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DESIGN AND *IN VITRO* EVALUATION OF GLIPIZIDE ONCE DAILY TABLET USING NATURAL GUMS

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Abstract:

The main purpose of the present work is to study Lannea coramondelica gum and Terminalia catappa gum functionality as release retardant agents in the design of once daily matrix tablets of Glipizide. Lannea coramondelica gum(LCG) and terminalia catappa gum(TCG) are purified forms of exudates obtained from the respective trees by an established method. Fourier transform infrared spectroscopy studies were performed to find out the interactions between gum and drug. Here matrix tablets of Glipizide were prepared with gums bywet granulation technique. The granules were evaluated for angle of repose, bulk density and compressibility index. The granules showed satisfactory flow properties. Tablets thus formulated were evaluated for various quality control tests like weight variation, hardness, friability etc. All Glipizide matrix tablets were found to have better uniformity of weight and drug content with low SD values. The dissolution study proved that the LCG and TCG can be used as a matrix forming material for making extended release tablets. The kinetic release data fitted into different mathematical models (Zero order, First order, Higuchi, Peppa's. Most of the solid matrix formulations followed Higuchi or zero order kinetics.

KEYWORDS: *Glipizide, Lannea coramondelica gum (LCG) and Terminalia catappa gum (TCG)), matrix tablets.*

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INTRODUCTION:

Pharmaceutical excipients are the additives used to convert pharmacologically active compounds into pharmaceutical dosage forms suitable for administration to patients. There are number of excipients listed in official and other publications [1], which indicate the importance of these excipients in the design of dosage forms. The growth of novel forms of drug delivery has resulted in a need for new excipients to support the desired properties, this is very much essential to suit individual requirements of a particular drug or dosage form. For example, development of bioadhesive formulation necessitated the identification of new bioadhesive polymers like Chitosan[2]. In recent times, there is a growing trend of using substances in place of synthetic ones because of their low toxicity, low cost and abundant availability. However, these natural substances suffer with drawbacks like purity, sources variation and microbial contamination. If these factors can be identified and controlled efficiently, natural substances can be good substitutes to synthetic ones. Despite all the above mentioned reasons, there has been tremendous improvement in the usage of these natural gums as pharmaceutical excipients for oral use.[3] Diabetes mellitus is a chronic metabolic disorder characterized by high blood glucose concentration caused by insulin deficiency, often combined with insulin resistance. Glipizide is an oral hypoglycemic agent, which is a commonly prescribed drug for the treatment of patients with type II diabetes mellitus. It is a weak acid (pKa = 5.3) practically insoluble in water and acidic environment but highly permeable (class 2) according to the Biopharmaceutical Classification System (BCS). The oral absorption is uniform, rapid and complete with a bioavailability of nearly 100% and an elimination half life of 2–4 h. Glipizide is reported to have a short biological half-life (3.4 ± 0.7 h) requiring it to be administered in 2 to 3 doses of 2.5 to 10 mg per day.[4,5] Hence, selected glipizide as a model drug for the development of controlled release matrix tablets. The main objective of the present work is to study functionality of Lannea coramondelica gum and Terminalia catappa gum as a matrix forming agent for extended release of drug from tablet formulations.

MATERIALS AND METHODS:

Glipizide was obtained as a gift sample from the Dr. Reddy's labs, Hyderabad, India. The Avena sativa (oats) were procured from local market of Visakhapatnam. Lactose, Magnesium stearate and were procured from Molychem, Mumbai.

Preformulation [6]

The pure and physical mixture of drug and gums were subjected to IR spectroscopic studies using FT-IR spectrophotometer.

