RESEARCH ARTICLE

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Fabrication and Characterization of Edible Jelly Formulation of Stevioside: A Nutraceutical or OTC Aid for the Diabetic Patients

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Abstract: Based on the fact that stevioside, a glycoside obtained from *Stevia rebaudiana Bert* has the chief characteristic of regulating hyperglycemic episodes. The present nutraceutical research describes an innovation that stevia product containing jelly based formulations have not yet designed as hypoglycemic aids for over-the-counter (OTC) prospective. The main objectives of this study involved the development of edible jelly formulations containing stevioside which will impart glucose lowering as well as artificial sweetening characteristics, just like edible jelly brand products such as Juzt Jelly®, Jelly Belly®, Boleto®, Jolly Candy®, FrutBite® in India. Therefore, the diabetic patients will get a better hypoglycemic control, non-calorific product, will also enjoy the sweetness, patient-friendly, convenient, without specific dose and frequency and will be much cheaper than existing market products. The formulation was prepared by the heating method which comprises of stevioside, HPMC K100, HPMC K15, sodium metabisulphite, ascorbic acid, glycerine, propylene glycol, triethanolamine along with essence and colors. The organoleptic properties and physicochemical parameters (like stickiness, texture, grittiness, viscosity, drug content and pH) of the formulations were determined. Techniques like FT-IR analysis, differential scanning calorimetry analysis, X-Ray diffraction, etc were studied exhaustively to determine the characteristics of the optimized formulation (F9). *In-vitro* dissolution study was carried out in simulated gastric fluid without enzyme. The hypoglycemic potential of the optimized formulation (F9) was studied on Swiss albino rat and the results were compared with standard drug metformin. This research opened new doors for nutraceutical research that have perspectives of commercialization as OTC products in near future.

INTRODUCTION

Diabetes Mellitus Type-II (DM-II) is a chronic metabolic disorder of carbohydrate characterized by high blood sugar because the cells do not properly use insulin. [1] It has severely affected a large section of the population having a strong hereditary tendency (387 million people worldwide have diabetes at present). By the survey of World Health Organization (WHO) in 2010, more than 4 million people of age groups 20 to 79 have died due to (DM-II). WHO has also projected that diabetes death will double between by the end of 2030. [2] More than 80% of diabetes deaths occur in low and middle-income countries. [3] Despite enormous efforts in developing newer leads and novel strategies for the management of diabetes, it remained the key concern across the globe. The search for alternative or unexplored classes of substances for managing hyperglycemia attracted the attention of scientists globally.

India is one of the largest consumers of sugar in the world, owing to cultural and food habits. [4] In the country, the diabetic population of the age group of 25-45 is about 15% and is quite increasing at an alarming pace. [5] Along with the complications of DM-II, poverty remained the chief problem among the masses which impairs the regular management of hyperglycemia by pharmacological approach. Due to non-availability of the anti-diabetic drugs in rural areas, compromise in purchasing power, greediness towards sweet confectionaries and precipitation of secondary symptoms, cumulatively leads to decreased quality of life among DM-II patients. In most of cases, an artificial sweetening agent is incorporated. However, in the majority of the cases, the safety of the chemical sweetener such as aspartame, cyclamate, saccharin, sucralose etc. is a big challenge. [6]

Natural products are the most promising therapeutic candidates in management or treatment of various ailments. [7-9] The anti-hyperglycemic effect of these formulation are for their ability to restore the function of pancreatic tissues by increasing insulin output or inhibit the intestinal absorption of glucose or to the facilitation of metabolites in insulin-dependent processes. [10] Stevioside, a glycoside obtained from *Stevia rebaudiana Bert* has the chief characteristic of regulating hyperglycemic episodes. Natural glycoside like stevia does induce hypoglycemic response when ingested, making them attractive natural zero calories or low calorie sweeteners to diabetic and miscellaneous carbohydrate-controlled diets. [11] Many therapeutic agents or artificial sweeteners have the tendency to absorb in oral, buccal cavity and the acidic media. [12] Medicated jellies are such examples that would permit more rapid therapeutic action by the patient of any age. Therefore, the identification of natural products based jelly formulation to manage hyperglycemic episodes represents an attractive strategy to develop potential anti-diabetic formulations.

Even though several nutraceutical like SteviaLife® and nanomedicine formulations have been developed by several companies over the years which do have both commercial value and applications as pharmaceutical aids. [13-15] Based on the fact that stevia product containing jelly based formulation have not yet designed as hypoglycemic aids for over-the-counter (OTC) prospective. The main objective of this study was to develop a jelly based product containing stevioside which will impart glucose lowering as well as artificial sweetening characteristics, thereby will act as a drug system. The work is quite similar to the development of edible jelly brands like Juzt Jelly®, Jelly Belly®, Boleto®, Jolly Candy®, FrutBite®, etc (Figure 1). It was achieved by selection and characterization of drug candidate (stevioside) and their formulation components for systematic release of drug from jelly. It is convenient to administer anywhere, anytime and does not require water.

