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Comparative Evaluation Studies of Natural Superdisintegrants for Fast Dissolving Tablets of Gliclazide

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ABSTRACT

The main objective of this study was to formulate and evaluate the fast dissolving tablets of Gliclazide with natural superdisintegrants. Various formulations were prepared by direct compression using different concentrations of natural superdisintegrant i.e. isolated mucilage of Plantago ovata, isolated mucilage of Aloe vera and extracted mucilage of Hibiscus rosasinesis. The initial compatibility studies between the drug and excipients were carried out using FTIR spectroscopy. The blend was evaluated for additive properties. The tablets were evaluated for physical parameters and in vitro drug release. The disintegration time and in vitro drug release of optimized formulation (P4) was found to be 2.41±0.05 secs. The optimized formulation was subjected to stability studies for three months. The formulation was found to be stable, with insignificant change in the hardness, disintegration time, drug content and in vitro drug release pattern.

Keywords: Fast dissolving tablet, isolated mucilage of Plantago ovata, isolated mucilage of Aloe vera and mucilage of Hibiscus rosasinesis

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INTRODUCTION:

The tablet is the most widely used dosage form because of its convenience in terms of self administration, compactness and ease in manufacturing. However, geriatric and pediatric patients experience difficulty in swallowing conventional tablets, which leads to poor patient compliance. To overcome these problems, scientists have developed innovative drug delivery systems known as Fast dissolving tablets (FDT)[1-3]. These are novel types of tablets that disintegrate/disperse/dissolve in saliva. The target populations for these oral disintegrating dosage forms have generally been pediatric, geriatric, and bedridden or develop mentally disabled patients who have difficulty in swallowing (Dysphagia). Patients with persistent nausea, sudden episodes of allergic attacks or coughing , who are traveling , or who have little or no access to water are also good candidates for FDTs. The benefits in terms of patient compliance, rapid onset of action, increased bioavailability and good stability make these tablets popular as a dosage form of choice in the current market. Some drugs are in such cases bioavailability of drug is significantly greater than those observed from conventional tablet dosage form. The basic approach used in the development of the FDTs is the use of superdisintegrants. Many approaches have been developed to manufacture FDTs. These include vacuum drying direct compression, lyophilization and molding. The direct compression method is inexpensive and convenient for producing tablets of sufficient mechanical strength[5, 6].

Gliclazide belongs to the second generation of hypoglycemic Sulphonylureas. Gliclazide causes hypoglycemia by stimulating insulin release from pancreatic ß cells. The acute administration of Gliclazide to type 2 Diabetes Mellitus patients increases insulin release from the pancreas.

MATERIALS AND METHODS

Materials

Gliclazide were obtained as a gift sample from Modern Lab., Indore (M.P). Plantago ovata seeds purchased from local market, Berhampur, India. Microcrystalline cellulose, mannitol, magnesium stearate, talc were purchased from S.D. Fine Chemicals, India.

Isolation of Mucilage of Plantago ovata

The seeds of Plantago ovata were soaked in distilled water for 48 hrs and then boiled for few minutes for complete release of mucilage into water. The material was squeezed through muslin cloth for filtering and separating out the marc. Then, an equal volume of acetone was added to the filtrate so as to precipitate the mucilage. The separated mucilage was dried in oven at temperature less than 60°C, powdered, sieved (#80) and stored in a desiccators until use [7].

Isolation of Mucilage of Aloe vera

The inner mucilaginous parenchymatous tissues of leaves of Aloe vera plants were separated out with the help of a sterile knife and homogenized in a blender (National blender, Matushita Co. Japan) at 30 rpm. The homogenized mass was separated with a G3 sintered glass filter under vacuum, freeze dried using a bench-top freeze-dryer (MC 2L, Cyberlab, USA) and subsequently stored at 40°C. The ratio of AVG to lyophilized powder was 200:1[8].

Isolation of Mucilage of Hibiscus rosasinesis

The fresh Hibiscus rosasinesis leaves were collected and washed with water. The leaves were crushed and soaked in water for 5–6 h, boiled for 30 min and left to stand for 1 h to allow complete release of the mucilage into the water. The mucilage was extracted using a multi layer muslin cloth bag to remove the marc from the solution. Acetone (in the quantity of three times the volume of filtrate) was added to precipitate the mucilage. The mucilage was separated, dried in an oven at 35°C, collected, grounded, passed through a # 80 sieve and stored in desiccators at 30 °C & 45% relative humidity till use [9].

Drug-Excipient Interaction Studies

The physical mixture of pure drug sample, drug and natural superdisintegrant (mucilage of Plantago ovata) in the ratio 1:1 were subjected to IR spectral studies using FTIR spectrophotometer (Model-IR Affinity-1, Shimadzu, Japan).

