IJMPR, 2026, 10(8), 01-12

ISSN: 2319-5878

INTERNATIONAL JOURNAL OF MODERN PHARMACEUTICAL RESEARCH

www.ijmpronline.com

Research Article

Impact Factor: 7.533

Coden USA: IJMPR3

FORMULATION DEVELOPMENT AND IN-VITRO EVALUATION OF HERBAL BUCCAL SPRAY HAVING ANTI-DIABETIC ACTIVITY

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Article Received on: 02/07/2026 **Article Revised on: 22/07/2026** **Article Published on: 01/08/2026**

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https://doi.org/10.5281/zenodo.21715904

How to cite this Article: *[1]Susdayal, [2]Nitish Kumar, [3]Amresh Gupta. (2026) Formulation Development And In-Vitro Evaluation Of Herbal Buccal Spray Having Anti-Diabetic Activity. International Journal of Modern Pharmaceutical Research, 10(8), 01–12.

ABSTRACT

Gymnema sylvestre is a traditional medicinal plant belonging to family Asclepiadaceae. Mainly leaves of *Gymnema sylvestre* have been used for the treatment of madhu meha or "honey urine" for more than 2,000 years in India. Recently novel dosage forms have gained significant popularity in the treatment of diabetes like buccal spray, nasal spray, buccal film etc. due to its outstanding characteristics. This research was based on the development and *in-vitro* evaluation of herbal buccal spray. *Gymnema sylvestre* leaves were collected, dried, and powdered which were subjected to continuous and exhaustive Soxhlet apparatus using different solvents like petroleum ether, chloroform, and methanol. This methanolic extract were used in the novel formulation. Preformulation study to establish the compatibility between the drug and polymers by FT-IR revealed that drug and polymers are satisfactorily compatible. Buccal spray of *Gymnema sylvestre* was prepared using different concentrations of penetration enhancers and co-solvents and were evaluated for different evaluation parameters like leak test, spray pattern, valve discharge rate, content uniformity, drug diffusion study, droplet size measurement and stability study. The results of the study show that buccal spray of *Gymnema sylvestre* was found good for the treatment of diabetes mellitus. It concluded that this formulation has better in-vitro profiles that can be further evaluated by using in-vivo or animal models to confirm its potential in human beings.

KEYWORDS: *Gymnema sylvestre*, Preformulation study, droplet size, buccal spray, anti-diabetic.

INTRODUCTION

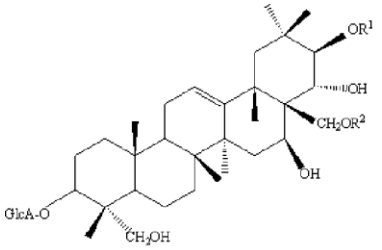
A novel drug delivery advanced technologies makes the tasks into goal ofdrug delivery (Al-Hilal et al. 2013). The oral transmucosal system bypasses the hepatic presystemic metabolism led to higher bioavailability whereas oral mucosa having small surface area which may lead to drug loss because of uncontrolled salivary flow and uncontrolled swallowing. The non-keratinized buccal mucosa of human is multistratified and drug diffusion across the buccal epithelium involves both the paracellular and transcellular routes. (Makwana, 2012). Various formulations have been explored and developed for the drug delivery through the mucous membrane of the oral cavity which include solids like tablets, patches, films, lozenges, wafers, microparticles; liquids dosage forms like solutions and suspensions; semisolid dosage forms like creams, gels,ointments, emulgels and chewing gums and sprays (Patel et al. 2011). The atmosphere of the buccal mucosa can be manipulated and controlled for the optimization of rate of drug permeation and drug dissolution with the perfect design of dosage form. Presently various formulations including tablets, films, sprays, gels, mouthwashes, pastes are used for the oral transmucosal delivery. Spray formulations have added value in the field of pharmacy as novel and patient convenient dosage forms (Sudhakar et al. 2006; Patel et al. 2011).

Drug profile

Thus traditionally, the term "destroyer of sugar" is used for *GS* because chewing of leaves will discriminate the sweetness. Among various activities, the plant is attributed to other activities like biting, astringent, harsh, thermogenic, calming, anodyne, stomach related, hepatic, diuretic, emetic, stimulant, purgative, cardioprotective, antipyretic, expectorant, anthelmintic, and UTI. This medicinal plant is also valuable in dyspepsia, stomachic, clogging, jaundice, hemorrhoids, vesical calculi, renal, cardiopathy, amenorrhea, bronchitis, conjunctivitis, leukoderma, and asthma (Saneja et al. 2010).

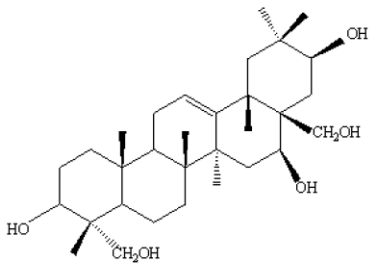
G. sylvestre leaves are rich source of saponins (triterpene) resembles to oleanane and dammarane. Saponins Oleanane k/a are gymnemic acids and gymnemasaponins, whereas saponins dammarane are gymnemasides principally gymnemic acid A-D, stigmasterol and β-amyrin related glycosides. Other important agents such as anthraquinones, flavones, pentatriacontane, hentri-acontane, phytin, chlorophylls, resins, tartaric acid, *d*-quercitol, butyric acid, formic acid, lupeol and alkaloids. Leaves contains acidic glycosides, anthraquinones and its derivatives (Kritikar 1998).

