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NATURAL GUM-BASED MATRIX TABLETS FOR SUSTAINED RELEASE OF LEVOSULPIRIDE AND ALPRAZOLAM: FORMULATION AND EVALUATION

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ABSTRACT

Natural plant-derived gums, being renewable and biocompatible, present promising applications in pharmaceutical formulations. In this study, hydrophilic gums extracted from Velama, Rekka, and Mardi plants were characterized for their potential in sustained-release tablet formulations. The extracted gums demonstrated sufficient yield and favorable physicochemical properties, including low moisture content and near-neutral pH, indicating suitability for moisture-sensitive drugs and reduced irritation. Micromeritic analyses confirmed satisfactory flow properties, and Preformulation and post-compression evaluations revealed excellent compatibility, mechanical strength, and stability under accelerated conditions. In vitro and in vivo studies demonstrated controlled drug release profiles, with Velama and Mardi gums showing superior matrix-forming capabilities compared to Rekka gum. This study highlights the efficacy of natural polymers in enhancing drug release efficiency, dosing accuracy, and patient compliance in pharmaceutical applications.

Key words: Levosulpiride, Alprazolam, Velama, Rekka, Mardi, Sustaied release tablet

1 INTRODUCTION

In recent years, the pharmaceutical industry has increasingly focused on the development of controlled and sustained-release drug delivery systems to improve therapeutic efficacy, reduce dosing frequency, and enhance patient compliance. These systems are designed to maintain optimal drug levels in the bloodstream over an extended period, minimizing fluctuations in drug concentration that could lead to adverse effects or therapeutic failures. The choice of excipients plays a critical role in determining the success of such formulations, with a growing interest in natural polymers due to their biocompatibility, renewable origin, and cost-effectiveness.

Plant-derived gums have emerged as promising candidates for use in controlled drug delivery systems. These natural biopolymers are widely recognized for their ability to form gels, matrices, and films, making them ideal for applications in sustained-release formulations. Gums are typically composed of complex polysaccharides, which exhibit desirable properties such as swelling, viscosity, and delayed solubility, enabling controlled drug release. Additionally, they are often biodegradable, non-toxic, and capable of providing a protective environment for sensitive drugs, enhancing their stability.

This study focuses on hydrophilic gums extracted from Velama, Rekka, and Mardi plants, which were selected based on their renewable availability and unique physicochemical properties. These gums were obtained through a systematic process involving plant incision, extraction, drying, pulverization, and purification. Initial physicochemical characterization revealed that these gums predominantly consist of carbohydrates, with near-neutral pH values, making them suitable for a wide range of drugs, including those with acidic, basic, or neutral properties.

Their low moisture content further suggests compatibility with moisture-sensitive drugs, while satisfactory micromeritic properties, including flowability and compressibility, make them suitable for direct compression in tablet manufacturing.

2 MATERIALS AND METHODS

2.1 Selection of Plant Materials and Drugs

The plant materials used in the study were selected based on extensive literature review. Gum obtained from Anogeissus latifolia, Buchanania lanzan, and Terminalia tomentosa were chosen as natural polymers, while HPMC (Hydroxypropyl methylcellulose) was selected as a synthetic polymer. Levosulpiride, a hydrophilic drug, and alprazolam, a lipophilic drug, were chosen as model drugs for the study which is obtained form Akhil Healthcare pvt ltd, Ahmedabad, India.

2.2 Collection and Purification of Gum Exudates

2.2.1 Collection of Gum Exudatest

Gum exudates were collected from selected Anogeissus latifolia (Velama), Terminalia tomentosa (Mardi), and Buchanania lanzan (Rekka) plants. The collection process involved inducing stress by making incisions on the trunks during the first week of January. The gum was then collected in February and March. The collected gum exudates were treated with petroleum ether and chloroform to remove pigments and chlorophyll. Afterward, they were carefully washed with distilled water, dried in the shade for 24 hours, and further dried at 30–40°C until a constant weight was obtained. The size of the dried gum was reduced using a grinder, and the powdered gum was passed through a #22 sieve and stored in an airtight container for further use.