Table 1: Tablet Formulations of Gliclazide FDT Containing Different Natural Superdisintegrants

Ingredient	H1	H2	H3	H4	A1	A2	A3	A4	P1	P2	P3	P4
Gliclazide	80	80	80	80	80	80	80	80	80	80	80	80
MCC	37.5	25	12.5	0	37.5	25	12.5	0	37.5	25	12.5	0
Plantago mucilage	12.5	25	37.5	50	-	-	-	-	-	-	-	-
Aloe mucilage	-	-	-	-	12.5	25	37.5	50	-	-	-	-
Hibiscus powder	-	-	-	-	-		-	-	12.5	25	37.5	50
Mannitol	66	66	66	66	66	66	66	66	66	66	66	66
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Total	200	200	200	200	200	200	200	200	200	200	200	200

Compression of tablets

All ingredients were triturated individually in a mortar and passed through #80 (Table 1). Then required quantity of all ingredients were weighed for a batch size of 100 tablets and mixed

uniformly in a mortar except magnesium stearate. Finally magnesium stearate was added as lubricant. This uniformly mixed blend was compressed in to tablets containing 30 mg drug using rotary tablet machine by direct compression method. Total weight of tablet was kept to be 200mg.

Evaluation of Tablets[10]

Hardness - Hardness or tablet crushing strength (Fc), the force required to break a tablet in a diametric compression, was measured using Pfizer Tablet Hardness Tester.

Friability test - Friability of tablets was determined using Roche Friabilator. This device subjects the tablets to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches at each revolution. Pre-weighed sample of tablets was placed in a friabilator and the tablets were subjected to 100 revolutions. Tablets were then dusted using a soft muslin cloth and reweighed.

$$\textbf{Friability (F) = (1- Wo / W) x 100}$$

Where,

Wo = weight of the tablets before the test.

W = weight of the tablet after the test.

Water absorption capacity

Water absorption ratio was determined by the following ratio

$$\textbf{R = 100 x Wb / Wa}$$

Where,

Wb = Weight of tablet before water absorption

W =Weight of tablet after water absorption

Wetting time

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper and the time required for complete wetting was measured.

In vitro disintegration time

Tablets were added to 10 ml of Sorenson's buffer solution of pH 6.8 at 37 ± 0.5°C. Time required for disintegration of the tablets was noted.

In vitro dissolution studies

Dissolution studies were carried out by USP-II dissolution apparatus. The tablet was taken from each formulation to carry out the dissolution study in the pH 6.2 buffer solution as dissolution medium (pH of saliva).

Swelling index

It is the volume in millilitres that is occupied by 1 gm of drug or any adhering mucilage after it has swollen in an aqueous liquid for 4 h. swelling index was calculated from mean readings of three determinations

CHARACTERIZATION OF OPTIMIZED FORMULATION P4

Angle of repose

Angle of repose was determined by using funnel method. The accurately weighed blend was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of blend. The drug (as solid dispersion) -excipient blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\text{Tan } \theta = h/r$$

Where,

h and r are the height and radius of the powder.

Bulk density

Apparent bulk density was determined by pouring a weighed quantity of blend into graduated cylinder and measuring the volume and weight.

BD = Weight of the powder / Volume of the packing.

Tapped Density

It was determined by placing a graduated cylinder, containing a known mass of drug-excipient blend. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 10cm at 2- second intervals. The tapping was continued until no further change in volume was noted.

TBD =Weight of the powder / volume of the tapped packing.

Compressibility Index

The Compressibility Index of the blends was determined by Carr's compressibility index.

Carr's compressibility index (%) = [(TBD-LBD) X 100] / TBD

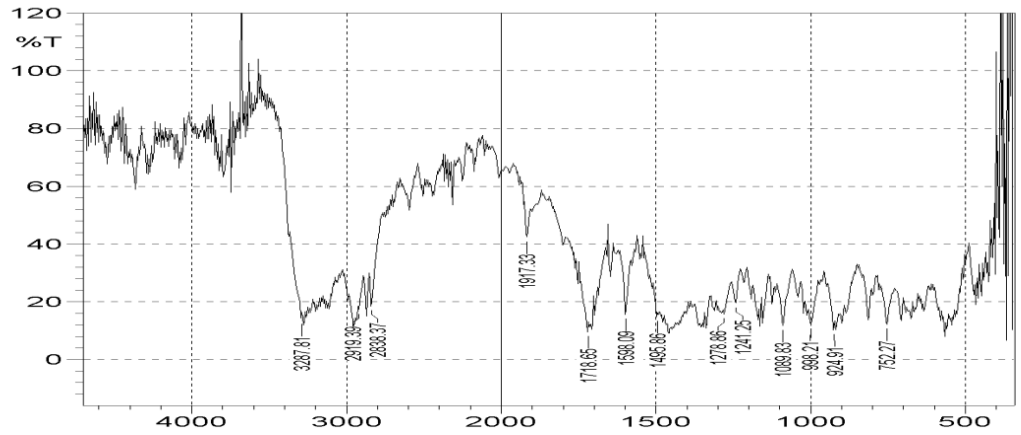
A similar index has been defined by Hausner's