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Figure 1: Marketed edible jelly products in Indian market

Table 1: Composition of Formulations

Ingredient	Quantity %									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Stevioside (in mg)	500	500	500	500	500	500	500	500	500	500
HPMC K100	7	8.50	10	7	8.5	10	7	8.5	10	8.5
HPMC K15	3	3	3	4.5	4.5	4.5	6	6	6	4.3
Ascorbic acid	5	5	5	5	5	5	5	5	5	5
Sodium metabisulphite	2	2	2	2	2	2	2	2	2	2
Propylene glycol	9	10	10	10	9	7	8	9	10	10
Glycerine	7	7	8	9	10	10	10	10	10	11
Triethanolamine	2	2	4	4	4	4	3	3	3	3
Colour	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Essence	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Water (q.s.)	100	100	100	100	100	100	100	100	100	100

The treatment can, if required, be terminated at any time. In addition, the drugs that are released from jelly will either be dissolved or suspended in the saliva and thus will be present in a readily bioavailable form. Therefore, the diabetic patients will get a better hypoglycemic control, non-calorific product, will also enjoy the sweetness of medicine, patient-friendly, convenient, without specific dose and frequency and will be much cheaper than existing market products.

MATERIALS AND METHODS

Drugs and Chemicals

Hydroxypropyl methyl cellulose (HPMC) of grades K100 and K15 were obtained as a generous gift from Colorcon Asia Pvt. Ltd., Mumbai, India. Ascorbic Acid, Sodium Metabisulphite and Glycerine were purchased from SD Fine Chem, Mumbai, India. Triethanolamine and Propylene Glycol was procured from Himedia Ltd., Mumbai, India. Carbopol 940 was procured from Kerry Ingredients India Pvt. Ltd., Mumbai, India. Colors and Essence were purchased from local confectionary shop. All other ingredients were of analytical grade and procured from registered vendors. Alloxan was purchased from Sigma-Aldrich Ltd., Germany. Double distilled water was used for the experiment.

Instrumentation

The Glucose strips (One Touch™) were purchased from a local pharmacy. The UV-spectrophotometric analysis was carried out using double-beam Shimadzu® Ultraviolet-Visible Spectrophotometer model UV-1800. The weighing was performed by Wensar® electronic balance model P6B100. Sonicator of model Transonic Digital S was used for the sonication. The pH of solutions was measured using Contech® digital pH meter. FTIR spectrophotometer (Thermo Nicolet, Avatar 370), X-ray diffractometer (Bruker AXS D8 Advance), differential scanning calorimetry system (Mettler Toledo DSC 822e), stability chamber (Remi, India), Brookfield DV-II+Pro viscometer and dissolution test apparatus USP 33 (Type II) apparatus was used for analytical investigations by Sophisticated Test and Instrumentation Centre (STIC), Kochi, Kerala, India.

Animals

Swiss albino rat aged 4-5 weeks, average weight 180-250 g were used for the anti-diabetic study after prior approval from Department Ethical Committee and CPCSEA (1389/a/10/CPCSEA). Animals were housed in clean polypropylene cages having 6 mice per cage under temperature controlled rooms (25–26°C, humidity 50–55%, 12 hr light and dark) with proper hygienic conditions. Free access to water and standard rodent pellets was allowed.

Formulation

Different formulations of composition (Table 1) for jelly preparations were planned. The formulation contained stevioside, HPMC K100, HPMC K15, sodium metabisulphite, ascorbic acid, glycerine, propylene glycol, triethanolamine along with essence and colors. Stevioside jelly was prepared by the heating method where firstly, the liquid base was prepared in a beaker dissolving the required amount of propylene glycol, glycerine, tri-ethanolamine, essence and color. The color was added in this prepared solution and starring few min. The prepared solution was boiled. Sufficient quantity of stevioside, HPMC K100, HPMC K15, ascorbic acid and sodium metabisulphite were weighed accurately, mixed and triturated in a mortar with pestle. The powder was added in prepared solution with continues starring for few min. Finally, the prepared solution of jelly was transferred in moulds and then allows it for cooling and setting. Figure 2 represents the three