2.3 Characterization of Gum

2.3.1 Physicochemical Properties of Gums

The purified gums were evaluated for various characteristics such as color, odor, taste, and physical sensitivity.

2.3.2 Solubility

The solubility of the gums was determined by placing 1 gram of each gum in separate test tubes and adding 5 ml of different solvents, including cold water, hot water, ethanol, methanol, diethyl ether, petroleum ether, and acetone. The mixtures were shaken vigorously and allowed to stand for some time. Solubility in each solvent was then noted at room temperature.

2.3.3 Preliminary Phytochemical Study

A preliminary phytochemical study was conducted to identify the chemical constituents present in the hydrophilic gums extracted from Velama, Rekka, and Mardi plants. This evaluation aimed to establish the qualitative composition of the gums, providing insights into their suitability for pharmaceutical applications. The study focused on detecting the presence of key phytochemical groups, including polysaccharides, proteins, alkaloids, saponins, tannins, flavonoids, and phenolic compounds, as these constituents influence the functional properties of gums in drug delivery systems.

2.4 Physicochemical and Micrometric Properties

2.4.1 Determination of Swelling Index

The swelling index is the volume in ml occupied by 1 gram of gum, including any adhering mucilage after it has swollen in an aqueous liquid for 4 hours. One gram of each gum sample was allowed to swell for 4 hours with a small amount of water. One ml of ethanol was added to each cylinder, and the volume was made up to 25 ml with water in measuring cylinders. The cylinders were shaken vigorously every 10 minutes for 1 hour and then allowed to stand for 24 hours. The volumes occupied by the gums were measured. The swelling index was calculated from the mean of three determinations.

Swelling Index % (SI) = V2/V1
V1= Initial volume in ml
V2 = Final volume in ml

2.4.2 Loss on Drying of Isolated Gum

The method for determining loss on drying was adopted from the British Pharmacopoeia 2004 for acacia. One gram of each gum sample was taken into separate petri dishes and dried in an oven at 105°C until a constant weight was achieved. The moisture content was determined as the proportion of moisture loss relative to the weight of the sample and expressed as a percentage.

2.5 Analytical Method

Determination of λmax and Calibration Curve of Levosulpiride in Phosphate Buffer pH 6.8 and 0.1 N HCl

2.5.1 Preparation of Stock Solution in pH 6.8 Buffer and 0.1 N HCl

A stock solution of 100 µg/ml Levosulpiride was prepared in phosphate buffer of pH 6.8. This solution was suitably diluted with the buffer to obtain a concentration of 10 µg/ml. The resultant solution was scanned in the range of 200-400 nm using a UV double beam spectrophotometer (Lab India UV-3000+).

2.5.2 Standard Calibration of Levosulpiride in Phosphate Buffer pH 6.8

100 mg of Levosulpiride was accurately weighed and dissolved in 100 ml of pH 6.8 phosphate buffer to obtain a concentration of 1000 µg/ml. From this solution, 10 ml was withdrawn and diluted to 100 ml to obtain a concentration of 100 µg/ml. Aliquots of 0.5, 1, 1.5, 2, and 2.5 ml were further diluted in 10 ml volumetric flasks with phosphate buffer to achieve concentrations ranging from 5-25 µg/ml. Absorbance was measured at 223 nm.

2.6 Formulation of Sustained Release Tablets

Conventional oral tablets typically contain similar components in addition to the active pharmaceutical ingredients, such as diluents, binders or adhesives, flow promoters, and lubricants. For this study, microcrystalline cellulose (PH102) was used as a directly compressible filler, 1% magnesium stearate as a lubricant, 1% talc as a glidant, and 5% PVP K30. Anogeissus latifolia (velama) gum, Buchanania lanzan (Rekka) gum, and Terminalia tomentosa (mardi) gum were used as natural polymers, and HPMC was used as a synthetic polymer in concentrations of 15, 30, and 45%. Sustained release tablets of Levosulpiride were formulated by the direct compression method as described below.

2.6.1 Direct Compression

Direct compression is defined as the process by which tablets are compressed directly from a powder mixture of API and suitable excipients without pre-treatment by wet or dry granulation.