Preparation of matrix tablets [8]

The extended-release matrix tablets of Glipizide, each containing 10 mg of the active ingredient, were produced through the wet granulation method. First, specific quantities of glipizide, Lannea coromandelica gum (LCG), Terminalia catappa gum (TCG), and lactose monohydrate were passed through a 60-mesh sieve. These components were thoroughly mixed using the geometric dilution technique. After blending, granulation was achieved by employing an adequate amount of a 5% gum solution prepared in isopropyl alcohol (IPA). The resulting wet dough mass was then passed through a 12-mesh sieve, and the wet granules were subsequently dried in an oven at 60°C for 30 minutes. The dried granules were further sifted through a 24-mesh sieve. Lastly, the granules were enhanced with 1% magnesium stearate and 1% talc by blending them for 2-3 minutes. The lubricated mixture of the extended-release tablets was compressed into tablet form using a 7 mm circular die and punches on a rotary tablet compression machine (Elite) until a hardness of 5–7 kg/cm2 was achieved.

Table 1: Composition of matrix tablets of Glipizide using LCG and TCG

Formulation	Glipizide	LCG	TCG	Mg. stearate	Talc	Lactose	Total weight
GL1	10	10		2	2	176	200
GL2	10	25		2	2	161	200
GL3	10	40		2	2	146	200
GL4	10	55		2	2	131	200
GL5	10	70		2	2	116	200
GL6	10	85		2	2	101	200
GT1	10		10	2	2	176	200
GT2	10		25	2	2	161	200
GT3	10		40	2	2	146	200
GT4	10		55	2	2	131	200
GT5	10		70	2	2	116	200
GT6	10		85	2	2	101	200

*all the quantities in mg

Evaluation of granules

Angle of repose (θ)

The frictional forces of granules can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane. The granules were allowed to flow through the funnel fixed to a stand at definite height. The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

$$\tan \theta = h/r$$

Where, θ is the angle of repose, h = height, r = radius

Bulk density

Both loose Bulk Density and tapped bulk density were determined. The accurately weighed amount of sample taken in a 25 ml measuring cylinder of Borosil the volume of packing recorded and LBD and TBD calculated by following:

LBD (loose Bulk Density) = Mass of Powder/ Untapped Volume of Powder

TBD (tapped bulk density) = Mass of Powder/ Tapped Volume of Powder

Hausner's ratio (H)

Flow properties of granules were determined by Hausner's ratio calculated by following formula:

H = Tapped bulk density/Lose bulk density

A Hausner ratio greater than 1.25 is considered of poor flowability.

Carr's Index

Percentage compressibility of granules was determined by carr's compressibility index calculated by following formula

Carr's Index = [(TBD – LBD)/ TBD] X 100

Evaluation of tablets

(a) Post Compression characterization of tablets

The prepared tablets were characterized for their physical properties like:

Hardness

The Hardness of the prepared tablets was determined using a Monsanto Hardness tester. It is expressed in kg / cm2

Weight Variation

Twenty tablets were selected randomly from the lot and weighed individually to check for weight variation. IP limit for weight variation in case of tablets less than 250 mg is 5.0%.

Friability

The Friability of the prepared tablets was determined using Roche friabilator. It is expressed in percentage. Ten tablets were initially weighed (Winitial) and transferred into the friabilator. The friabilator was operated at 25 rpm for 4mins. The tablets were weighed again (Wfinal). The % friability was then calculated by:

F= [(W initial-Wfinal)/ Winitial] X100

Drug Content
Twenty Tablets were weighed individually and the drug was extracted in methanol. The solution filtered through 0.45µm. The drug content was analyzed after suitable dilution by spectrophotometrically at 276nm.

CSFR [7,8]
The ratio of crushing strength-friability of tablets was determined as crushing strength friability ratio.