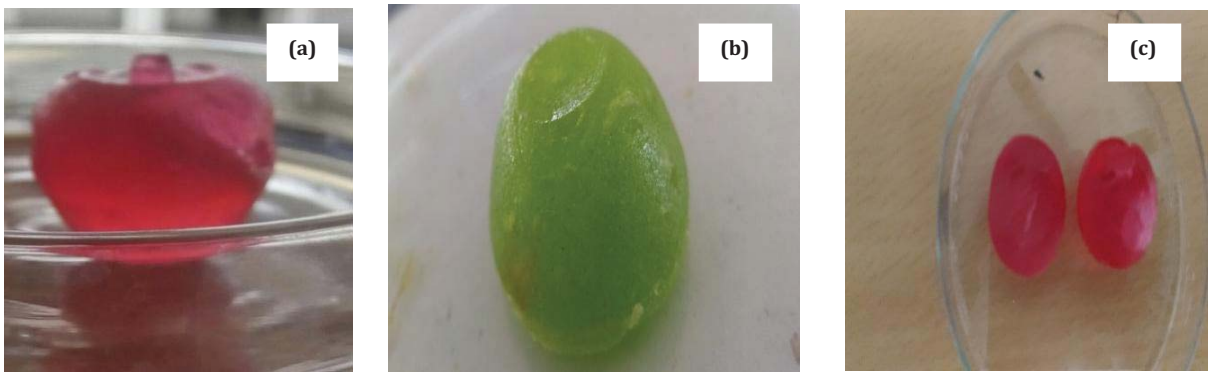

Figure 2: Stevioside jelly of optimized formulation (F9) in three different variants; (a) strawberry shape, (b) condensed dome shape, and (c) round shape

variants of the stevioside jelly product; (a) strawberry shape (b) condensed dome shape (c) round shape.

Characterization of Jelly Formulations

The prepared stevioside jelly formulations were evaluated as per the standard procedures reported in the literature. [16-18]

1. Physical Appearance

The fabricated stevioside jelly formulations were examined for their physical appearance in terms of clarity, texture and consistency, which are the prime characteristics of a nutraceutical formulation.

2. Stickiness and Grittiness

The texture of the stevioside jelly in term of stickiness and grittiness had been evaluated by visual inspection of the product after mildly rubbing the jelly sample between two fingers.

3. Determination of pH

The pH of the prepared jelly formulations was checked by using a calibrated digital pH meter at 25±1°C. For the purpose, 1g of the weighed formulation was dispersed in 100 ml of distilled water and the pH was noted.

4. Determination of Viscosity

The viscosity of the jelly formulations was carried out by using Brookfield viscometer using a non-Newtonian spindle no. 7 for the fixed time of 2 min at 50 rpm.

5. Drug Content (%)

Accurately weighed jelly formulations were crushed in a mortar with pestle. A quantity equivalent to 500 mg stevioside was accurately weighed and transferred into 100 ml volumetric flask containing 50 ml volume of 0.1 N HCl. The solution was sonicated for 15 min to dissolve the content. The volume was made up to 100 ml of the above solution and filtered through Whatman filter paper. The drug content was estimated by using UV-Visible spectrophotometer at 331 nm.

6. Infrared Spectral Analysis

The FT-IR analysis of stevioside (pure drug), polymers (HPMC K100, HPMC K15 and Carbopol 960) and selected formulations of stevioside were performed using spectrometer in the range of 4000–400 cm^{-1} by potassium bromide dispersion technique. [19]

7. Differential Scanning Calorimetry Analysis

Differential scanning calorimetry (DSC) thermogram analysis was used to determine the physical state of stevioside and optimized formulation (F9). The samples were heated in a platinum crucible in the range of 30-300°C at a scanning rate of 10°C/min in an atmosphere of nitrogen. Alpha alumina powder was used as the reference material. Indium was used as the standard material for the temperature calibrations.

8. X-Ray Diffraction Analysis

X-ray diffractometer was used to reveal the physical state characteristics of stevioside and optimized formulation (F9). The diffraction was measured after compactly packed in the cavity of an aluminium sample holder, using monochromatic CuK-radiation at a voltage of 40 KV with scanning speed of 4/min at room temperature.

9. *In-Vitro* Dissolution Study

The dissolution study was designed for 6 hr with an intension that blood glucose level generally gets fluctuated every 6 hr, due to breakfast at 7 to 8 pm, followed by a six-hour gap for lunch 1 pm to 2 pm, at last, the next six hour for dinner. [20] Therefore, the ideal jelly formulation must release the maximum drug within 6 hr of dissolution in acidic media. The *in-vitro* dissolution study of stevioside formulations were performed using dissolution test apparatus USP 33 (Type II) apparatus in 900 ml of dissolution medium in simulated gastric fluid without enzyme, pH 1.2 maintained at 37±0.5°C at a speed of 50 rpm. The formulations equivalent containing 500 mg of stevioside were separately placed in dissolution medium after cutting it into several tiny pieces of specific dimensions. From each vessel at a specific time interval, 1 ml of sample was withdrawn, filtered through Whatman filter paper (No. 41), diluted and analyzed spectrophotometrically at 331 nm. An equal volume of fresh medium which was prewarmed at 37±0.5°C, replaced in the dissolution medium after each sampling to maintain the constant volume throughout the test. The release studies were conducted in triplicate. The data were studied using PCP-Disso v2.08 software. [21]

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Table 2: Characterization Results of the Formulations