Antidiabetic property is due to the presence of Gymnemic acid. It is also served as sugar making agent, anti-inflammatory value. Antidiabetic novel agent gymnemic acids isolated from the fresh leaves of *G. sylvestre*. Followed by the SAR of the gymnemic acids and other major phytoconstituents of *G. sylvestre* were studied in detailed and elucidated (Khan et al., 2019).

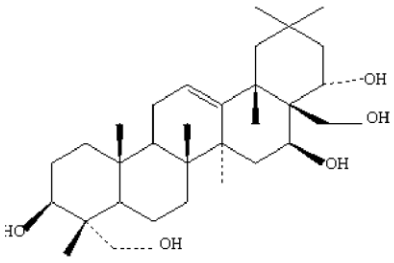


Gymnemic acid

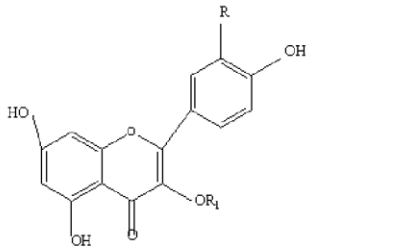
Gymnemic acid types	R^1	R^2
Gymnemic acid 1	Tigloyl	Ac
Gymnemic acid II	2-methylbutyroyl	Ac
Gymnemic acid III	2-methylbutyroyl	H
Gymnemic acid IV	Tigloyl	H



Gymnestrogenin



Gymnemanol



R = H, R_1 = beta-O-Glcp-(1--> 4)- alpha-L-Rhap-(1-->6)-beta-O-Galp

Kaempferol 3-O-beta-D-glucopyranosyl-(1-->4)-alpha-L-rhamnopyranosyl- (1-->6)-beta-D galactopyranoside

Figure 1: Gymnemic acid: Chemical structure.

This research was based on the development and *in-vitro* evaluation of herbal buccal spray of *Gymnema sylvestre*. The prime aim of the current investigation was to formulate and develop a novel buccal spray and evaluate through in-vitro parameters.

MATERIALS AND METHODS

1. Collection and Authentication

The leaves of *Gymnema sylvestre* were collected during January 2022 from the local surroundings in Lucknow, Uttar Pradesh. Further plant was authenticated from taxonomic Division of GIPS, Lucknow, Uttar Pradesh. A plant specimen was deposited for future reference (GIPS/Ph'Cog. /01/2022/002).

2. Reagents and Chemicals

Table 1: Materials used in the present investigation.

Chemicals	Manufacturers
Petroleum Ether (60-80^{o}C)	Ranchem Ltd. India.
Chloroform	
Methanol	
Chromic acid	
Ethanol	Baroda Chemicals Ltd
Oleic acid	Seva Fine Chemical Ltd. Mumbai
Linoleic acid	
Peppermint oil	Central Drug House, India
0.1 M Sodium citrate buffer	Seva Fine Chemical Ltd. Mumbai
Streptozotocin	
Citric acid	Sigma Aldrich (USA)

Sodium hydroxide	Seva Fine Chemical Ltd. Mumbai
Sodium citrate	
Potassium dihydrogen phosphate	
Hydrochloric acid	

Table 2: Equipment (s) used in the Present Investigation.

S.N.	Equipment (s)	Manufacturers
1	Digital Balance	Shimadzu Corporation, Japan
2	Soxhlet Apparatus	JSWC
3	Desiccator	JSWC
4	Oven	Tempo instruments and equipment
5	FT-IR	Shimadzu, Japan.
6	UV-VIS	Shimadzu, Japan.

3. Plant Extract Preparation

The collected (2.5kg) *Gymnema sylvestre* leaves were air dried and followed by tray dryer under favourable condition and powdered it. The powdered crude drug (1.2kg) was extract out with PE, chloroform, and methanol by Soxhlet extractor. The crude solution was further filtered and make syrupy mass by reduced pressure at 40^{o}C and kept in desiccator.

4. Preliminary phytochemical screening

The parameters were taken from Khandelwal, (2010) for detection of phytoconstituents using following methods.

For alkaloids

Mayer's reagents: Crude extract+ Potassium mercuric iodide gives cream precipitate.

Hager's reagents: The test solution + saturated 5% picric acid (Hager's reagent) yields instant yellow colour precipitate.

For carbohydrates

Fehling's Reagent: Mix equal vol of Fehling's solutions A & B, followed by heating for some times+ test extract in equal proportion. Gently boil for 5-10 min at water bath. Suddenly yellow, followed by brick red colour ppt. is produced.

Barfoed's reagent: Test solution + Barford's reagent, gently boil. Observed that brick red ppt suggests the indications of saccharides.

Molisch's test: Plant Extracts mixed with α-naphthol simultaneously add Conc. H2SO4, purple colour is produced indicate the confirmation of carbohydrates.

Benedict's test: Plant Extracts mixed with Benedict Reagent (173g Sodium citrate + 100 g Sodium carbonate + 17.3 g Copper sulphate) and boiled it for few min and allowed to cool, A red, green, or yellow ppt. produced indicate the confirmation of carbohydrates.

Fixed oils & fats

Cellulose paper: Cellulose filter paper gets completely treat with fixed oils.

Test for Proteins & Amino acids

Biuret test: Extract treated with NaOH solution and Dill. CuSO4 solution. A deep blue color indicates the confirmation of protein.

Ninhydrin test: Extract + ninhydrin exhibits blue colour ppt.

Millon's test: extract + reagent, mild heated, they produce yellow colouration.

Flavonoids

$FeCl_3$ test: Extract/fraction + little amount of $FeCl_3$ aq. solution give dark green colour.

Alkaline reagent test: Extract/fraction + NaOH sol. suddenly produces deep yellow ppt later on turns colourless by the addition of Dil. Acidic solution.

