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Development of Palatable Formulation of Antidiabetic Drug

R. A. Mahalle[1], M. U. Bhoir[1], P. R. Bhosale[1], P. V. Chaudhari[1], V. N. Chauhan[1], N. S. Chogale[1], A. Jain[1]
Shri. D.D. Vispute College of Pharmacy and Research Center Vichumbe, Panvel-410206.

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***Corresponding Author Email:** radhikamahalle15@gmail.com

Abstract

Aim: The objective is to develop palatable formulation by masking bitter taste of anti-diabetic drug. **Method:** In the current report advancement of natural chocolate by utilizing *Withania coagulans* was done. By utilizing fruits of *Withania coagulans*, lab made chocolates was ready and assessed for outward presentation, aspect, hardness, blooming test. Mobile phase for thin layer chromatography was developed using ethanol: water (5:5). **Result:** chocolate formulation provides a palatable means for delivering medicaments through oral delivery. The formulation provides sweetening property as compare to others, pH & stability profile to be satisfactory. **Conclusion:** From this study we can conclude that withanolides may be present in the extract which may be confirmed if future by isolation of components present in the extract.

Keywords
Withania coagulans, chocolate, Anti-diabetic, palatable

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INTRODUCTION OF DIABETES:

Diabetes, also known as diabetes mellitus, is a group of common endocrine diseases characterized by sustained high blood sugar levels. Diabetes is due to either the pancreas not producing enough insulin, or the cells of the body not responding properly to the insulin produced. Diabetes, if left untreated, leads to many health complications. Untreated or poorly treated diabetes accounts for approximately 1.5 million deaths per year. [1]

There is no widely-accepted cure for most cases of diabetes. The most common treatment for type 1 diabetes is insulin replacement therapy (insulin injections). Anti-diabetic medications such as metformin and semaglutide, as well as lifestyle modifications, can be used to prevent or respond to type II diabetes. Gestational diabetes normally resolves shortly after delivery.

As of 2019, an estimated 463 million people had diabetes worldwide accounting for 8.8% of the adult population. TypeII diabetes makes up about 90% of all diabetes cases. The prevalence of the disease continues to increase, most dramatically in low- and middle-income nations. Rates are similar in women and men, with diabetes being the 7th-leading cause of death globally. The global expenditure on diabetes-related healthcare is an estimated USD760 billion a year.

Signs and Symptoms

The classic symptoms of untreated diabetes are unintended weight loss, polyuria (increased urination), polydipsia (increased thirst), and polyphagia (increased hunger). Symptoms may develop rapidly (weeks or months) in type I diabetes, while they usually develop much more slowly and may be subtle or absent in type II diabetes.

Several other signs and symptoms can mark the onset of diabetes although they are not specific to the disease. In addition to the known symptoms listed above, they include blurred vision, headache, fatigue, slow healing of cuts, and itchy skin. Prolonged high blood glucose can cause glucose absorption in the lens of the eye, which leads to changes in its shape, resulting in vision changes. Long-term vision loss can also be caused by diabetic retinopathy. A number of skin rashes that can occur in diabetes are collectively known as diabetic dermadromes

Chocolate formulation as drug delivery system

Chocolate is highly sophisticated and much infinitely adaptable food that can be combined to create completely different taste and consistency sensations. Chocolate is an anhydrous medium resistant to microbial growth and hydrolysis for water-sensitive active agents. Chocolate abundantly contains compounds such as saturated fat, polyphenols, sterols, di and triterpenes, aliphatic alcohols, methylxanthines flavones, antioxidants Cocoa is the main ingredient of chocolate and it is loaded Chocolate in polyphenols.

Chocolate containing the drug in suitable quantity is known as medicated chocolate.

[36] There are four types of taste modalities, salty, sour, bitter, sweet through the combination of these elements we can detect the “flavours” Children’s tastes sensation is much differed than adult infants and more over children prefer sweet-tasting substance. Chocolate have been shown to help our body produce chemical known as “Serotonin”. It makes feel relaxed.