Batches	Clarity	Texture	Consistency	Stickiness	Grittiness	pH	Viscosity (cps)	% Drug Content
F1	Turbid form	Smooth	Fluid like	Sticky	More gritty	4.24 ±0.092	4800 ±692	87.46 ± 1.15
F2	Turbid form	Smooth	Fluid like	Sticky	Gritty	4.30 ±0.020	5333 ±611	88.46 ± 1.15
F3	Turbid form	Smooth	Thin	Sticky	Gritty	4.64 ±0.031	6133 ±230	89.46 ± 0.74
F4	Turbid form	Smooth	Thin	Slightly sticky	Slightly gritty	4.96 ±0.078	6400 ±400	90.21 ± 0.75
F5	Turbid form	Smooth	Thin	Slightly sticky	Slightly gritty	4.97 ±0.115	6933 ±230	90.96 ± 0.76
F6	Turbid form	Smooth	Thin	Slightly sticky	Slightly gritty	5.00 ±0.060	7200 ±400	92.22 ± 0.43
F7	Turbid form	Smooth	Thin	Slightly sticky	Slightly gritty	5.80 ±0.025	8266 ±832	93.24 ± 0.75
F8	Turbid form	Smooth	Thick	Non-sticky	Less gritty	5.92 ±0.066	8533 ±230	94.73 ± 0.75
F9	Turbid form	Smooth	Thick	Non-sticky	Less gritty	6.01 ± 0.020	9600 ±400	95.73 ± 0.87
F10	Turbid form	Smooth	Very thick	Non-sticky	Less gritty	5.91 ±0.081	8000 ±400	93.74 ± 0.85

10. Accelerated Stability Studies

The optimized formulation (F9) was studied for stability and kept under the accelerated conditions of temperature and moisture (40°C±2°C and 75%±5% RH) for the period of 90 days. The pharmaceutical optimized jelly formulation was recorded in terms of all attributes at day 0, day 45 and day 90. Aluminum foil was used to cover the jelly and kept in the plastic bottle for the duration of 3 months. The jelly was retested for the organoleptic properties, drug content and *in-vitro* drug release studies.

Antidiabetic Activity

All formulations were subjected to anti-diabetic study in alloxan-treated rats as per the protocol. [22] The hypoglycemic activity produced by the formulation F9 was evaluated by determining the blood glucose level. The animals were divided into three different groups; control, test and standard with six animals in each group and were placed in separated metabolic cages. Except for control group, the animals of remaining two groups fasted for 24 hr. Diabetes was then induced by alloxan monohydrate (50 mg/kg i.p.). Diabetes was induced in 12 hr fasted rats by intraperitoneal injection of 50 mg/kg body weight of alloxan. The rats with a blood glucose level above 350 mg/dl were selected for the experiment. After 48 hr of diabetes induction, the drug formulation was administered. Group I served as control which received normal saline solution through the oral route. Group II test served as the test sample (optimized formulation F9). Group III received the standard drug, metformin (50 mg/kg). Blood samples were withdrawn at 0 hr, 1 hr, 2 hr, 3 hr and 5 hr by tail tipping method. The blood samples were analyzed for the blood glucose level, using glucometer where a drop of blood obtained by tipping tail was placed on inserted gluco strips on the glucometer. Blood glucose level was read form digital display of the glucometer with its customized test strips. The experiment was conducted in a triplicate manner and the mean±SD was expressed.

RESULTS AND DISCUSSION

Among the formulations, batch F9 had the highest drug content and displayed % cumulative drug release in dissolution studies. The formulation also demonstrated optimized viscosity and thus selected as the optimized formulation. From the above study, it was concluded that the stable stevioside loaded jelly can be formulated by selecting appropriate ratios of different concentration of polymer.

Characterization of Jelly Formulations

1. Organoleptic Properties

All fabricated batches had a smooth texture and had a continuous homogenous constitution. Although, the formulations appeared turbid in general appearance, quite contrasting features than that of marketed products which are always translucent or transparent. The formulation F1 to F3 showed high stickiness, formulation F4 to F7 displayed slightly stickiness characteristics, while formulation F8 to F10 exhibited no such stickiness. It can be concluded that as the concentration of HPMC K100M was increased from 7% to 10% and the concentration of HPMC K15M was increased from 3% to 6%, the stickiness, grittiness gets decreased for jelly. From the evaluation study, it was observed that at 10% concentration of HPMC K100M and 6% HPMC K15M showed acceptable jelly formulation. Table 2 represents the observed characteristic features of jelly formulations.