2.6.2 Blending of Ingredients

Levosulpiride, directly compressible filler (MCC 102), polymer, talc, and PVP K30 were sifted through sieve #60 and mixed for about 15 minutes to achieve a uniform blend. Magnesium stearate was passed through sieve #100 and mixed with the blend for approximately 5-7 minutes.

2.6.3 Tableting

The resulting uniform blends of composition (tablets of average weight 200 mg) were prepared on a 9-station Karnavati Mini press DL2 Bi-layer tablet machine fitted with flat 8 mm punch and die sets. Each batch size was 100 tablets. The compressed tablets were stored in a closed glass container for 15 days, during which no significant chemical changes were observed. Tablets were prepared using different concentrations of single natural and synthetic polymers, as well as combinations of natural-natural and natural-synthetic polymers, such as Anogeissus latifolia (velama) gum, Buchanania lanzan (Rekka) gum, Terminalia tomentosa (mardi) gum, and HPMC, as given in the formulation design table.

2.7 Experimental Design

The compositions of the formulations are shown in Table 1. The dose of Levosulpiride was 50 mg. The concentrations of PVP K30, talc, and magnesium stearate were kept constant at 5%, 1%, and 1% respectively. MCC was used as the filler. Following preliminary studies, a second set of formulations were prepared without rekka gum.

Set A Formulations contained only individual natural and synthetic polymers (12 batches).
Set B Formulations contained combinations of two polymers, resulting in 24 batches.

For Set A, the total polymer content in the tablets was varied at three ratios: 15%, 30%, and 45% of the total tablet weight. For Set B, the total polymer content was kept constant at 45%, but the polymers were combined in three different ratios: 1:1, 1:2, and 1:3.

Table 1: Composition of Levosulpiride SR Tablet

Formulation Code	Drug	NP (AL)	NP (BL)	NP (TT)	HPMC	PVP K30	Talc	Mg. Stearate	MCC
LS1	50	30				10	2	2	106
LS2	50	60				10	2	2	76
LS3	50	90				10	2	2	46
LS4	50		30			10	2	2	106
LS5	50		60			10	2	2	76
LS6	50		90			10	2	2	46
LS7	50			30		10	2	2	106
LS8	50			60		10	2	2	76
LS9	50			90		10	2	2	46
LS 10	50				30	10	2	2	106

LS 11	50				60	10	2	2	76
LS12	50				90	10	2	2	46
LVS 1	50	45			45	10	2	2	60
LVS 2	50	60			60	10	2	2	60
LVS 3	50	22.5			67.5	10	2	2	60
LVS 4	50			45	45	10	2	2	60
LVS 5	50			30	60	10	2	2	60
LVS 6	50			22.5	67.5	10	2	2	60
LVS 7	50	45		45		10	2	2	60
LVS 8	50	60		60		10	2	2	60
LVS 9	50	22.5		67.5		10	2	2	60
LVS 10	50	60			30	10	2	2	60
LVS 11	50	67.5			22.5	10	2	2	60
LVS 12	50			60	30	10	2	2	60

3 EVALUATION OF POST-COMPRESSION PARAMETERS

3.1 Shape and Colour of Tablets

Prepared tablets were examined under a lens for shape, and colour was observed by keeping the tablets in light.

3.2 Thickness Test

Three tablets were randomly picked from each formulation, and their thickness was measured individually. Thickness is expressed in millimeters, and the standard deviation was calculated. The tablet thickness was measured using a dial caliper (Mitutoyo, Japan).

3.3 Weight Variation Test

Twenty tablets were randomly selected from each batch, and their average weight was determined. Each tablet was weighed individually and compared with the average weight. The U.S. Pharmacopoeia allows a small variation in the weight of a tablet. The following percentage deviation in weight variation is allowed

- Tablets weighing 130 mg or less: ±10%
- Tablets weighing 130-324 mg: ±7.5%
- Tablets weighing more than 324 mg: ±5%

3.4 Hardness Test

The hardness of the tablets was measured using a Monsanto hardness tester, and results were expressed in Kg/cm².