Hauser's ratio = Tapped density/ poured density

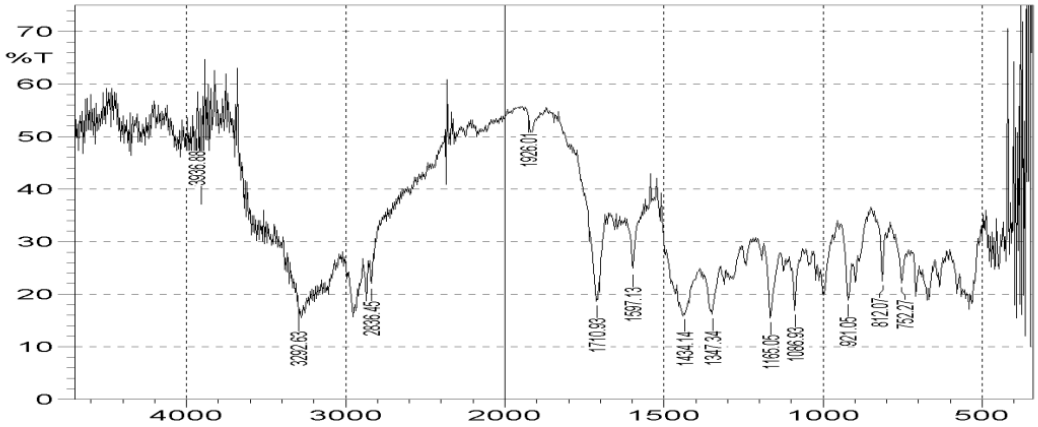
RESULTS AND DISCUSSION

In the present study, Gliclazide fast dissolving tablets were prepared by using natural superdisintegrant such as isolated mucilage of Plantago ovata, Aloe vera and hibiscus

rosasinesis. IR spectroscopic studies revealed that drug was compatible with all the excipients as shown in Figure 1a and 1b. All the natural superdisintegrants were compared with the standard formulation containing drug and excipients with microcrystalline cellulose alone and the results were found to be not promising for the fast dissolving tablets.



a) IR spectra of Gliclazide



b) **IR spectra of Physical mixture of Gliclazide and Plantago ovata mucilage**

Figure 1 - IR spectra of a) Gliclazide b) Physical mixture of Gliclazide and Plantago ovata mucilage

The hardness of the tablets was found to be between 2.41±0.05 to 3.26±0.065 kg/cm^2 and friability was found to be below 1% indicating good mechanical resistance as shown in Table 2. The drug content was found to be optimum in all the cases. The blend of the optimized formulation containing Gliclazide and Plantago ovata mucilage was evaluated for parameters like angle of repose was found to be 25.01±0.94. Bulk density was found to be 0.574±0.011 g/cm^3 and tapped density 0.730 ± 0.003 g/cm^3. Hausner's ratio was found to be 1.28±0.009 as shown in Table 3.

Table 2: Evaluation of Gliclazide FDT Containing Different Natural Superdisintegrants

parameters	Hardness ($Kg/cm^{2)}$	Friability(%w/w)	DT time (sec)	Wetting time (sec)	Dispersion time (sec)	Water absorption ratio (%)
H1	3.26±0.065	0.076±0.0008	85.17±0.74	78.25±0.75	115.20±0.73	51.24±0.76
H2	2.93±0.10	0.165±0.0007	69.19±0.74	64±0.65	82.09±0.70	59.48±0.62
H3	2.74±0.04	0.25±0.012	58.96±0.64	38.05±0.86	47.16±0.72	63.44±0.81
H4	2.5±0.05	0.28±0.005	32±0.66	23.15±0.52	35.96±0.64	82.09±0.70
A1	3.06±0.09	0.086±0.002	72±0.80	63.21±0.79	102±0.67	55±0.73
A2	2.96±0.08	0.185±0.0004	59.33±0.48	48.82±0.66	75.57±0.69	63.52±1.03
A3	2.43±0.04	0.29±0.008	36.61±0.79	29.26±0.73	43±0.60	69.43±0.46
A4	2.23±0.04	0.35±0.002	21.7±0.40	16.11±0.49	19.31±1.04	84.33±0.64
P1	3.12±0.077	0.085±0.0005	45.4±0.47	31.61±0.49	64.36±0.56	59.16±0.45
P2	3.0±0.07	0.27±0.006	34.38±0.52	29.06±0.65	42.16±0.52	65.03±0.64
P3	2.5±0.06	0.38±0.006	25.23±0.59	19±0.67	31.5±0.5	73.2±0.77
P4	2.41±0.05	0.45±0.006	24.23±0.59	11.21±0.45	13.25±0.42	86.11±0.49