Further chocolate is also having some advantages like quick onset of action, reduction in the drug dose of manufacture and scale, increases drug loading capacity. Some drugs are bitter in taste due to which oral administration of bitter drugs leads to patient incompliance especially in children. To overcome this limitation, it is advisable to formulate dosage form, which is most acceptable for paediatric patients. Chocolate is one of the most palatable and favourite in children as well as adults and geriatric, so we have developed chocolate drug delivery system. [37]

Most of the activities of *Withania coagulans* is due to presence of active constituent, ‘withanolides’ which are a group of steroidal lactones with an ergostane skeleton. Withanolides which are named after the name of the source plant *Withania* species, are generally defined as C-28 steroidal lactones. Modifications either of the carboxylic skeleton or of the side chains result in many novel structural variants of withanolides or ergostane-type steroids. As withanolides have been reported to possess anti-tumorous, anti-angiogenic, chemo preventive and inflammatory activities thus may represent useful leads for development of potential anti-cancer drug. In addition, withacoagin, coagulan, withasomidienone, withaferin, 3-β-hydroxy-2, 3-dihydro-withanolide E, free amino acids, essential oil etc. have been isolated from the berries as well as aerial parts of the plant. [28]

Phytochemical Screening of *Withania coagulans* Dunal

The plant extracts were subjected to preliminary phytochemical screening for the detection of various plant constituents present. The term qualitative analysis refers to the establishing and proving the identity of a substance. The active ingredients, after isolation, can be incorporated into the modern medicine system for the development of newer formulation for therapeutic ailments. Systematic investigation of the plant material for its phytochemical behaviour involves four different stages. i. Procurement of raw material and quality control. ii. Extraction, isolation, purification and characterization of the constituents of interest. iii. Investigation of biosynthetic pathways of the particular compound. Quantitative evaluation.

Qualitative Phytochemical Analysis:

The 50% ethanol extracts of root of *Withania coagulans* were subjected to the following chemical tests separately for the identification of various active constituents. [24]

MATERIAL AND METHOD:

Excipients

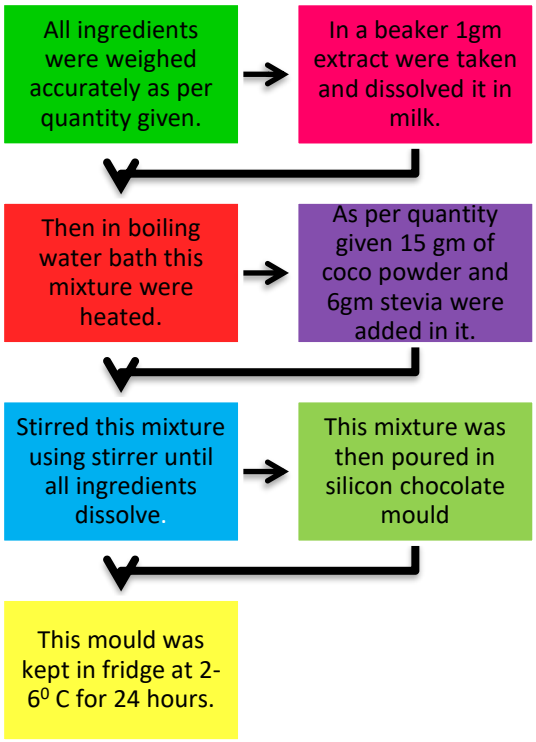
1. Stevia: - Stevia is a sugar substitute made from the leaves of the stevia plant. It's about 100 to 300 times sweeter than table sugar, but it has no carbohydrates, calories, or artificial ingredients. Not everyone likes the way it tastes. Some people find it bitter, but others think stevia tastes like menthol.

2. Coco Powder: -Cocoa powder, an unsweetened chocolate product, adds deep chocolate flavour to desserts and beverages. Cocoa powder occurs when the fat, called cocoa butter, gets removed from the cacao beans during processing. The leftover dried solids get ground into the product sold as cocoa powder. [43]

3. Cocoa Butter: -Cocoa butter, also called Theobroma oil, is a pale-yellow, edible fat extracted from the cocoa bean. It is used to make chocolate, as well as some ointments, toiletries, and pharmaceuticals. Cocoa butter has a cocoa flavour and aroma. Its melting point is slightly below human body temperature. [44]

4. Milk: -The solvent is the substance used to dissolve the solute and is more in quantity in the solution than

the solute. The solution is defined as a homogeneous mixture of two substances that do not react with each other. In chocolate, the hot water or milk acts as the solvent to dissolve the cocoa powder, the solute.