3.5 Friability Test

Friction and shock are forces that often cause tablets to chip, cap, or break. The friability test, closely related to tablet hardness, is designed to evaluate the tablet's ability to withstand abrasion during packaging, handling, and shipping.

Friability of the tablets was determined using a Roche friabilator. Ideally, friability should be below 1%, indicating good mechanical resistance of the tablets. For tablets with an average weight of 0.65 g or less, a sample of whole tablets corresponding to about 6.5 g is taken. For tablets with an average weight of more than 0.65 g, a sample of 10 whole tablets is taken.
Thirty-five tablets were introduced into the drum and rotated 100 times. The tablets were then removed, loose dust was removed, and they were reweighed accurately. The friability (f) is calculated using the formula:

$$f=(W0-W/W0)\times 100$$

Where:

W0=Weight of the tablets before the test
W=Weight of the tablets after the test

3.6 Uniformity of Drug Content

The uniformity of drug content test is mandatory for tablets with 10 mg or less weight of the active ingredient. From each batch, ten tablets were randomly selected, finely powdered, and dissolved in 10 ml of 6.8 phosphate buffer. The solution was sonicated for 20 minutes to ensure complete leaching of the drug from the complex. The solution was then filtered through Whatman filter paper No. 41. From this solution, 1 ml was taken and diluted up to 100 ml with 6.8 phosphate buffer. The drug content was determined spectrophotometrically at 223 nm.

4 RESULT AND DISCUSSION

4.1 Percentage Yield of Gum

Percentage yield of gums were calculated laboratory developed methods. Obtained yield is tabulated in Table 2. It is known that the gum (polysaccharide) is mixture of a number of dissimilar macromolecular substances and the gum yield and composition of polymer can vary depending on the method of isol-

ation. and composition of polymer can vary depending on the methods of isolation. The yield was found 35.45%, 30.23 and 14.21% w/w for velama gum, rekka gum and mardi gum respectively (shows in table 3).

Table 2: Percentage yield of isolated gum

S. No.	Name of the gum	Percentage yield
1	Velama Gum	35.45%
2	Rekka Gum	30.23%
3	Mardi Gum	14.21%

Table 3: Results of phytochemical study

Tests	Velama Gum	Rekka Gum	Mardi Gum
Carbohydrates	+	+	+
Glycoside	-	-	-
Tannins	-	-	-
Steroids	-	-	-
Saponins	-	-	-
Flavonoids	-	-	-
Gum	+	+	+
Polysaccharide's	+	+	+

All three gums confirm the test for gum and carbohydrate and absence of glycoside, Tannins, saponins, steroid, flavonoids, starch which shows the purity of gum.

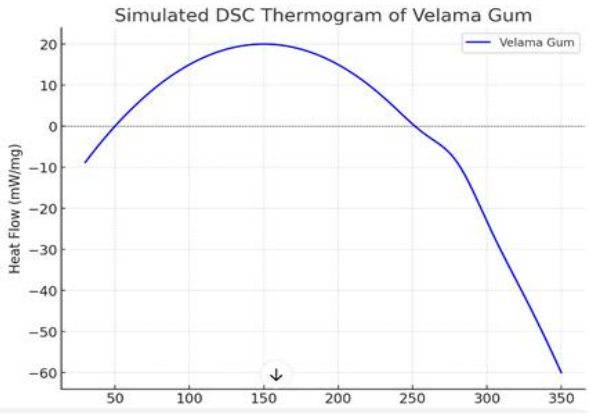

Figure 1: DSC thermogram of Velama gum

4.2 Analytical Development

4.2.1 Determination of Analytical Wavelength

The pure drug Levosulpiride was scanned over a range of 200-400 nm to determine its λmax. The UV spectrum of Levosulpiride does not show a sharp peak for absorption maxima, as shown in Figure 4. In the range of 200 to 230 nm, the maximum absorption was observed at 223 nm in pH 6.8 phosphate buffer. This value corresponds to the λmax reported in the literature.