Lead acetate reagent: Extract/fraction + little quantity of 10% lead acetate produces yellow color precipitate.

Zinc-HCL reduction test: Extract/fraction + zinc dust + HCl produces magenta red colour.

Shinoda test: Extract/fraction + magnesium turnings + conc. HCL, exhibits pink to magenta red colour upon heating.

Test for sterols

Salkowski reagent: Extract/fraction + Con H_2SO_4, mixed well and keep aide. The base layer changes red colour suggesting the sterols are reported.

Saponin Glycosides

***Foam formation test*:** Extract treated + water mixed up toughly a persist froth formation was observed.

Test for Starch

Iodine test: Extract + Aq. Iodine solution. Appears navy blue color, and becomes disappears on heating at water bath and again reappears navy blue color on cooling.

Tannic acid: Extract + 5% tannic acid. Buff ppt.

Tannins & polyphenolic

$FeCl_3$: Plant extract + few ml of ferric chloride solution

exhibits dark red colour.

5. Physicochemical analysis

The following physicochemical parameters were taken from guidelines of WHO, 2002.

Determination of loss on drying

2 g of fine powdered material was transferred in a tarred disc (without preliminary drying) dried at temp. 105˚C for 30 min and weigh accurately. Again, dry the drug and weigh after 1 h time difference until no any changes b/w two successive readings and to not more than 0.25%. This weight loss is considered as moisture content and percentage of moisture loss was calculated.

Total ash

Weighed 2 g accurately of fine crude drug was incinerated in porcelain dish at a temp 450˚C all the organic content will burn out only inorganic residue is there then cooled and weighed and then calculated the %age of total ash as compared to the fresh drug.

Calculation of water-soluble ash

The total ash was boiled with 25ml distilled water and filter the insoluble content by ashless filter paper followed by rinsed with fresh boiled water and incinerate again at temp up to 450˚C till constant weight changes, subtracted the %age of water-soluble ash as compared to fresh air-dried powdered material and analyzed.

Calculation of acid insoluble ash

The total ash was boiled with 25ml Dil. HCl and filter the insoluble content by ashless filter paper, and again rinsed with boiled water and further incinerated at a temp 450˚C up to constant changes and determine the percentage of acid-insoluble ash as compared to air dried fresh drug.

Calculation of extractive value

5 g of dried fine powdered plant was extracted with 100ml of solvent for one day, frequently mixed it after 6h kept aside for 18 h, followed by filtration and to take precautions to avoid loss of menstruum concentrated to 25 ml of filtrate was dryness in dish and concentrated at 105˚C up to constant weight changes. The %age of menstruum-miscible matter as compared to the fresh dried material was determined.

Preformulation analysis

Preformulation analysis were carried out for the checking out the compatibility of excipients i.e., polymers along with the novel medicinal agent, excipients, and modern analytical evaluation in base of remarkable experimental dosage forms (Thapa et al., 2020). FT-IR was performed. The results for the same are discussed below.

Solubility of extract

Solubility of the excipients is prerequisite investigation of preformulation evaluation while very poorly soluble agents can intensely decrease production in novel drug discovery. The solubility saturation of *Gymnema sylvestre* leaves extract was analysis in various organic solvents viz. chloroform, methanol, diethyl ether, phosphate buffer pH 7.4, 6.8, 4.0, 1.2.

Compatibility study of drugs with polymers by FT-IR

The drug excipient interaction is possible in any formulation due to their intimate contact. Therefore, assessment of their compatibility with each other is most important to confirm the stability of the product's along with their therapeutic value and efficacy. Whereas the selected polymers for formulations developments having negligible therapeutic importance (inert), polymers may participate in chemical interaction and leads a chronic breakdown of API, that is it is very useful for the compatibility study of drugs and polymers. The interaction between drug and polymer was examined by FT-IR (Fourier Transform Infrared) spectroscopy.

6. Method of Analysis of *Gymnema sylvestre* Extract

Preparation of phosphate buffer pH 6.8

22.4 ml of 0.2 M NaOH and 50 ml of 0.2 M potassium dihydrogen phosphate were added into a 200 ml volumetric flask to prepare phosphate buffer pH 6.8 and water was added to make up volume.

Determination of λ max of *Gymnema sylvestre*

Approximately 10 mg extract of *Gymnema sylvestre* was added to volumetric flask having capacity of 100ml. 10 ml of phosphate buffer at pH 6.8 (PBS 6.8) were incorporated to dissolve the extract. 100µg/ml stock preparation was made by adding the PBS 6.8 up to the mark. Then this stock solution was again diluted with PBS 6.8 and was captured by UV spectrophotometery. The UV spectra was taken in a range of 200-600 nm.

Preparation of standard calibration curve of *Gymnema sylvestre* using UV

Calibration curve of *Gymnema sylvestre* was developed in PBS 6.8 at 278.5 nm. Stock solution containing 100µg/ml was prepared and kept aside. 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 ml of stock solution were discarded and again diluted up to 10 ml with buffer solution at a concentration of rage 10, 20, 30, 40, 50, 60, 70, 80, 90 and 100µg/ml respectively. At 278.5 nm wavelength the absorbance of solutions was scanned by UV-VIS spectrophotometer.

7. Formulation of Herbal Buccal Spray

Composition of buccal spray

The formulation containing therapeutically active ingredient (drug substance) was dissolved in solution or mixtures of excipients like solvent, cosolvent, viscosity modifiers, penetration enhancer, preservatives, taste masking agent and sweeteners/flavors, emulsifying agents, buffering systems in non- pressurized dispensers that convey a spray holding metered dose of drug (Huang et al, 2012).