Procedure for formulation of chocolate

Evaluation of formulation:

Evaluation of chocolate base: -

Taste, texture and mouth feel characteristics assessment-

Taste, texture and mouth feel characteristics of chocolate were evaluated by taking panel of 10 human volunteers.

B) Evaluation of medicated chocolates:

a) Physical appearance-

Formulations were checked for their colour, odour, taste and melting time at room temperature

C) Blooming test

a) Fat bloom-

At the point when the slight layer of fat precious stones structure on the outer layer of chocolate plan. This will make the chocolate lose its sparkle and a delicate white layer will show up, giving the completed article an unappetizing look. Fat blossom is brought about by the recrystallization of fat or potentially a movement of a filling fat to the chocolate layer. Capacity at a consistent temperature will defer the presence of fat sprout.

b) Sugar bloom-

This is rough and irregular layer on top of chocolate formulation. This is caused by condensation (when chocolate is taken out of the refrigerator). This moisture will dissolve the sugar in the chocolate. When the water evaporates, sugar recrystallizes into rough, irregular crystals on surface. This results into unpleasant look.

D) Physical observation

1) Diameter:

The diameter was calculated using digital vernier calliper

Diameter = 2.7cm

1) Height (Thickness)

The height was calculated using digital vernier calliper

Height = 1.53cm

E) Stability:

Stability study of optimized formulation was done for 3 weeks at 2-6^0 C and the data was recorded.

G) Hardness:

Hardness in chocolate is directly related to the sensory perception that a consumer may have at the moment he/she tastes the product. High values of fracture resistance in chocolates are desirable, as they indicate good brightness, resistance to damage due to changes in temperature, physical changes, suitable mouth feel, and melting rate behaviour.

Hardness of chocolate was measured by Monsanto Hardness Tester.

RESULTS AND DISCUSSIONS:

Authentication certificate:

specimen#:rm p 012226850; Dated:25.12.2022.

Preformulation Study of *Withania coagulans*

Organoleptic study:

Appearance: Yellow-brown powder

Determination of solubility:

Withania coagulans was soluble in water and ethanol.

Determination of ash value:

i) Total Ash value: = 15.2 %

ii) Acid Insoluble Ash value: = 12.8 %

iii) Water Soluble Ash value: = 25.7 %

Percentage yield of extract:

10 gm of powdered drug gives 1.89gm of extract

%Yield = 100*1.89/10

= 18.9%

5.3. TLC:

Thin layer chromatography was carried out by doing randomisation in the mobile phase and a new mobile phase was developed the containing ethanol and water in equal concentration i.e. (5:5) shows the spots on the TLC plate concluding that the withanolides may be present in the extract as withanolides are soluble in ethanol as well as water. By performing TLC, we can conclude that if the isolation of the extract is is done withanolides may be present and can be isolated from the extract. This can be used for further study on withanolides and *Withania coagulans* extract.

Distance travelled by solute = 4.5cm

Distance travelled by solvent = 5.0cm

Rf value = 0.9

Evaluation of Medicated Chocolate

Hardness:

Hardness in chocolate is directly related to the sensory perception that a consumer may have at the moment he/she tastes the product. High values of fracture resistance in chocolates are desirable, as they indicate good brightness, resistance to damage due to changes in temperature, physical changes, suitable mouth feel, and melting rate behaviour.

Dimensions:

Dimensions like diameter and height was measured and recorded using instrument.

Height = 1.53cm

Diameter = 2.7cm

Compatibility:

From the IR of Extract and Formulation, we observe that both are compatible. The results require further investigation

1) Causes of Diabetese

Feature	Type 1 diabetes	Type 2 diabetes
Onset	Sudden	Gradual
Age at onset	Mostly in children	Mostly in adults
Body size	Thin or normal	Often obese
Ketoacidosis	Common	Rare
Autoantibodies	Usually present	Absent
Endogenous insulin	Low or absent	Normal, decreased or increased
Heritability	0.69 to 0.88	0.47 to 0.77
Prevalence	<2 per 1,000	~6% (men), ~5% (women)

2) Physio-Chemical Properties[28]

Test	Observation 1	Observation 2	Observation 3
Total cash value	19.9	19.2	19.25
Acid-insoluble ash	13.9	12.55	13.7
Water-soluble extractive value	29.7	29.0	27.1
Alcohol-soluble extractive value	6.8	6.5	6.0