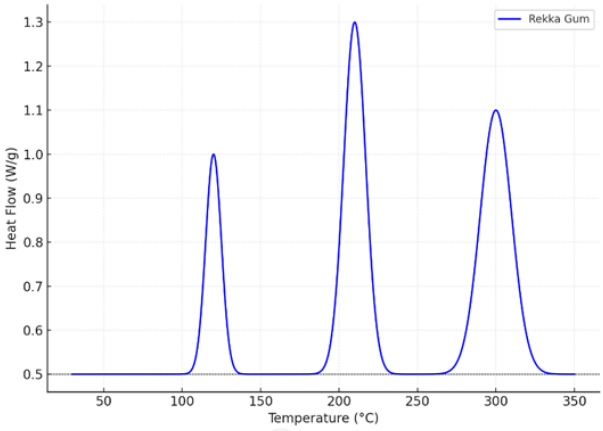

Figure 2: DSC thermogram of Rekka gum

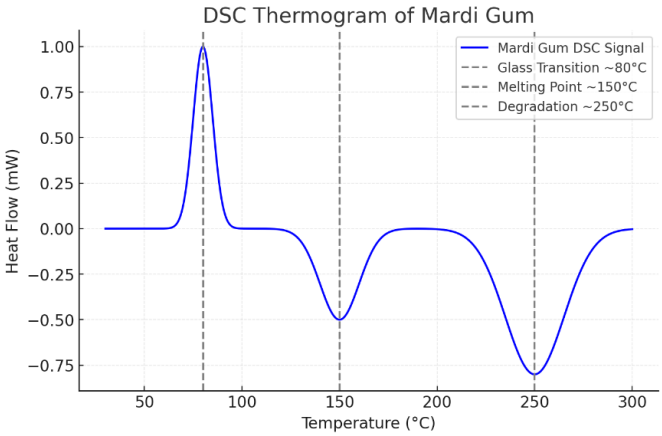

Figure 3: DSC thermogram of Mardi gum

4.2.2 Calibration Curve of Levosulpiride

The standard calibration curve of Levosulpiride was obtained by plotting Absorbance vs. Concentration. Table 4 shows the absorbance values of Levosulpiride. The standard curve is shown in Figure 5. The standard calibration curve has a slope of y = 0.063x + 0.008 and a correlation coefficient of 0.999 at pH 6.8 and at pH 1.2 it has a slope of y = 0.039x + 0.086 and a correlation coefficient of 0.976. The curve was found to be linear in the concentration range of 0-25 µg/mL (Beer's range) at 223 nm. The calculations of drug content and in vitro dissolution studies were based on this calibration curve.

4.3 Formulation Studies

4.3.1 Formulation of Levosulpride SR Matrix Tablet

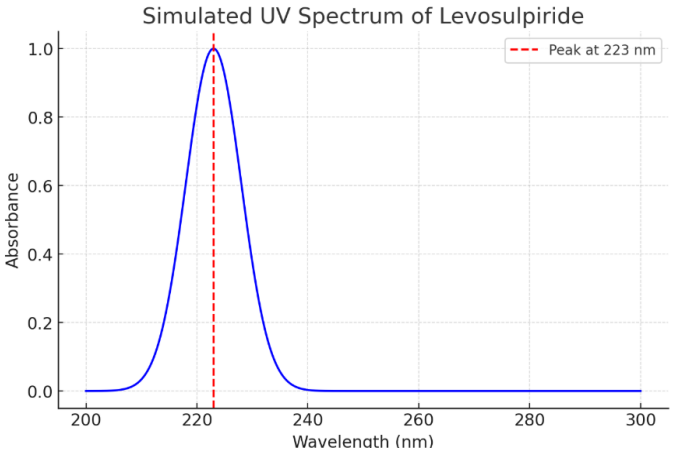

Figure 4: UV Spectrum of Levosulpiride

Table 4: Results of absorbance of Levoulpiride

S. No.	Concentration (µg/ml)	pH 6.8	pH 1.2
1	0	0	0
2	5	0.286±0.005	0.342±0.004
3	10	0.632±0.003	0.531±0.002
4	15	0.945±0.002	0.687±0.003
5	20	1.254±0.001	0.88±0.004
6	25	1.565±0.006	1.02±0.026

