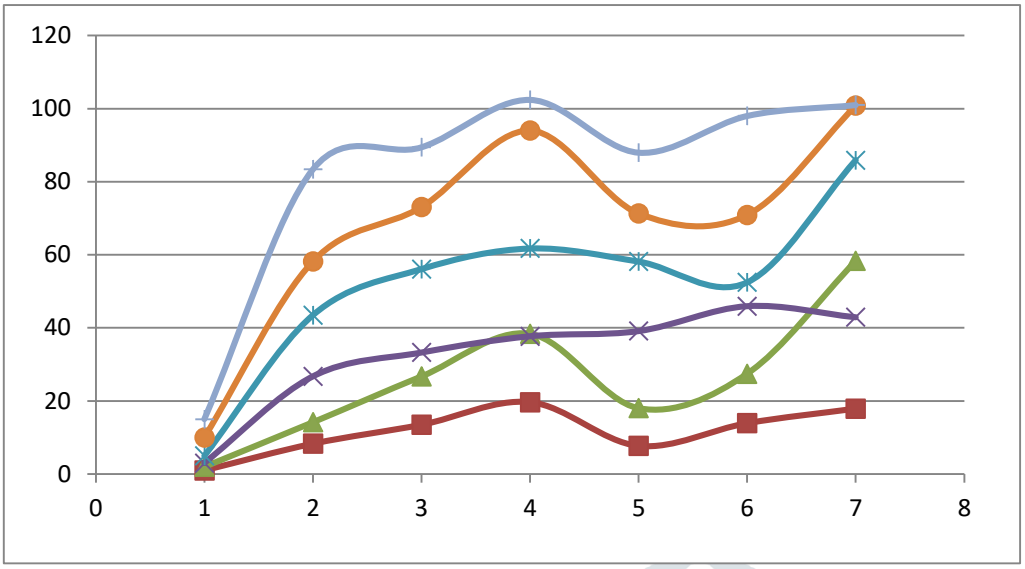
Formulation code	Average weight (mg)	Hardness (Kg/cm^2)	Thickness (mm)	Friability (%)	Content uniformity (%)	Disintegration time (Sec)	Wetting time (sec)
F1	399±0.37	2.6±0.13	3.10±0.03	0.47±0.09	97.6±0.02	25	9
F2	400±0.53	2.5±0.10	3.20±0.015	0.52±0.03	97.8±0.07	11	7
F3	404±0.37	2.3±0.14	3.10±0.03	0.51±0.015	97.1±0.05	18	8
F4	399±0.28	2.22±0.28	3.20±0.035	0.52±0.03	95.4±0.04	9	6
F5	396±0.51	2.2±0.1	3.30±0.03	0.61±0.015	96.4±0.05	8	7
F6	409±0.28	2.0±0.1	3.10±0.04	0.73±0.013	97.1±0.052	5	5

Table No-6 :Post-compressional characcteristics

Dissolution profile:

Time (mins)	F1	F2	F3	F4	F5	F6
2	0	0	0	0	0	0
5	8.29	13.46	7.75	13.9	13.38	17.88
10	14.19	26.73	38.39	18.03	27.47	58.31
15	26.73	33.26	37.72	39.13	45.95	45.91
20	43.5	56.1	61.73	58.16	52.47	85.9
25	58.16	73.06	74.01	71.29	70.91	96.45
30	80.23	89.03	87.96	97.59	97.01	99.97

Table No 7: % drug release of glibenclamide



Dissolution profile of %drug release of Glibenclamide

DISCUSSION

In the present study, an attempt has been made to formulate and evaluate sublingual tablets of Glibenclamide by direct compression technique. These tablets were evaluated for pre-compression parameters such as bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose and for post compression parameters such as hardness, weight variation, drug content uniformity, wetting-time, water absorption ratio, disintegration time and *inviro* dissolution studies.

Pre-compression parameters of blends - The bulk density of pre-compression blends was found to be in the range of 0.370 to 0.399 g/cc, tapped density in the range of 0.39 to 0.407 gm/cc, the Carr's index values were in the range of 2.21 to 5.76%, Hausner's ratio in the range of 1.02 to 1.06 and angle of repose between 25.30 to 26.43.All the values were found to be within the prescribed limits according to the I.P, thus ensuring good flow properties to the formulation blends.

Post compression parameters:

Hardness and friability: The hardness of the tablet formulations was found to be in the range of 2.0 to 2.6 kg/cm^2 . The friability and thickness values were found to be in the range of 0.54 to 0.73 and 3.10 to 3.30% respectively , which was found to be according to the I.P limits and thus ensuring good mechanical strength to all the formulations.

Uniformity of weight: All the prepared mouth dissolving tablets of Glibenclamide were evaluated for weight variation. The weight of all the tablets was found to be uniform with low values of standard deviation and within the prescribed IP limits .

Uniformity of drug content: The values indicates uniform drug content within the tablets The percent drug content of all the tablets was found to be in the range of 95.4 to 98.8percent

***Disintegration time*, wetting time and water absorption ratio:** Among the tablets prepared F6 formulation was found to be promising and has shown an *in vitro* disintigration time of 05 sec, wetting time of 05 sec which was found to be within the I.P limits.

In vitro dissolution study:

In vitro dissolution studies were performed in pH7.4 phosphate buffer maintained at a temperature of 37±0.5^{0}c at an RPM of 50 in a USP II apparatus, the absorbances were noted at 300 nm. The dissolution results showed gradient increase with the increase in the concentration of the superidintegrants. Among all the formulation F6 was found to show best results with 99.97 % release within 30 min

CONCLUSION:

In this study, a comprehensive evaluation of the dissolution rates of Glibenclamide with different superdisintegrants was performed. Crosspovidone demonstrated a more rapid dissolution because of its unique chemistry, particle size and particle morphology that result in high interfacial activity, which significantly aids dissolution. Maximum increase in dissolution rate was observed in F6 (6% crosspovidone) as crosspovidone uses both swelling and wicking mechanisms to generate volume expansion and hydrostatic pressure necessary to provide rapid disintegration in mouth. Moreover crosspovidone is nonionic ,therefore ionic interaction between this superdisintegrant and drug was impossible

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