The solvent mostly utilized are water and ethanol or

isopropyl alcohol or their combination with various fatty acid oils.

PEG (grade 400-1000), propylene glycol etc. can act as co-solvents whereas polyvinyl alcohol, miglyol, glycerin etc. are generally used as viscosity builders.

Penetration enhancer can be selected from wide range of materials like surfactants, bile salts, fatty acids, salicylic acid etc. which are generally utilized for enhancement of buccal transmucosal absorption. Various flavors and sweeteners (e.g., aspartame, neotame, sucralose, saccharine sodium etc.) can be selected as per the requirement.

8. Preliminary Trial

Ex-vivo Transmucosal Diffusion Study using Different Penetration Enhancers (Majid et al. 2021)

Ex-vivo investigation was carried out on goat buccal mucosa, obtained from local slaughterhouse, using Franz diffusion cell. A receiver and donor components were respectively filled with PBS 6.8 while former received 25 ml and later received just enough to moisten the inter compartment membrane (Goat buccal mucosa). The temperature of assembly was kept constant at 37ºC±0.05ºC and stirred constantly by stirrer. Various penetration enhancers like ethanol, PEG 400, Linoleic acid, Tween 80, PG and Oleic acid were used for study. Every 3 min, 3 ml of sample was withdrawn for 15 min duration and volume made up using PBS 6.8. Absorbance was measured at 278.5 nm keeping PBS 6.8 as blank. The concentration of drug diffused was computed from the given equation.

$$Y=0.172X + 0.003$$

Where, Y = Absorbance
X = Concentration

9. Formulation Batches of Herbal Buccal Spray

The drug *Gymnema sylvestre* was dissolved in water. The oleic acid, linoleic acid was used as penetration enhancers. The ethanol was used as co-solvent and also enhances the permeability of the drug. The Stevia rebaudiana was added to the solution as adjuvants. Along with that it also exerts antidiabetic activity. The Peppermint oil was added as a flavoring agent. All these excipients were used in formulation and all the batches were decided on trial-and-error method.

10. Procedure to formulate the solution for Buccal Spray

In this formulation Stevia rebaudiana was added to the water and made the solution. Then drug was added slowly to the vehicle and dissolved by continuous stirring. The oleic acid with continuous stirring followed by addition of peppermint oil.

Table 3: Formulation Batches for the Herbal Spray.

F. No.	GSE (mg)/spray	Stevia (mg)	Oleic acid (ml)	Linoleic acid (ml)	Ethanol (ml)	Peppermint oil	Water (ml)
H1	150	100	1	2	3	q.s.	20
H2	150	100	2	1	3	q.s.	20
H3	150	100	1	1	2	q.s.	20
H4	150	100	1	2	2	q.s.	20
H5	150	100	2	2	3	q.s.	20
H6	150	100	2	1	2	q.s.	20
H7	150	100	1	1	3	q.s.	20
H8	150	100	2	2	2	q.s.	20

Dose Calculation

The container capacity is 30 ml and net volume filled in each container is 25 ml. Here each Spray delivers 0.125ml volume, so 25 ml can be sprayed for 200 times. The drug content desired to be delivered per spray should be multiplied by 200 times. Here, it was desired that one spray should deliver 150mg in all formulation batches.

11. Evaluation Parameters for Herbal Buccal Spray

Leak test

- ***Immediate Leak test***

Final containers will allow to reduced size in 50 ^{0}C hot Distilled water for few secs, and then filling. Bubble formation indicates that leakage is there in the container.

- ***Delayed Leak analysis***

weighed containers accurately were kept at 25 ^{0}C for 1 month after that the containers were reweighed. The difference in weight of the bottle indicated the leakage in the container.

Spray Pattern

The comparing spray pattern method is impingement the spray at the piece of a cellulose paper. Clear colored patterns were observed on the paper when the spray was sprayed on it from 3 cm distance. The spray patterns were compared on the basis of their shape and width or diameter, using a graduated scale/ruler.

Pump discharge rate

Pump discharge rate of buccal spray was determined by spraying a known weight and discharging the contents for 10 times. By reweighing the container after ten sprays, the change in weight per unit spray i.e., the average weight dispensed per spray was calculated and considered as valve discharge rate, which can be expressed as grams per spray. After that it is converted in to ml with help of density of liquid.

Droplet size determination (Abmann et al. 2021)
Droplet size distribution was examined by using optical microscopy. Glass slide was taken and the formulation was sprinkled. Minimum 100 particles were measured from various 25 regions under microscope (40X).

Dose uniformity
One of the most critical quality control parameters of the Buccal spray is its dose uniformity i.e. uniformity of the drug content per unit spray. To investigate dose uniformity, one puff from product was sprayed in a beaker and that sprayed content was diluted with PBS 6.8. After making sufficient dilutions, absorbance was measured by 278.5 nm by UV/VIS spectrophotometer keeping PBS 6.8 as blank. Uniformity of the dose dispensed, was assured by measuring at least 3 dispensed doses per product.

Stability Checking
Stability is to determine the shelf-life of the drugs to retain its potency for long period of time. Stability checking is evaluated to check that the active agents maintain its potency and does not expire before the expiry dates. After the period of each month, formulation checked for drug content per spray.

RESULTS AND DISCUSSIONS

1. Pharmacognostic studies of *Gymnema sylvestre*

Pharmacognostic studies of the leaves and crude leaf powder obtained from *Gymnema sylvestre* were carried out; the obtained results were comparable and fulfilled the standard literature values.

Table 4: Preliminary Pharmacognostic Characterization.