2. Drug Content and pH

The drug content in formulations was observed in the range of 87.46–95.73%. The highest drug content of 95.73% was determined in formulation F9 in which the

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Table 3: *In-Vitro* Dissolution Study

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
60	25.58 ±0.65	23.53 ±0.63	26.61 ±0.80	24.63 ±0.57	28.61 ±0.63	25.58 ±0.73	29.50 ±0.47	32.94 ±2.46	43.55 ±0.62	28.49 ±0.60
120	29.39 ±0.52	34.53 ±0.42	39.62 ±0.59	31.71 ±0.50	35.33 ±0.52	39.66 ±0.45	35.41 ±0.49	42.34 ±0.61	59.66 ±0.61	34.57 ±0.58
180	39.55 ±0.35	41.11 ±0.90	49.34 ±0.52	46.63 ±0.49	46.50 ±0.47	45.70 ±0.59	40.63 ±0.54	61.48 ±0.51	68.67 ±0.63	47.35 ±0.58
240	44.77 ±0.76	44.81 ±0.46	52.67 ±0.59	53.64 ±0.52	53.58 ±0.52	50.77 ±0.66	49.47 ±0.46	67.69 ±0.62	76.92 ±0.57	50.74 ±0.80
300	46.72 ±0.43	52.65 ±0.48	60.69 ±0.67	63.91 ±0.73	67.75 ±0.48	65.60 ±0.49	60.68 ±0.61	74.53 ±0.63	85.99 ±0.65	57.53 ±0.78
360	49.54 ±0.69	58.91 ±0.50	64.19 ±0.72	69.67 ±0.51	74.80 ±0.65	78.86 ±0.74	82.66 ±0.64	86.12 ±0.52	92.81 ±0.54	67.94 ±0.37

Table 4: Stability Study of Optimized Formulation (F9)

Parameter	Stability Study		
	0 Day	45 Day	90 Day
	Physical Appearance		
Clarity	Turbid form	Turbid form	Turbid form
Texture	Smooth	Smooth	Smooth
Consistency	Thick	Thick	Thick
Stickiness	Non-sticky	Non-sticky	Non-sticky
Grittiness	Less gritty	Less gritty	Less gritty
Drug Content (%)	95.73±0.87	95.58±0.56	95.54±0.53
Time Interval	**Cumulative Drug Release (%)**		
(min)	**0 Day**	**45 Day**	**90 Day**
60	43.55±0.62	43.15±0.61	42.87±0.65
120	59.66±0.61	59.36±0.73	58.94±0.61
180	68.67±0.63	68.29±0.67	67.97±0.57
240	76.92±0.57	76.41±0.65	76.09±0.68
300	85.99±0.65	85.47±0.65	85.25±0.63
360	92.81±0.54	92.48±0.63	92.14±0.61

Table 5: Hypoglycemic Data of Formulations

Group No.	Group Name	Blood Glucose Level at hr in mg/dl				
		0 hr	1 hr	2 hr	3 hr	5 hr
I	Control group (Saline)	351.6±0.57	349.7±0.64	348.3±0.57	347.1±0.72	344.8±0.32
II	Formulation (F9) (500 mg)	353.4±0.57	339.3±0.53	328.3±0.53	299.4±0.51	285.7±0.52
III	Metformin (50 mg/kg)	361.8±0.57	339.5±0.67	306.9±0.87	271.4±0.58	212.7±0.25

concentration of polymeric content was highest (HPMC K15M was 6% and HPMC K100M was 10%) revealing possible drug loading in the polymeric matrix. The pH of formulations was measured to be in the range of 4.24 to 6.01. Formulation F9, the optimized formulation, demonstrated pH of 6.01 which is nearer to neutrality. This reflects its acceptability among the patients due to pH near to neutrality, an essential criterion for formulation development. Table 2 describes the experimental characteristics of stevioside formulations.

3. Viscosity

The drug content was observed in the range of 4800–9600 cps. It can be concluded that as the concentration of HPMC K100M was increased from 7% to 10% and the concentration of HPMC K15M was increased from 3% to 6%, the viscosity increased simultaneously. As compared to the formulations having the lowest polymer concentration, the optimized formulation F9 exhibited twice the viscosity which can be correlated with the stiff consistency and drug loading properties of the formulation. The combination of glycerine, triethanolamine and propylene glycol played a crucial role in maintaining the consistency of the formulations. It has been observed that as the concentration of triethanolamine gets increased from 2 to 4%, the consistency gets enhanced gradually. An equal concentration (10%) of glycerine and propylene glycol provided the most optimum viscosity essential enough to develop the product. Table 2 highlights the viscosity of the formulations.