(b) In-vitro characterization of tablets [9,10]
Drug release from extended release tablet was determined by using dissolution test (USP Type II) apparatus (LabIndia). In vitro dissolution study for first two hours was carried out in 900 ml of 0.1N hydrochloric acid (pH 1.2) and then after two hours pH 1.2 buffer was replaced by pH 6.8 phosphate buffer for 22 hours at 37±0.5ºC at 75 rpm. 10 mL of dissolution medium was withdrawn using a syringe fitted with 0.45 µm pre filter at regular time intervals and the same volume of (37±0.5ºC) fresh dissolution medium maintained at 37±0.5ºC was replaced and then the absorbanceof the samples was measured at 276 nm using UV spectrophotometer (LabIndia). The cumulative % drug release was calculated for all the batches.The drug release experiments were conducted in triplicate (n=3).

Kinetics of Drug Release [11,12]
The cumulative amount of glipizide released from the tablets at different time intervals were fitted to various model dependent kinetic methods like Zero order, First order, Higuchi, and Korsmeyer- Peppas.

RESULTS AND DISCUSSION:

Preformulation:In FT-IR studies, glipizide showed characteristic peaks at 3325.73 cm-1(3500-3300) (N-H); 2943.00 and 2854.81 cm-1(3000-2850) (C-H); 1688.80 and 1650.11 cm-1(1950-1600) (C=O); 1159.31 cm-1 (1220-1020) (C-N) in combination with drug and gums. As there is no significant change in the spectra, it indicates that drug is compatible with gums.

Table 2: Evaluation parameters of granules

Formulation code	Loose Bulk Density(g/cc)	Tapped Bulk Density(g/cc)	Hausner's Ratio	Carr's Index	Angle of Repose(θ)
GL1	0.89	0.98	1.10	9.67	26.22
GL2	0.85	0.93	1.09	8.60	25.78
GL3	0.86	0.95	1.10	9.47	22.54
GL4	0.88	0.96	1.09	8.33	30.15
GL5	0.89	0.95	1.07	6.31	28.02
GL6	0.78	0.87	1.11	10.34	19.28
GT1	0.84	0.94	1.12	10.64	27.05
GT2	0.78	0.88	1.19	11.36	26.21
GT3	0.86	0.95	1.10	9.47	22.54
GT4	0.88	0.96	1.09	8.33	30.15
GT5	0.89	0.95	1.07	6.31	28.02
GT6	0.78	0.87	1.11	10.34	19.28

Loose bulk densities, tapped bulk density of all the formulations are within the specified limits (0.74 to 0.98). Hausner's ratio of all the formulations exhibited good flow (< 1.25) with the limits from 1.07 to 1.19. The Carr's compressibility index of the granules varied from 6.28 to 11.36 which is less than 12. It indicates good flow according to limits of carr's compressibility index.

The angle of repose of all the granules was within the range of 19.28 to 30.15 which indicates good flow.

Table: 3 Evaluation parameters of prepared matrix tablets

S. No	Formulation code	Uniformity of weight(mg)	Hardness (kg/cm2)	Friability (%)	Drug content (%)
1	**GL1**	199±0.5	4.08±0.25	0.51±0.07	100.5±1.0
2	**GL2**	198±0.56	4.10±0.5	0.48±0.08	101.5±1.25
3	**GL3**	199±0.45	4.12±0.5	0.43±0.07	99.8±1.25
4	**GL4**	201±0.60	5.10±0.25	0.41±0.06	98.9±1.0
5	**GL5**	198±0.56	5.15±0.5	0.32±0.08	100.5±1.25
6	**GL6**	201±0.60	5.10±0.25	0.41±0.06	98.9±1.0
7	**GT1**	199±0.59	5.20±0.5	0.29±0.07	101.5±1.0
8	**GT2**	199±0.62	5.50±0.25	0.20±0.08	101.5±1.25
9	**GT3**	198±0.65	5.30±0.5	0.23±0.06	100.5±1.25
10	**GT4**	198±0.56	4.10±0.5	0.48±0.08	101.5±1.25
11	**GT5**	199±0.62	5.50±0.25	0.20±0.08	101.5±1.25
12	**GT6**	198±0.56	4.10±0.5	0.48±0.08	101.5±1.25

All values are expressed as mean± SD (n=3)