Pharmacognostic parameters	Observation
Physical Tests	Leaves are opposite, usually elliptic, or ovate
Shape	
Color	Slight yellowish green
Odor	Pleasant aromatic
Taste	Bitter
Length (l & w)	2-5cm X 1-4cm
Extractive value	5.6 %
Loss on drying	1.084 %w/w
Total ash	5.8 %w/w
Acid insoluble ash	1.22 %w/w
Water insoluble ash	3.52 w/w

Extractive value
An approximate yield of *Gymnema sylvestre* methanolic extract was observed 5.6 %. The extracts were stored in a vacuum desiccator till further use in the formulation.

Preliminary Phytochemical Studies
The *Gymnema sylvestre* methanolic extract was carried out for the Phytochemical screening tests.

Table 5: Summery of Preliminary Phytochemical Screening of *Gymnema sylvestre.*

Phytoconstituents class	Name of Test	Inference (GSE)
Alkaloid	Mayer's	(+)
	Dragendorff's	(+)
	Wagner's	(+)
Carbohydrates	Molisch's	(-)
	Fehling's	(-)
	Benedict's	(-)
Phenolic compound	$FeCl_3$	(+)
	Sodium hydroxide Test	(-)
Flavonoid	Shinoda Test	(-)
	Lead acetate	(-)
Steroid	Steroid Test	(+)
Glycoside	Legal's Test	(+)
	Killer Killani Test	(+)
Tannins	Matchsticks Test	(-)
	Gelatin Test	(-)
Quinone	Quinone Test	(+)
Sterol	Sterol Test	(+)

2. Preformulation studies

Solubility study
Extract of *GS leaves* were noticed that it is practically soluble in water, methanol, ethanol, and Phosphate buffer solution having pH 6.8. It was observed that less soluble in CHCl3& DCM.

Compatibility study of drugs with polymers by FT-IR

FTIR spectroscopy analysis used to check interactions in b/w extract and the drug excipients used. Drug polymer physiochemical changes was standardized by checking b/w the FTIR spectrum of Drug and Drug-excipients mixture. Sample was scanned with IR grade Kpelles range of 500-4000 per cm by FTIR.

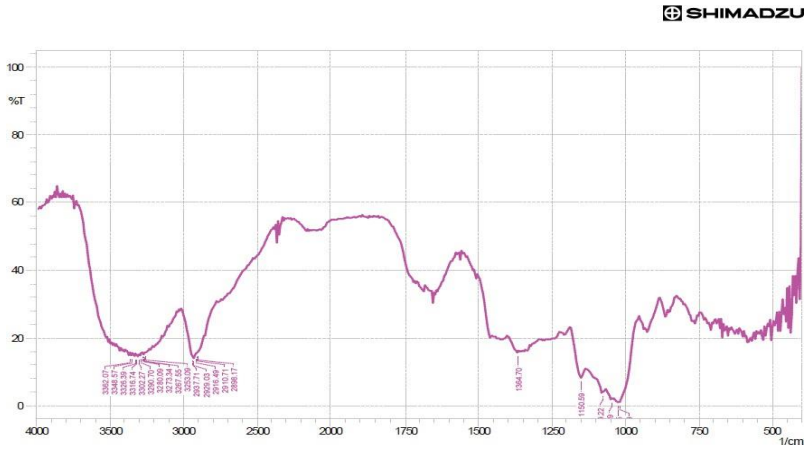


Figure 2: FTIR Spectra of *Gymnema sylvestre.*

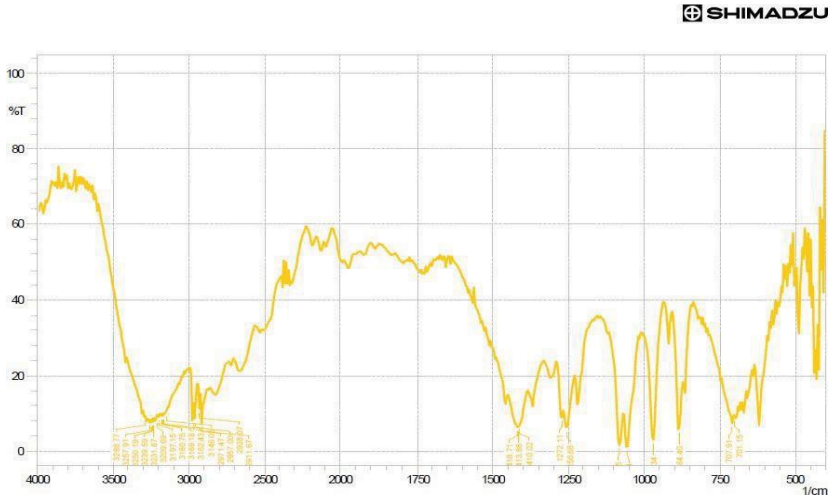


Figure 3: FTIR Spectrum of *Stevia Rebaudiana.*

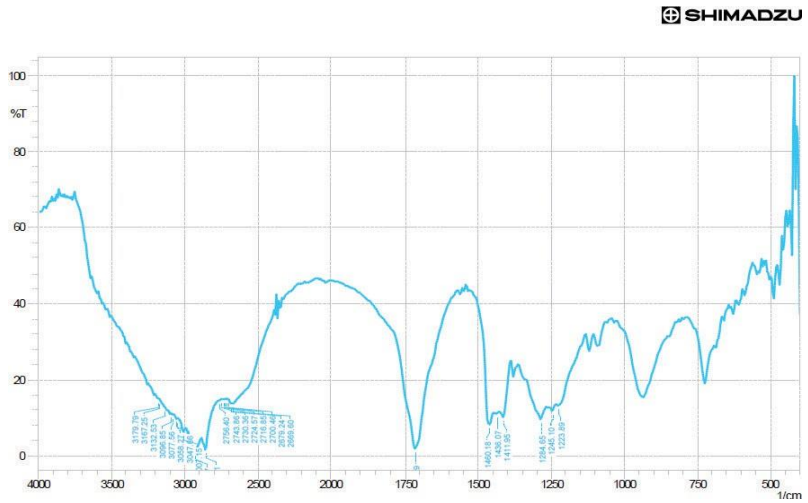


Figure 4: FT-IR Spectrum of Oleic acid.