4. Infrared Spectral Analysis

The FTIR spectrum of stevioside and formulations of both the types have concluded that there were no such drug-polymer interactions (Figure 3). The peaks appeared in case of pure drug (Figure 3a) remained same for the optimized formulation (Figure 3b). The advanced sophisticated analytical techniques have also confirmed (in

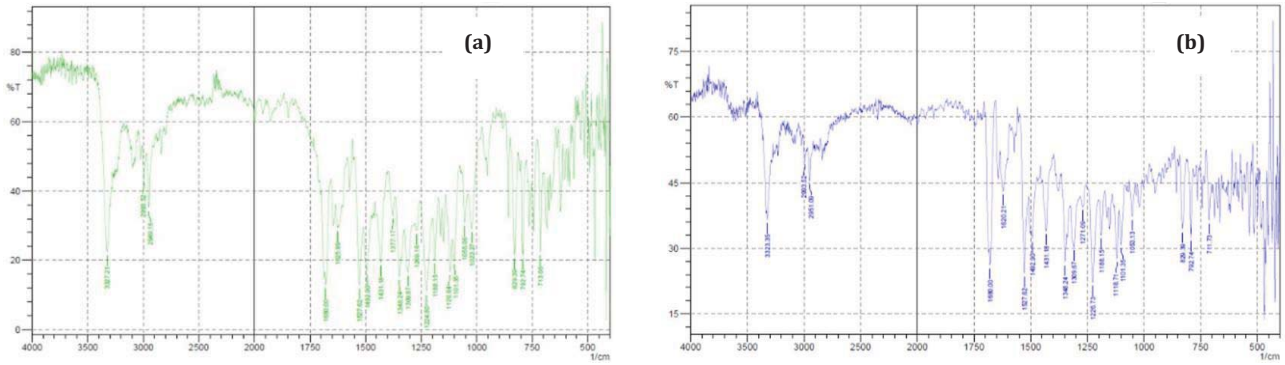

Figure 3: FT-IR spectra of (a) Pure drug (b) Optimized formulation (F9)

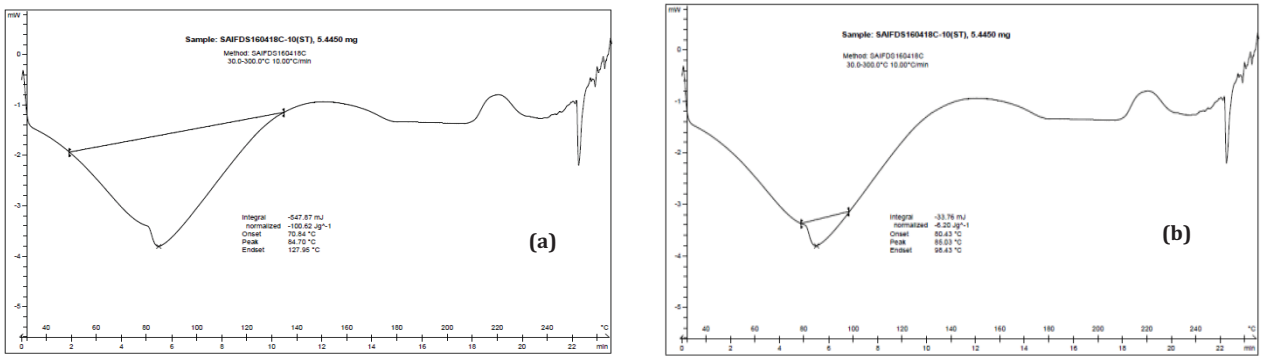

Figure 4: DSC thermograms of (a) Pure drug (b) Optimized formulation (F9)

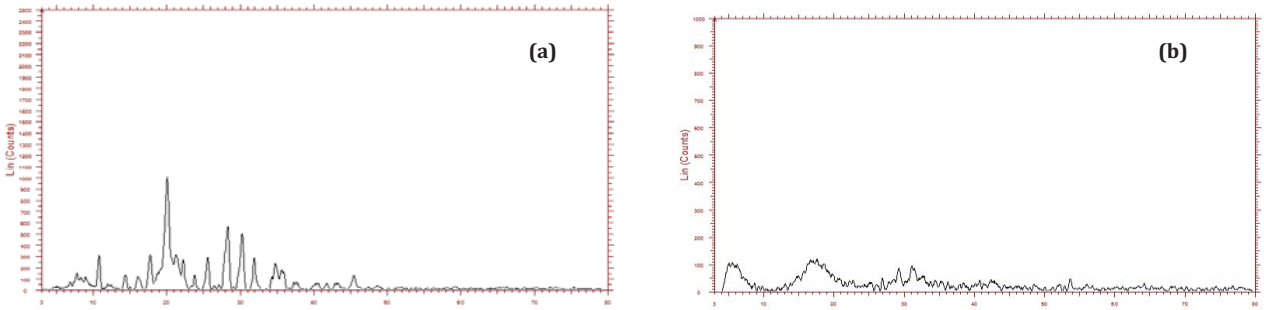

Figure 5: XRD crystallography of (a) Pure drug (b) Optimized formulation (F9)

later sections) that this polymer did not interact with the drug.

