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Formulation and Characterization of Extended Release Vildagliptin Matrix Tablets Using Natural Gums

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ABSTRACT

The primary objective of this study is to investigate the potential of Lannea coromandelica gum (LCG) and Terminalia catappa gum (TCG) as agents to slow down the release of Vildagliptin in the development of once-daily matrix tablets. Both LCG and TCG are refined exudates obtained from their respective trees using established methods. To determine any interactions between the gums and the drug, Fourier transform infrared spectroscopy studies were conducted. Matrix tablets of Vildagliptin were created using these gums through the wet granulation technique. The granules were subjected to assessment for parameters such as angle of repose, bulk density, and compressibility index, which indicated favorable flow properties. The resulting tablets were then subjected to various quality control tests, including weight variation, hardness, and friability. All Vildagliptin matrix tablets exhibited uniform weight and drug content, with low standard deviation values. Dissolution studies confirmed that LCG and TCG can be employed as materials for forming the matrix in extended-release tablets. Kinetic release data analysis revealed that most of the solid matrix formulations conformed to Higuchi or zero-order kinetics.

Keywords: Vildagliptin, Lannea coramondelica gum (LCG) and Terminalia catappa gum (TCG)), matrix tablets.

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INTRODUCTION

Pharmaceutical excipients serve as additives employed to transform biologically active compounds into pharmaceutical forms suitable for patient administration. Various official publications [1] list a multitude of these excipients, underscoring their vital role in crafting dosage forms. The emergence of innovative drug delivery methods has spurred the necessity for new excipients that cater to specific requirements of particular drugs or formulations. An example of this is the development of bioadhesive formulations, which demanded the discovery of novel bioadhesive polymers such as Chitosan [2]. Recent times have witnessed a growing inclination towards using natural substances over synthetic ones due to their reduced toxicity, cost-effectiveness, and widespread availability. Nonetheless, natural substances are hampered by challenges like purity issues, source variations, and microbial contamination. With effective identification and control of these factors, natural substances can effectively replace synthetic ones. Despite these considerations, there has been substantial progress in utilizing natural gums as pharmaceutical excipients for oral applications [3-5].

Diabetes mellitus is a chronic metabolic disorder marked by elevated blood glucose levels resulting from insulin deficiency, often coupled with insulin resistance.Vildagliptin belongs to a novel category of oral medications for managing diabetes and acts as a specific and reversible inhibitor of Dipeptidyl peptidase 4 (DPP-4), the enzyme responsible for deactivating incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). These hormones play a significant role in regulating glucose levels. Vildagliptin can be used independently or in combination with other antidiabetic drugs. Following oral ingestion, it is quickly absorbed in the gastrointestinal tract (GIT). Vildagliptin has a biological half-life of 1.5 hours. To ensure sustained and consistent blood levels over an extended duration and reduce the frequency of dosing, sustained-release formulations have been developed.[6]

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 METHOD

Vildagliptin was received as a gift sample from Lee Pharma, Visakhapatnam (India). Lannea coramodelica gum and Terminalia catappa gum were procured from local market. All other ingredients used were of analytical grade and procured from SD Fine-Chem Ltd., Mumbai (India).

Preparation of matrix tablets [5]

The extended-release matrix tablets of Vildagliptin, each containing 10 mg of the active ingredient, were produced through the wet granulation method. First, specific quantities of Vildagliptin, 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 Vildagliptin using LCG and TCG

Formulation code	Vildagliptin	LCG	TCG	Mg. stearate	Talc	Lactose	Total weight
VL1	100	50		3	3	144	300
VL2	100	75		3	3	119	300
VL3	100	100		3	3	94	300
VL4	100	125		3	3	69	300
VL5	100	150		3	3	44	300
VL6	100	175		3	3	19	300
VT1	100		50	3	3	144	300
VT2	100		75	3	3	119	300
VT3	100		100	3	3	94	300
VT4	100		125	3	3	69	300
VT5	100		150	3	3	44	300
VT6	100		175	3	3	19	300

*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.