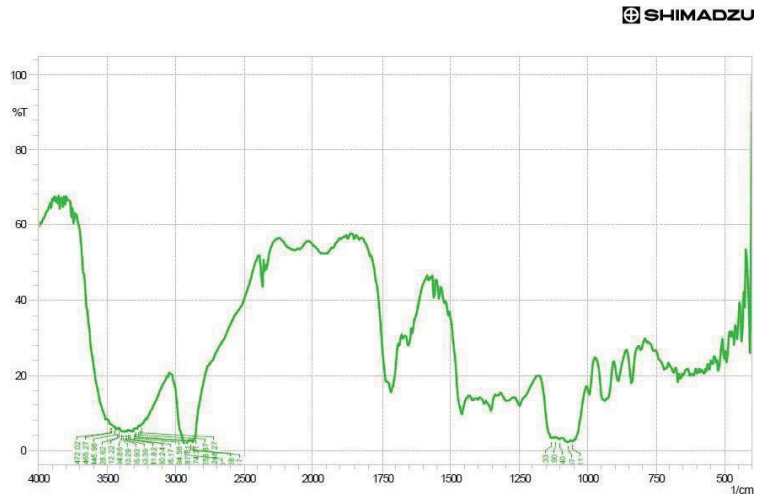


Figure 5: FT-IR Spectrum of Drug-excipient mixture.

3. Spectrophotometric Estimation of *Gymnema sylvestre*

Determination of λ max of *Gymnema sylvestre*

λ max of *Gymnema sylvestre* was determined as described in section 4.8.2. The spectra show peak at 278.5 nm.

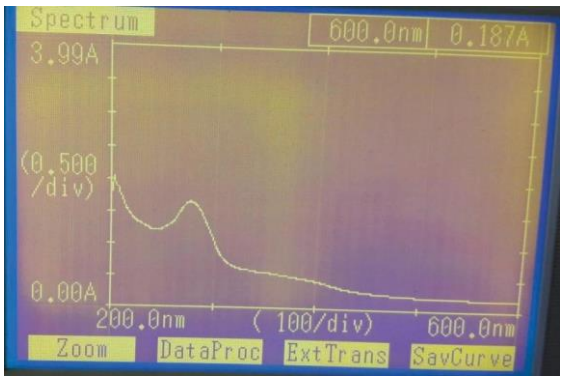


Figure 6: Spectra for *Gymnema sylvestre* in Phosphate Buffer solution pH 6.8.

Standard Calibration Curve of Drug

Calibration curve of drug was made by the absorbance of *Gymnema sylvestre* solutions containing 10-100µg/ml of test drug in phosphate buffer solution pH 6.8. Figure 7.6 revealed a respective reference standard calibration chart along with intercept, slope, and regression coefficient of 0.003, 0.172 and 0.998 respectively. The linear curve was found of range 10-100µg/ml at λ max 278.5nm. The analysis of the test drug conc, *In-vitro* diffusion rate was as per the curve.

Table 6: Absorbance of *Gymnema sylvestre* Standard Solution.

Concentration (µg/ml)	Absorbance				
	I	II	III	Avg.	Std. Dev
10	0.18	0.12	0.175	0.158333	0.435145
20	0.331	0.336	0.34	0.335667	0.859463
30	0.508	0.53	0.528	0.522	1.279657
40	0.683	0.776	0.773	0.744	1.681723
50	0.875	0.859	0.847	0.860333	2.137733
60	1.064	1.029	1.005	1.032667	2.565189
70	1.187	1.215	1.193	1.198333	2.995982
80	1.358	1.402	1.373	1.377667	3.419787
90	1.553	1.587	1.595	1.578333	3.832558
100	1.676	1.721	1.718	1.705	4.283549

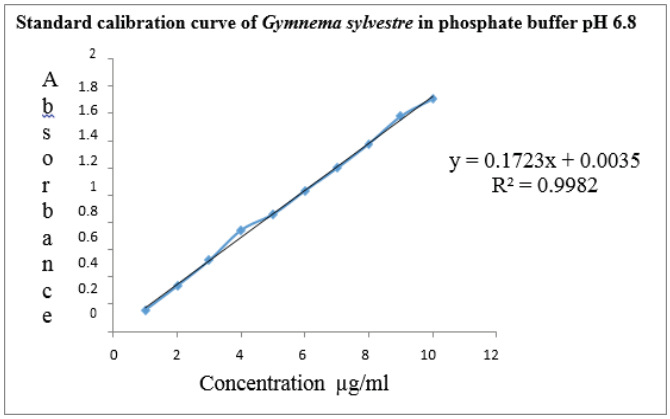


Figure 7: Calibration curve of *Gymnema sylvestre* standard solution.

4. Evaluation of Herbal Buccal Spray

Leak test

- ***Immediate leak test***

Not a single container showed bubbling during the test and therefore no container was found to have leakage.

- ***Delayed leak test***

There were no weight changes of the container was found out as container leakage.

Spray Pattern

Table 7: Result of Spray Pattern.