5. Differential Scanning Calorimetry Analysis

The DSC thermograms of the pure drug (stevioside) and optimized formulation (F9) described marked changes (Figure 4). Stevioside demonstrated a pointed endothermic peak at 84.70°C over the entire scanning range of 30°C-300°C, representing the melting point of drug (Figure 4a). The data hereby confirmed the crystalline nature of the drug. The optimized formulation showed a very broad endothermic peak (Figure 4b) in contrast to the pure drug, proposing hasty renovation into the amorphous form. The drug particles linger in the highly dissolved state in the formulation representing melting behavior of the drug and inhibition of crystallization. [23]

6. Powder X-Ray Diffraction Analysis

Figure 5 depicted the P-XRD study of drug and the optimized formulation (F9). In the case of the pure drug, numerous strong crystalline peaks were observed stating the crystallinity (Figure 5a). The P-XRD pattern of F9 (Figure 5b) illustrated the loss of crystallinity due to no such appearance of characteristic peaks supports complete dispersion of the drug in the polymeric matrix. In presence of HPMC, the drug successfully converted into an amorphous form which compels quick dissolution of stevioside. [23]

7. *In-Vitro* Dissolution Studies

The *in-vitro* drug release profiles of fabricated formulations (F1 to F10) were studied (Table 3). All formulations demonstrated different levels of drug release, ranging from 45.94% - 92.81%. It has been observed that as the polymeric content gets increased, the drug release from formulation also enhances significantly. The primary reason may be the very high aqueous solubility of the drug which promotes rapid dissolution in the media. The second reason may be based on the fact that at low concentration of polymers, monomolecular micelles are formed which endorse dissolution of the drug in media. The formulations F1 and F2 containing 3% of polymer exhibited lowest drug

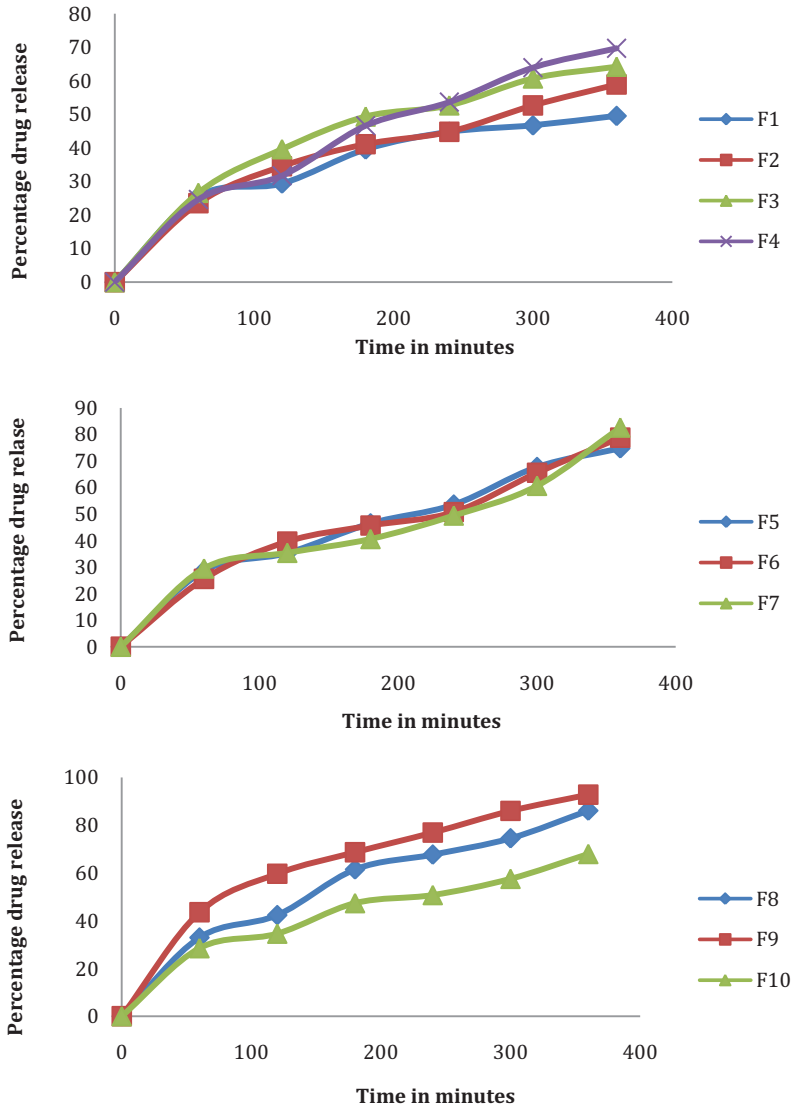

Figure 6: Dissolution profiles of fabricated formulations

release of less than 60% in 6 hr schedule. This is based on the fact that as the concentration increases, the micelles aggregate to form multi-molecular micelles which solubilize the drug to still high extent. The formulations F7 and F8, containing 6% HPMC K15 demonstrated drug release of more than 85% in 6th hr. Based on the 6 hr design, only the formulation F9 released 92.81% drug in the final hr among all the batches (Figure 6), hence, was considered optimized. Formulation F9 comprised of utmost polymeric composition, viz. 10% HPMC K100 and 6% HPMC K15, which eventually enhanced the dissolution rate by presenting additionally obtainable room for adjacent hydrophilic drug particle resulted in speedy hydration of stevioside and therefore result in superior wettability and augmentation in the dissolution. In another way, when the drug and the polymer get in contact with aqueous media, the polymers get hydrated into its solution state, which as a result endorse the release of the drug into the media upholding the solubilization of the drug. Additionally, reduction of particle size, transformation of the crystalline nature of pure drug into the amorphous form and enhanced exposed surface area assist elevated drug release rates. [24]

In the formulation F9, the maximum drug content, high water solubility and improved hydration in the media attributed to highest drug release.