3) Phytochemical screening of *Withania coagulans*:

Plant constituents and test reagents	Hydro alcoholic extract of *Withania coagulans*
1) Carbohydrates	
a) Molish's test	Positive
b) Fehling's reagent	Positive
2) Proteins	
a) Biuret test	Negative
3) Amino acids	
a) Ninhydrin test	Negative

4) Steroids	
a) Salkowski test	Positive
5) Glycosides.	
a) Keller Killani test	Negative
b) Borntrager's test	Negative
6) Flavonoids	
a) Shinoda test	Negative
7) Alkaloids.	
a) Dragendorff's test	Positive
b) Mayers test	Positive
c) Wagner's test	Positive

4) IR of Extract

Wavelength (cm-1)	Comment
3826.77	O-H Stretch
3317.56	O-H Stretch
2345.44	O=C=O Stretch
1388.75	C-H Bends
1334.74	O-H Bends
1226.73	C=O Stretch
1049.28	C=O Stretch
995.27	C=C Bends
925.83	C=C Bends
725.23	C=C Bends
702.09	C=C Bends
555.50, 455.20, 48.91	Miscellaneous Halo Compounds
2871.79	C-H Stretch

5) Physical appearance of formulation:

Formulations were checked for their colour, odour, taste and melting time at room temperature.

Formulation	Colour	Odour	Taste	Melting behaviour
F1	Brown	Pleasant	++	+
F2	Dark Brown	Unpleasant	-	-
F3	Brown	Pleasant	+	-
F4	Brown	Unpleasant	+	++
F5	Dark brown	Pleasant	+++	+++

6) Selection of Excipient

Ingredients	Category
1) Cocoa powder	Chocolate base
2) Extra pure cocoa butter	Binder
3) Lecithin (80%)	Lubricant
4) Stevia	Sweetener
5) Milk	Solvent
6) Extract	Active Pharmaceutical Ingredient

7) Hardness

Formulation	F1	F2	F3	F4	F5
Hardness	4.5 ±2 kg/cm2	4.4 ±2 kg/cm2	7.5 ±2 kg/cm2	7.5 ± 2 kg/cm2	8.65 ±2 kg/cm2

8) Blooming tests:

Test	Observations
Fat bloom	No
Sugar bloom	No

9) Stability studies:

Stability study of optimized formulation was done for 3 weeks at 2-6^0 C and following data was recorded

Parameters	Week 1	Week 2	Week 3
Appearance	Dark brown	Dark brown	Brown
Taste	Pleasant taste	Pleasant taste	Pleasant taste
Odour	Chocolate smell	Chocolate smell	Chocolate smell
pH	6.63	6.63	6.53

10) IR Spectral peaks of Formulation

Wavelength (cm-1)	Comment
3317.56	O-H Stretch
2893.22	O-H Stretch
2337.72	O=C=O Stretch
1635.64	C=C Stretch
7489.05	C-H Bends
1373.32	O-H Bends
1219.01	C-O Stretch
1157.29	C-O Stretch
1049.28	C-O Stretch
725.23	C=C Bends
694.37	C=C Bends
601.79	Halo Compounds
555.50	Halo Compounds
447.49	Halo Compounds