Batch No.	Diameter of spray pattern (cm)			Average diameter (cm) ± SD
H1	3.05	2.7	2.95	2.9 ± 0.18
H2	2.9	2.85	3.1	3.0 ± 0.13
H3	2.65	2.45	2.65	2.6 ± 0.12
H4	3.3	3.15	3	3.2 ± 0.15
H5	2.95	3.15	2.6	2.9 ± 0.28
H6	2.75	3	2.9	2.9 ± 0.13
H7	3.1	3.2	3.05	3.1 ± 0.08
H8	3.2	3.2	3.05	3.2 ± 0.09

The results of spray pattern measurement study (Table 7.4), revealed that all the formulations had an average diameter within the range of 2.6-3.2 cm.

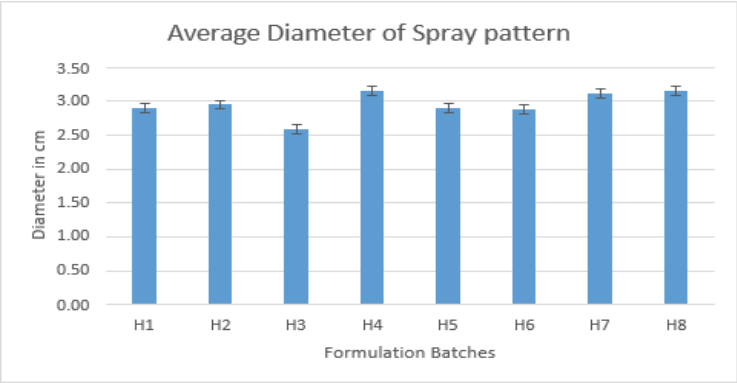


Figure 8: Average Diameter of Spray Pattern.

Valve Discharge Rate

Discharge rate was reported as below-

Table 8: Result of Value Discharge Rate.

Batch No.	Initial weight (gm)	Weight After 10 Sprays (gm)	Content Discharge/ spray (mg)	Average content discharge/ spray (mg) ± SD
H1	33.544	32.259	1.285	1.218±0.08
	32.241	31.11	1.131	
	30.874	29.636	1.238	

H2	33.377	32.267	1.11	1.1997±0.08
	31.864	30.617	1.247	
	30.476	29.234	1.242	
H3	33.319	31.985	1.334	1.2503±0.10
	31.794	30.651	1.143	
	30.275	29.001	1.274	
H4	33.275	31.994	1.281	1.2237±0.07
	31.99	30.75	1.24	
	30.61	29.46	1.15	
H5	33.18	31.99	1.19	1.2233±0.09
	31.9	30.75	1.15	
	30.46	29.13	1.33	
H6	33.363	32.18	1.183	1.171±0.03
	32.1	30.91	1.19	
	30.75	29.61	1.14	
H7	30.89	29.641	1.249	1.2987±0.04
	29.634	28.317	1.317	
	28.015	26.685	1.33	
H8	32.259	30.89	1.369	1.3193±0.06
	30.748	29.493	1.255	
	28.319	26.985	1.334	

The results of valve discharge rate measuring study, showed the valve discharge rate of all the formulation were within the average range of 1.171-1.319 mg.

Droplet Size Determination

Droplet size distribution was standardized by optical microscopy. On a glass slide, the formulation was sprayed and 10 fine particles in various zones were counted using a binocular 2000 microscope having magnification 40X.

Calculation for Calibration Factor

Calibration factor = no. of eye-piece / no. of micrometer * 10

= 26 / 20 * 10

= 13

Table 9: Results of Droplet Size Determination.

Batch No.	H1	H2	H3	H4	H5	H6	H7	H8
1	32.5	32.5	26	13	19.5	39	32.9	45.5
2	39	19.5	13	32.5	26	32.5	13	13
3	26	26	19.5	45.5	32.5	26	26	26
4	32.5	39	26	39	39	32.9	32.5	19.5
5	45.5	32.5	39	26	13	19.5	39	32.5
6	26	26	19.5	32.5	26	26	19.5	39
7	32.5	39	26	19.5	19.5	13	13	32.5
8	39	19.5	32.5	39	39	29	26	13
9	32.5	26	26	32.5	32.9	19.5	32.5	26
10	39	39	19.5	45.5	39	32.5	39	39
Average droplet size (µm) ± SD	34.45 ± 6.2	29.9 ± 7.63	24.7 ± 7.4	32.5 ± 10.6	28.64 ± 9.3	26.99 ± 7.8	27.34 ± 9.6	28.6 ± 11.1

The results of Droplet size determination measurement study (Table 9), revealed that all the formulations had an average droplet size within the range of 24.7- 34.45 µm.

Dose Uniformity

Table 10: Result of Dose Uniformity.

Batch No.	Dose content (mg)			Average drug content (mg) ± SD
H1	89.4	90.48	94.7	91.5 ± 2.80
H2	93.76	86.46	92.13	90.8 ± 3.83
H3	93.73	88.42	86.84	89.7 ± 3.61
H4	89.71	89.18	86.75	88.5 ± 1.58
H5	94.84	90.57	85.24	90.2 ± 4.81
H6	87.94	90.78	90.78	89.8 ± 1.64

H7	91.11	94.6	89.76	91.8 ± 2.50
H8	93.68	95.81	86.9	92.1 ± 4.65

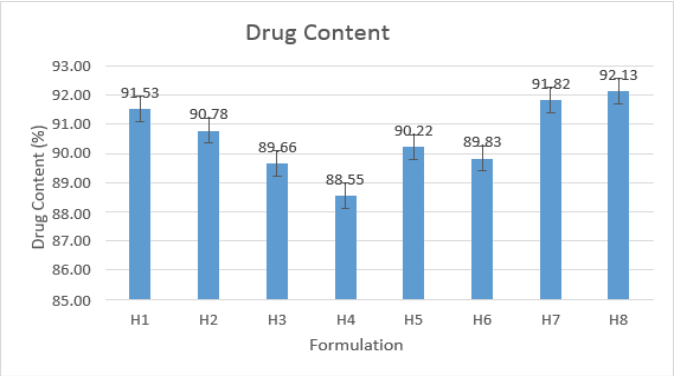


Figure 9: The % Drug Content of Formulation Batches.