8. Accelerated Stability Studies

The study presented no substantial transformation in the organoleptic characteristics, drug content and *in-vitro* drug release of the optimized formulation (F9). No noteworthy variation in grittiness, texture, stickiness, appearance, consistency and clarity was observed after both 45 days and 90 days. Only, a miniature difference in drug content (0.19%) was noticed after 3 months, which supported that the prepared jelly formulation was found to be stable for the given duration of time. Table 4 portrays the outcomes and dissolution profile of optimized formulation at two different intervals.

Antidiabetic Activity

From the animal experiment, it was observed that the treatment with optimized stevioside jelly formulation F9 has satisfactorily reduced the elevated blood glucose level in the diabetic animals. The results are not very

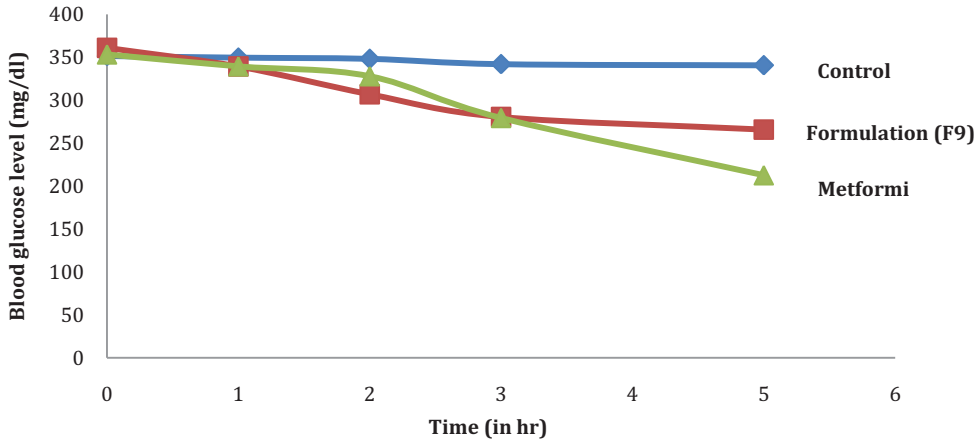

Figure 7: Hypoglycemic profile of stevioside formulation (F9) and its comparison with standard drug metformin

comparable with that obtained after the treatment with metformin (50 mg/kg), the standard and the most prescribed drug for the management of DM-II. At the first hour, a nearly equal hypoglycemic effect was demonstrated by both optimized formulation and the standard drug (339 mg/dl). After the lapse of 2 hr, a marked difference in hypoglycemic activity was observed (Table 5). Metformin reduced blood glucose level twice (16%) as compared to stevioside (8%). The hour 3rd presented that F9 exhibited antihyperglycemic activity by 16%, twice as compared to the second hour, but lesser in contrast to standard drug. After 5 hr of administration of formulation F9, the blood glucose level was found to be 285 mg/dl (i.e. 27% reduction in random glucose level), which was only fair to exhibit hypoglycemic activity. In an overview, with contrast to the optimized formulation, the standard drug metformin showed brilliant 42% reduction in blood glucose levels, i.e. from 361.8 mg/dl to 212.7 mg/dl (Figure 7). In actual practice, the formulation has nutraceutical properties only which finds prospective in managing hyperglycemic episodes in random state and is not recommend prescribing in the management of chronic diabetes mellitus, which are dose and frequency bounded.

CONCLUSION

The current study highlighted an approach in developing stevioside based jelly formulation in form of a candy to develop a patient-friendly formulation that will provide a chance to patients in managing hyperglycemic episodes. The study highlighted that as the concentration of polymer gets increased, the stickiness, grittiness gets decreased. But, the composition did not produce a clear, transparent and elegant product which is the prime feature of commercialized product. The characterization of optimized formulations revealed that the crystalline drug gets converted into amorphous form while formulating it into a jelly product. However, in this study, it was observed that the optimized formulation did not show a very promising hypoglycemic activity (27%) as compared to standard drug metformin (42%). The formulation was found to be very stable over the duration of 90 days, with no significant difference in drug content, drug release and organoleptic properties. This product will have the perspective as over-the-counter (OTC) aid which has no real chronic anti-diabetic therapeutic effect but may find application as pharmaceutical aid, which should be justified by medical personnel to the patient. This study opened new doors for the therapeutic perspective of natural products in coming future.

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