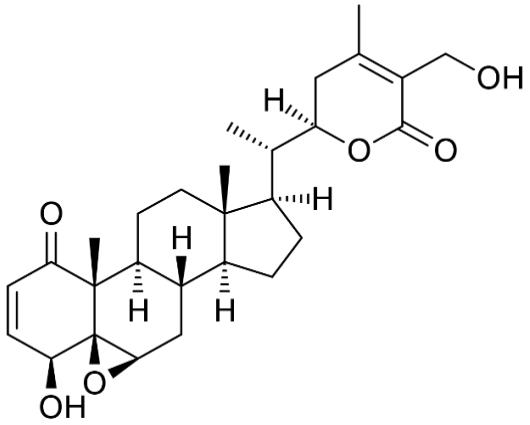


Figure 1: Withanoloids

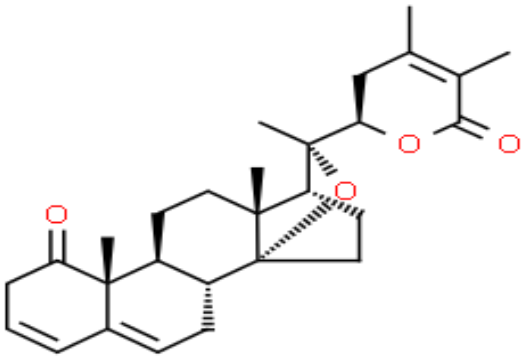


Figure 2: Coagulin

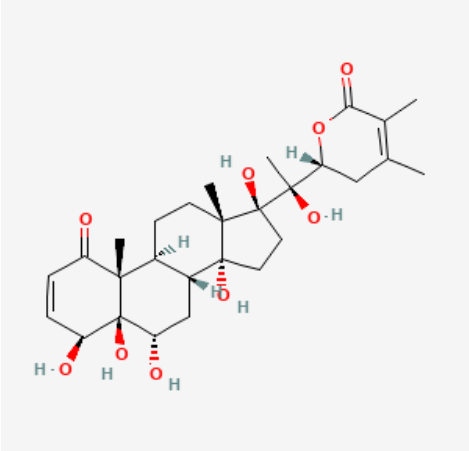


Figure 3: Withaperurin

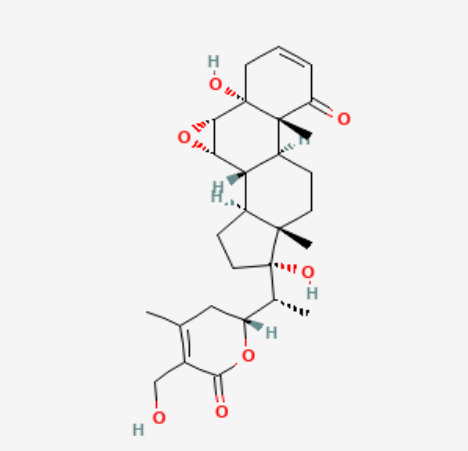


Figure 4: 27-Hydroxy Withanolide

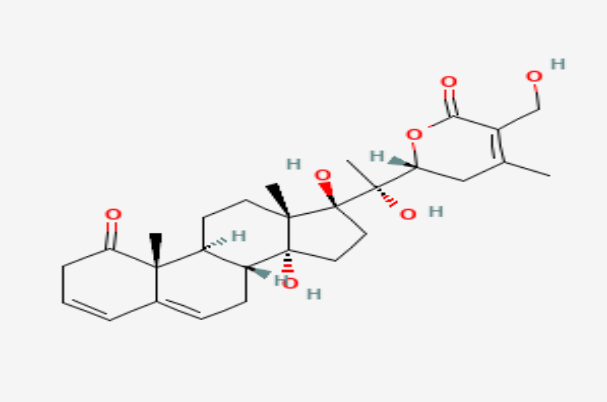


Figure 5: Ajugin E

Figure 6: Fail batches Of Formulation

Figure 7: Successful Batch of Formulation

Figure no: 8 Height of the chocolate formulation

Figure 9: Hardness of the chocolate formulation

CONCLUSION:

From the above result, it can be concluded that the F5 batch as an optimized batch, provides sweetening property as compared to others, pH & stability profile to be satisfactory.

Studies have suggested that eating chocolate, especially dark chocolate, could boost both memory and mood. The Organoleptic properties of chocolate are excellent for masking unpleasant flavours associated with some active agents and imparting a smooth and creamy texture to compositions of active agents. Thus, chocolate formulation provides a palatable means for delivering medicaments through oral delivery.

In the current report advancement of natural chocolate by utilizing *Withania coagulans* was done. By utilizing fruits of *Withania coagulans*, lab made chocolates was ready and assessed for outward presentation, aspect, hardness, blooming test.

From above results, we presumed that the chocolates give smooth and velvety surface to the detailing and are great for covering the bitter taste related with the medications.

Mobile phase for thin layer chromatography was developed using ethanol: water (5:5). From this study we can conclude that withanolides may be present in the extract which may be confirmed if future by isolation of components present in the extract.

As we know learning is a continuous and never-ending process, the present study can prove useful for future research on *Withania coagulans*.

The percent drug content and other quality evaluations of the formulation would be done in future using this report as reference.

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