***In-vitro* Diffusion Study**

The transmucosal diffusion through buccal mucus membrane was evaluated to ensure a systemic availability of the active agents. The formulation was designed such that one puff delivers 150 mg drug. So, two puffs, one puff on each side of buccal cavity, will deliver total 300 mg drug which is the actual dose of drug.

Table 11: Cumulative Amount of Drug Diffused.

Time (min)	% Cumulative Drug Diffused							
	H1	H2	H3	H4	H5	H6	H7	H8
0	0	0	0	0	0	0	0	0
3	19.57	17.14	17.38	18.56	14.85	19.88	19.98	13.47
6	32.86	23.11	26.97	30.32	28.23	33.85	34.61	29.45
9	49.88	42.48	40.23	45.85	42.36	50.12	41.43	43.49
12	62.15	62.59	59.82	59.4	57.43	64.42	59.49	60.21
15	80.77	81.65	84.2	79.2	78.6	85.55	81.56	83.81

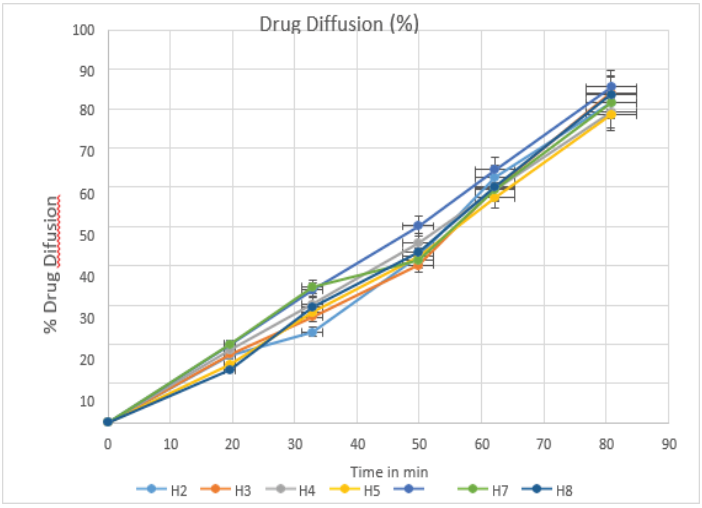


Figure 10: The % Cumulative Amount of Drug Diffused.

Stability study

The following table depicts the stability study of formulations-

Table 12: Stability Study.

Tests	Time (Months)					
Parameters	1	2	3	4	5	6
Leak test	No Leakage					
Spray pattern (cm)	2.6	2.59	2.53	2.57	2.58	2.56
Valve discharge rate (mg/spray)	1.24	1.27	1.22	1.26	1.25	1.27

Droplet size determination (µm)	19	24	23	26	17	20
Dose uniformity (mg)	88.96	93.37	87.13	89.67	90.48	89.82
In-vitro diffusion study (%)	83.56	81.81	81.69	84.67	84.72	83.94

The stability checking suggests that the dosages form H3 was physiochemically stable with negligible remarkable alteration of the experimental designs when kept at 60±2^{0}C and 75±5 % RH conditions. There was no as such difference in the results shown in the table 7.9. Thus, it was concluded that the buccal spray of *Gymnema sylvestre* was stable.

Good health is a popular dimension of the value of life. But today prevalence of diabetes is enhancing at a warning with increasing urbanization and changing lifestyle pattern. DM is a chronic disease with complex underlying etiology. It was characterized by hyperglycemia and other metabolic abnormalities due to glucose intolerance. Apart from insulin and oral hypoglycemic agents, phytotherapy are the most alternative therapy which includes a variety of herbal medicinal plants and they are evaluated and believed to be an outstanding candidate for diabetes and have been recommended as non-toxic efficient and with less or no side effects by the world HealthOrganization. *GS* is a folk plant (F. Asclepiadaceae). Mainly leaves of *Gymnema sylvestre* have been used for the treatmentof madhu meha or "honey urine" for more than 2,000 years in India. Recently novel dosage forms have gained significant popularity in the treatment of diabetes like buccal spray, nasal spray, buccal film etc. due to its outstanding characteristics. *Gymnema sylvestre* leaves were collected, dried and powdered which were subjected to continuous and exhaustive Soxhlet apparatus using different solvents like petroleum ether, chloroform and methanol. This methanolic extract were used in the novel formulation. Preformulation study was to standardize to establish a compatibility between the GS extract and polymers by FT-IR. The study revealed that drug and polymers are satisfactorily compatible.

All the formulations showed a better impact when observed through in-vitro estimations in terms of particle size, preformulation study, ash value, solubility, in-vitro drug release and stability.

CONCLUSION

Stability study revealed that the maximum stability of buccal spray at 60 C ± 2^0 C and at 75% RH for 6 months. Clinical studies of the developed formulations were performed to optimize the promising results linked with the buccal spray that linked a correlation in between GS and polymer with very promising significance attitude for future reference.

It concluded that this formulation has better in-vitro profiles that can be further evaluated by using in-vivo or animal models to confirm its potential in human beings.

SOURCE OF FUNDING

Nil.

CONFLICT OF INTEREST

None.

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