The quality control tests adopted for the prepared tablets are shown in the Table 2. The percent of weight variation for tablets passed weight variation test as the percentage weight variation was within the Pharmacopoeial limits of 5%. Tablet weight of all formulations varied from 198mg to 201mg and weight was found to be uniform. The thickness of the tablets ranged between 1.98 mm to 2.15mm. The drug content in all the formulations was within the range of 99.8% to 101.5%. The hardness of the tablets ranged between 4.08 kg/cm2to 5.50 kg/cm2. The percent friability of the prepared tablets was well within the acceptable limit. The results indicated that the tablets possessed enough mechanical strength to maintain integrity of the tablets.

Table 4: CSFR values of tablets

Formulation	Crushing strength(N)	Friability	CSFR
GL1	40.01	0.51	78.46
GL2	40.21	0.48	83.77
GL3	40.40	0.43	93.96
GL4	50.02	0.41	121.99
GL5	50.51	0.32	157.83
GL6	50.02	0.41	121.99
GT1	51.00	0.29	175.85
GT2	40.40	0.43	93.96
GT3	50.02	0.41	121.99
GT4	51.98	0.23	225.99
GT5	40.21	0.48	83.77
GT6	53.94	0.20	269.69

The crushing strength-friability ratio (CSFR) is a parameter used to evaluate the quality of tablets. The CSFR is a ratio of tablet strength (crushing strength) and weakness (friability). Higher CSFR values are indicative of tablets high quality. The CSFR values of all tablets range from 78.46 to 269.69. This indicates tablets of higher quality.