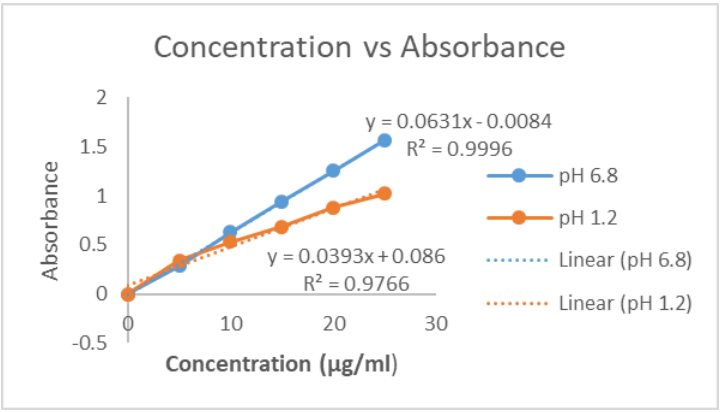

Figure 5: Calibration Curve of Levosulpiride in pH 6.8 and pH 1.2

Sustained release (SR) tablets of Levosulpiride were prepared using the direct compression method. Natural gums (Velama, Rekka, and Mardi) and the synthetic material HPMC were used as single rate-determining materials at concentrations of 15%, 30%, and 45%. Additionally, combinations of two polymers were used in ratios of 1:1, 1:2, and 1:3 at 45%. The tablets were compressed using 8 mm concave-faced punches.

4.3.2 Evaluation of Levosulpiride SR Matrix Tablet

The prepared tablets from all batches were evaluated based on various parameters given in table 5.

Table 5: Results of post compression parameters

Batch No.	Weight Variation (%)	Friability (%)	Thickness (mm)	Hardness (Kg/Cm^2)	Drug Content
LS1	198.12	0.866	4.05	5.4	98.12
LS2	197.23	0.996	4.15	5.3	98.23
LS3	199.23	0.845	4.25	5.5	98.45
LS4	198.45	0.785	4.17	5.6	99.23
LS5	199.23	0.867	4.42	5.4	99.45
LS6	199.12	0.834	4.78	5.8	99.34
LS7	201.23	0.934	4.68	5.4	98.78
LS8	202.13	0.814	4.63	5.8	98.40
LS9	207.35	0.723	4.54	5.5	99.12
LS10	200.78	0.876	4.75	5.7	99.45
LS11	210.12	0.767	4.35	5.8	99.49
LS12	199.34	0.912	4.25	5.4	99.90
LVS1	206.34	0.876	4.17	5.3	98.76
LVS2	208.23	0.785	4.24	5.6	98.90
LVS3	209.12	0.856	4.23	5.4	98.34
LVS4	206.34	0.945	4.37	5.7	98.96
LVS5	204.12	0.745	4.53	5.8	99.20
LVS6	206.12	0.712	4.39	5.6	99.45
LVS7	209.34	0.698	4.26	5.4	99.34
LVS8	204.34	0.756	4.52	5.7	103.76
LVS9	206.23	0.776	4.51	5.4	102.23
LVS10	203.12	0.867	4.28	5.6	99.58
LVS11	203.22	0.676	4.37	5.8	99.12
LVS12	200.12	0.645	4.10	5.3	100.01

5 CONCLUSION

In this study, hydrophilic gums were extracted from plants through incisions, collection, drying, pulverization, isolation, and purification. The yield of these natural gums was found to be sufficient compared to other gums, owing to their renewable source. Physicochemical characterization revealed that the gums primarily consist of carbohydrates, with positive tests indicating the presence of polysaccharides. The pH of 1% w/v solutions of Velama, Rekka, and Mardi gums in water were near-neutral (5.2, 6, and 5.6, respectively), suggesting they may cause fewer irritations in uncoated tablets, making them suitable for drugs with various properties. Their low moisture content indicated suitability for moisture-sensitive drugs, and Velama and Mardi gums exhibited good swelling indices, beneficial for matrix formation. Micromeritic studies showed satisfactory flow properties, and acid insoluble ash values indicated high purity.

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