Table 3 - Characterization of Optimized Formulation P4

Parameter	Angle of repose (θ)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Hausner's ratio	Compressibility index (%)
P4	25.01±0.94	0.574±0.011	0.730 ±0.003	1.28±0.009	21.36 ±1.202

The most important parameter that needs to be optimized in the development of fast dissolving tablets is the disintegration time of tablets. In the present study disintegration time of all batches were found in the range of 24.23±0.59 to 85.17±0.74 secs fulfilling the official requirements (3 min) for dispersible tablets as shown in Table 2.

In-vitro drug release studies were done for the selected formulations from each batch. The drug release was found to show maximum drug release in case of P4 with 99.98% in 30 minutes as shown in Table 4 and Figure 2.

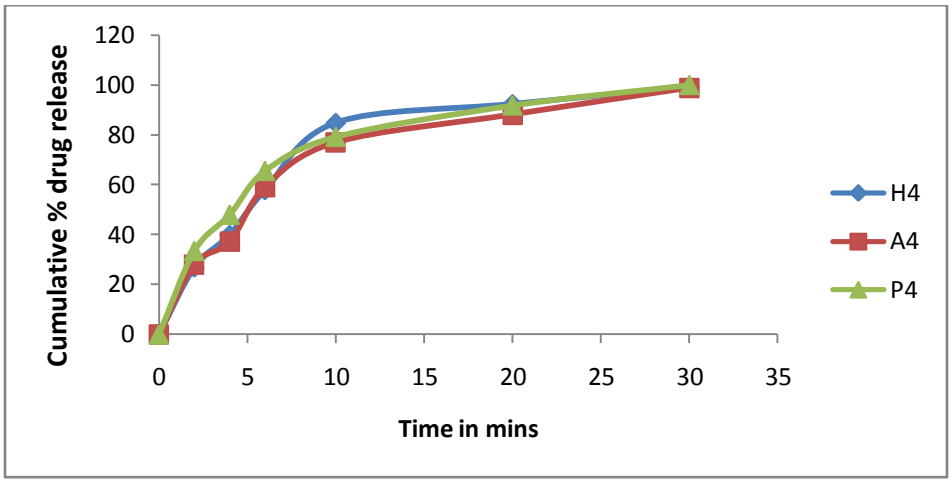


Figure 2 – Cumulative % drug release for Gliclazide FDTS with the natural superdisintegrants (selected formulations based on disintegration time and hardness)

Table 4- In-Vitro Drug Release Study of Gliclazide FDT

Time in mins	H4	A4	P4
0	0	0	0
2	26.83	27.98	33.45
4	39.89	37.13	47.98
6	57.87	59.11	65.55
10	84.81	76.98	79.19
20	92.32	88.17	91.78
30	99.08	98.87	99.98

This rapid disintegration of the fast dissolving tablets were due to penetration of saliva into the pores of the tablets, which leads to the swelling of super disintegrant to create enough hydrodynamic pressure for quick and complete disintegration of the tablet. Batch P4 was selected as optimized batch containing Plantago ovata mucilage as superdisintegrant in 25% concentration. It showed less disintegration time of 24.23 secs. Mucilage of Plantago ovata showed less disintegration time as comparison to other natural superdisintegrants. The formulation P4 was found to be the best, as this formulation showed less disintegration time and possessing good tableting properties.

The swelling index for the mucilage of Plantago ovata was found to be 97±2.45% v/v. The stability of this optimized formulation was known by performing stability studies for three months at accelerated conditions of 40°C±75 % RH on optimized formulation. The formulation was found to be stable, with insignificant change in the hardness, disintegration time as shown in Table 5.

Table 5- Stability Data of Optimized Formulation P4

Parameters	Time in months			
P4	**0 (Initial)**	**1st month**	**2nd month**	**3rd month**
Hardness (kg/cm^2)	2.41±0.05	2.47 ±0.80	2.5 ±0.63	2.52 ±0.67
Disintegration time (sec)	24.23±0.59	24.76 ±0.26	25.6± 0.34	25.7±0.09

CONCLUSION

From the above data, it can be concluded that mucilage of Plantago ovata is having better disintegrant property than other natural superdisintegrants namely, mucilage of Aloe vera and Hibiscus rosasinesis powder.

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