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

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.

(b) In-vitro characterization of tablets [7,8]

Drug release from extended release tablet was determined by using dissolution test (USP Type II) apparatus (Lab India). 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 absorbance of 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 9, 10

The cumulative amount of Vildagliptin 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

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)
VL1	0.64 ±0.03	0.73 ±0.03	1.14	11.33	30.3 ±0.6
VL2	0.55 ±0.03	0.60 ±0.05	1.09	8.33	28.9 ±0.8
VL3	0.56 ±0.04	0.61 ±0.06	1.09	8.20	28.6 ±0.9
VL4	0.57 ±0.03	0.64 ±0.03	1.12	10.94	27.5 ±0.7
VL5	0.49 ±0.05	0.53 ±0.02	1.08	7.55	28.9 ±0.8
VL6	0.58 ±0.04	0.63 ±0.06	1.09	7.94	29.7 ±0.6
VT1	0.63 ±0.05	0.72 ±0.04	1.14	11.50	30.6 ±0.6
VT2	0.62 ±0.04	0.70 ±0.06	1.13	11.43	28.6 ±0.9
VT3	0.45 ±0.04	0.48 ±0.04	1.07	6.25	27.1 ±0.9
VT4	0.64 ±0.04	0.72 ±0.03	1.13	11.11	29.3 ±0.6
VT5	0.43 ±0.06	0.46 ±0.04	1.07	6.52	28.3 ±0.6
VT6	0.58 ±0.04	0.65 ±0.03	1.12	10.77	28.5 ±0.7

Loose bulk densities, tapped bulk density of all the formulations are within the specified limits (0.43 to 0.64). Hausner's ratio of all the formulations exhibited good flow (< 1.25) with the limits from 1.07 to 1.14. The Carr's compressibility index of the granules varied from 6.25 to 11.50 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 27.1 to 30.6 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	VL1	299±0.5	4.18±0.25	0.35±0.2	100.4±0.7
2	VL2	298±0.56	4.11±0.5	0.24±0.3	101.8±0.7
3	VL3	299±0.45	4.12±0.5	0.25±0.1	100.2±0.9
4	VL4	301±0.60	5.05±0.25	0.41±0.2	99.9±1.1
5	VL5	298±0.56	5.05±0.5	0.23±0.1	100.4±1.2
6	VL6	301±0.60	5.00±0.25	0.15±0.2	100.8±1.3
7	VT1	299±0.59	5.00±0.5	0.23±0.1	100.5±1.1
8	VT2	299±0.62	5.50±0.25	0.44±0.2	101.3±1.2
9	VT3	298±0.65	5.30±0.5	0.38±0.1	99.3±1.0
10	VT4	298±0.56	4.12±0.5	0.29±0.3	99.6±1.2
11	VT5	299±0.62	5.05±0.25	0.39±0.2	100.2±0.8
12	VT6	298±0.56	4.10±0.5	0.35±0.1	100.9±1.3

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 298mg to 301mg and weight was found to be uniform. The drug content in all the formulations was within the range of 99.3% to 101.8%. The hardness of the tablets ranged between 4.10 kg/cm2 to 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.