In-vitro drug release studies

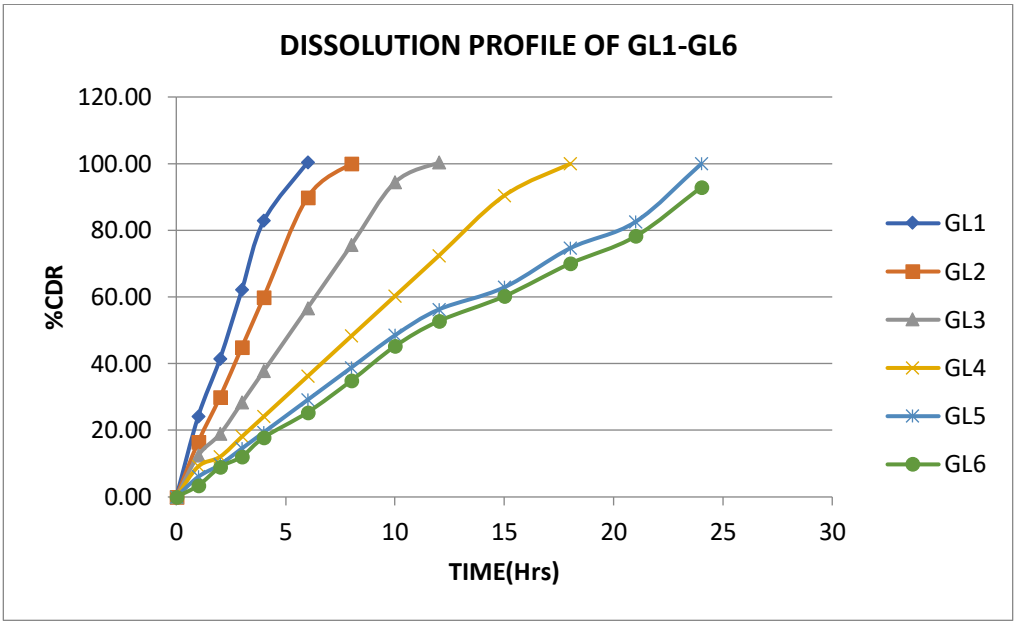

Figure 3: Drug release profiles of glipizide matrix tablets (a) GL1-GL6

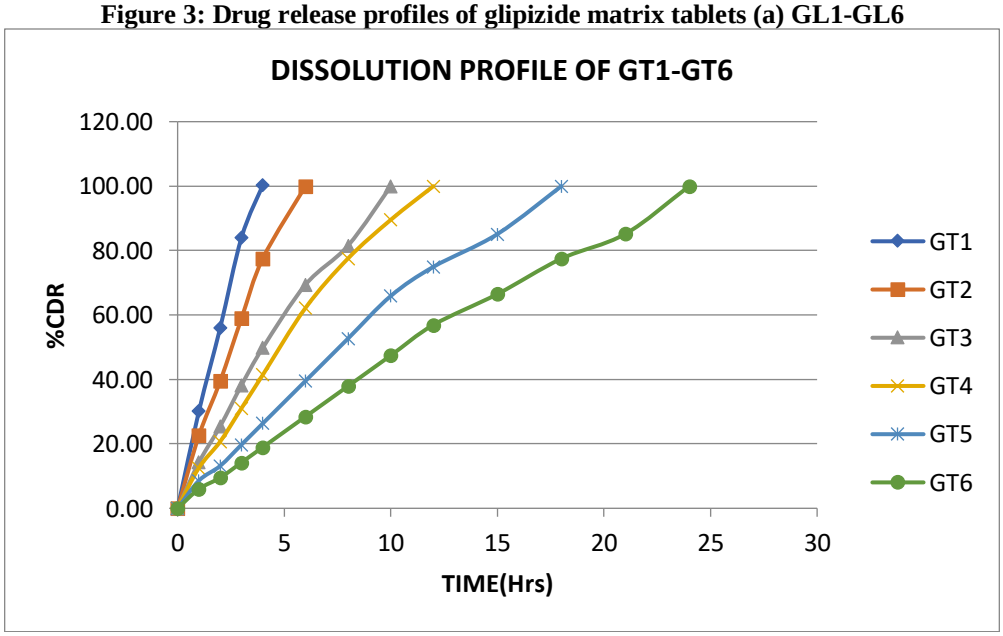

Figure 4: Drug release profiles of glipizide matrix tablets GT1-GT6

Release kinetics is an essential aspect of drug formulation development and kinetic data are also employed in setting in vivo-in vitro correlation of dosage forms. The kinetic data of all formulations are graphically represented in Figures 3-6. Table 5 present the kinetics of release of all formulations. The kinetic model with the highest correlation coefficient value (R2) was selected as the model that best described the dissolution data. All the formulations followed zero order release, Higuchi and peppa's model of release mechanism.

Table 5: Correlation coefficient R2 of all formulations

Formulation	ZERO	FIRST	HIGUCHI	KORSE MEYER	n
GL1	0.9588	0.9526	0.9349	0.9893	0.769
GL2	0.9750	0.9364	0.9002	0.9885	0.843
GL3	0.9892	0.9305	0.8807	0.9936	0.903
GL4	0.9950	0.9358	0.8678	0.9970	0.934
GL5	0.9865	0.9603	0.8929	0.9957	0.864
GL6	0.9902	0.9665	0.8822	0.9958	0.892
GT1	0.9884	0.9437	0.9359	0.9966	0.851
GT2	0.9771	0.9505	0.9267	0.9956	0.814
GT3	0.9750	0.9614	0.9210	0.9972	0.803
GT4	0.9777	0.9550	0.9104	0.9949	0.822
GT5	0.9841	0.9569	0.8950	0.9955	0.854
GT6	0.9910	0.9566	0.8872	0.9976	0.883

CONCLUSION:

The both the gums efficiently controlled drug release up to 24 hours but at higher proportions than glipizde.. GL6 and GT6 are retarded the release of drug from tablet for 24 hours. The present study revealed that LCG and TCG appears to be suitable for use as a release retardant in the manufacture of extended release tablets because of its good post compression parameters and better in vitro dissolution studies.

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