In-vitro drug release studies

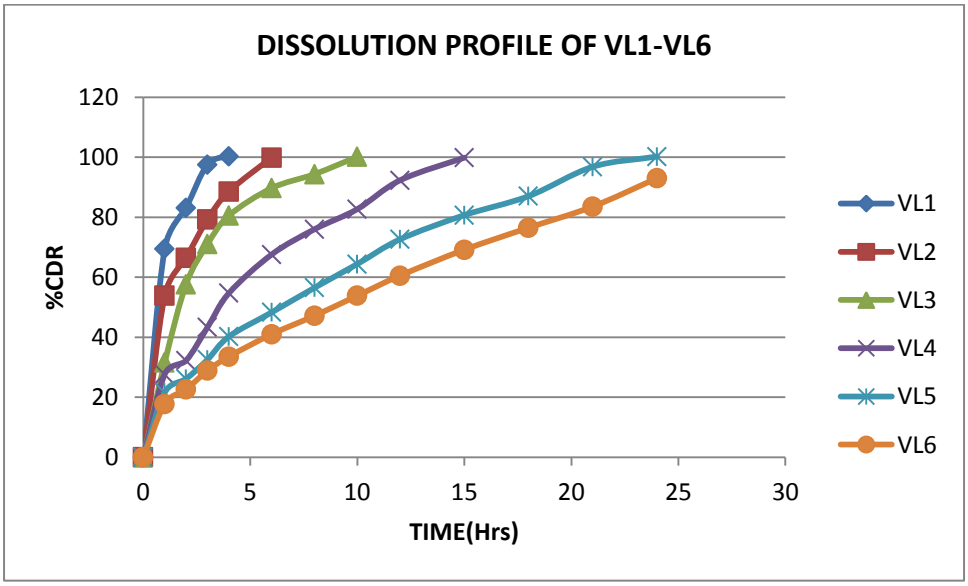

Figure 1: Drug release profiles of Vildagliptin matrix tablets VL1-VL6

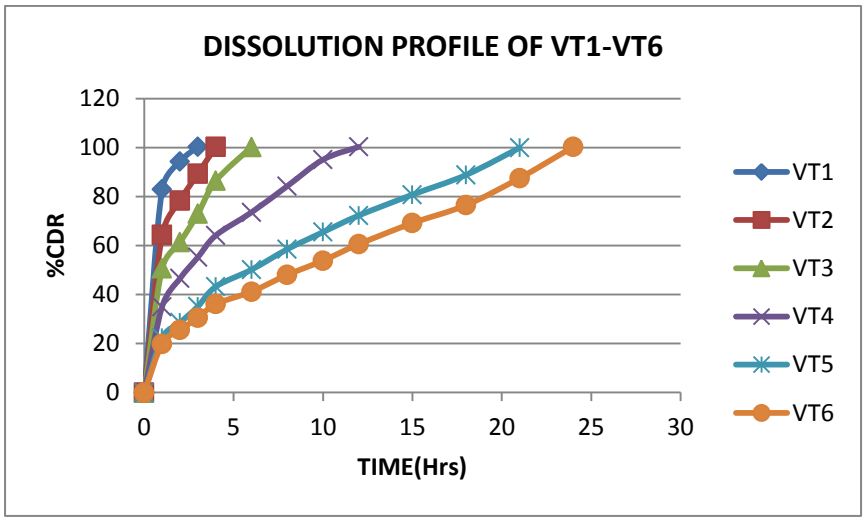

Figure 2: Drug release profiles of Vildagliptin matrix tablets VT1-VT6

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 1-2. 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	Korsemeyer	n
VL1	0.6282	0.9934	0.9506	0.9978	0.276
VL2	0.5815	0.9813	0.9704	0.9990	0.354
VL3	0.4862	0.9980	0.9473	0.9705	0.390
VL4	0.7285	0.9835	0.9941	0.9941	0.503
VL5	0.7659	0.9759	0.9968	0.9980	0.527
VL6	0.8232	0.9699	0.9916	0.9979	0.565
VT1	0.6310	0.9988	0.9272	0.9999	0.173
VT2	0.6955	0.9878	0.9715	0.9993	0.323
VT3	0.6768	0.9721	0.9862	0.9966	0.408
VT4	0.6084	0.9703	0.9899	0.9991	0.429
VT5	0.7509	0.9647	0.9975	0.9980	0.516
VT6	0.8247	0.9441	0.9810	0.9878	0.569

CONCLUSION

Both LCG and TCG effectively extended the control of drug release for a duration of 24 hours, albeit in higher quantities compared to Vildagliptin. VL6 and VT6 notably delayed the drug release from the tablet for a full day. This study indicates that LCG and TCG seem well-suited for use as release-retarding agents in the production of extended-release tablets, thanks to their favorable post-compression characteristics and superior results in in vitro dissolution tests.

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