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Formulation and evaluation of a chocolate based drug delivery system of Niclosamide

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Abstract
The aim of this investigation was to develop an oral chocolate-based drug delivery system for the paediatric population for addressing worm infestation in children. By using the heating and congealing method, specific proportions of the drug and additives were integrated into the chocolate base. Evaluation parameters included various aspects such as appearance, texture, viscosity, hardness, weight variation test, drug content, disintegration, bloom test, melting point and drug release test. Findings indicated favourable physical qualities, appropriate rheological properties, efficient drug release, excellent melting point and negligible bloom. Overall, the developed chocolate-based drug delivery system demonstrated promising qualities for oral use in the paediatric population, suggesting its potential as a dependable and safe oral dosage for managing worm infestation in children.

Keywords: Chocolate based drug delivery system, Niclosamide, nutraceuticals, cocoa butter, carob powder

Introduction

Patients find the oral route of drug administration to be the most convenient. However, patient compliance is a major concern particularly in paediatrics. The basis of effective treatment is adherence to the therapeutic regimen, which is critically dependent on the patient's acceptance of the dosage form. Due to bitter taste, this type of repetitive oral delivery of medications causes discomfort in the patient. There are numerous ways of improving patient compliance [1]. Children's compliance rates range from 11% to 93%, and the main contributing elements are the characteristics of the dose form (size, dosing volume, etc.), the taste, and the consistency of the caregiver [2]. In a recent study with 153 paediatric participants, taste aversion was the key factor in patient noncompliance [3]. The development of palatable dosage forms to minimise taste aversion has been addressed by using taste-masking techniques, taste-receptor blocking, and mixing with food or beverages prior delivery [4]. Increasing acceptance of cocoa related items by the paediatric population, such as chocolate and chocolate milk, have traditionally been employed as palatability enhancers [5].

Chocolate due to its anhydrous nature prevents microbial growth and hydrolysis to a large extent as compared to normal drug delivery systems. In many active agents it acts as a well suited vehicle. Due to its organoleptic characteristics, it gives the formulation an appealing look, masks the unpleasant taste of the drug if any and a creamy texture thus aiding in patient compliance of the drug formulation [6]. Chocolate is also known to reduce the risk of possible coronary heart diseases and due to various of its nutritious qualities, some being the presence of flavonoids, it imparts the chocolate antioxidant properties, partially accounting for its protective effect [7]. Chocolate is a relatively high in calories and sugar and its consumption should be looked after, excess intake can contribute to weight gain and can backfire the patient with hypertension, diabetes, and other metabolic disorders in general. Hence frequent dosage drugs cannot be incorporated in this delivery system [8]. Chocolate is derived from cocoa beans, the fruit of

the *Theobroma cacao* tree in the Sterculiaceae plant family. Chocolate is an adaptable food that can be combined to create completely different taste and texture sensations. Cocoa kernels contain 0.19-3.0% of theobromine (stimulates the central nervous system, facilitates muscular exertion, acts as a diuretic and appetite stimulant) and the husks contain 0.19- 2.98% of this alkaloid. The seeds also contain 0.05-0.36% caffeine (increases resistance to fatigue and watchfulness, although may be harmful in large doses chocolate contains it in small amounts), cocoa fat or butter (nibs 45- 53%, husk 4-8%) [9]. Phenyl ethylamine which is a psychostimulant, Tryptophan is known to increase the production of serotonin, an anti-depressant and a natural stress-reducer, Catechins are antioxidants that may help protect the body against cardiovascular diseases and possibly cancer, are found in substantially higher quantities in chocolate, Phenols reduce the risk of cardiovascular disease CVD, because of their fat content, cocoa and chocolate are high in calories. The most common sources of caffeine are chocolate and tea [13]. However, it may trigger headache [10], heatburn [11], atopic dermatitis [12] is a common sources of caffeine [13] and may cause behavioural changes [14].

Carob powder is an excellent substitute for cocoa in formulations. *Ceratonia siliqua* also called locust bean or St. John's bread, is a tree of the pea family Fabaceae, grown for its edible pods. Although the pulp has historically been utilised as animal feed, researchers are now concentrating on its usage as a valuable food component. Carob powder is another item prepared from carob pods without seeds. Carob powder has a significant potential to replace cocoa because it has a chocolate-like scent and flavour after roasting [15].

Carob pulp includes 6-11% moisture, 2-7.6% protein, 0.4-1.3% fat, 7.6-38% fibre, 2-3.4% ash, 40.7-54.7% of sugars, 1.2-7.0% of total polyphenols and trace amounts of theobromine & caffeine [16-19]. Carob is free of tyramine and caffeine, replacing chocolate with it can help avoid migraines, which are thought to be triggered by tyramine and caffeine in chocolate. It gives an anti-diabetic effect and treats diabetes and hyperglycaemia by preventing the transit and absorption of intestinal glucose [20]. When prediabetic patients drink a carob pod inositol-enriched beverage, they produce a reaction that is BMI dependent and their insulin resistance is improved [21]. Carob is oxalate free. Hence, Oxalate stops calcium from binding; as a result, kidney stone risks are reduced [22]. Gallic acid and its derivatives in it are responsible for the anti-proliferative effect in human colon cell lines that block DNA synthesis and prevent human colon cancer. This action reduces the tumor growth and prevents angiogenesis [23]. Methanol, chloroform, and hydro-alcohol based extracts of dry carob were highly efficient against diverse microorganisms including 15 bacterial and 8 fungal species [24]. Ethanolic extract of leaves was partially active against Newcastle Disease Virus [25]. It has excellent antioxidant qualities that treat other chronic lifestyle related illnesses and have anti-obesity benefits. The carob seed peel and pods have antihypertensive and anti-inflammatory properties. Carob has a lot of fibre, eating foods fortified with fibre will have fewer calories, which will helps in weight management [26].

Due to the rising prices of cocoa and prediction of even more rise in the price, it is becoming important to find a substitute for cocoa. Carob powder, that is obtained from the carob pods, can be chosen as a good alternative for cocoa but now it turns out to be even better and healthier than cocoa itself for the reasons mentioned further. Carob powder along with other substituents like cocoa powder also contains sucrose hence making it naturally sweeter as compared to cocoa and further leading to lesser additions of artificial sugar in products. Not only is it sweet but it also lacks caffeine and theobromine whose presence is a limitation in consumption of cocoa powder [27]. Carob is also known to contain three times more calcium, moderately more fibre and significantly less fat as compared to cocoa. Due to its fibre content, it aids in digestion and can also help prevent constipation, which is one of the side effects of niclosamide [28]. To conclude carob contains many bioactive compounds and hence can be used over cocoa powder to produce healthier products [29].

Some of the most prevalent parasites in the world are helminths, or worms. They are members of the flatworms, commonly known as Platyhelminthes (flukes and tapeworms), and the roundworms, also recognized as Nematoda. The poor tropical and subtropical regions are where people get the worst helminth infections, though some also happen in developed nations; other, less dangerous diseases are spread all over the world. Climate, hygiene, dietary habits, and interaction with vectors may affect how susceptible someone is to infection. Numerous infestations in one person are not uncommon. Many helminths in the human body reside in the gut, but some either colonise the tissues or move there with their larvae. By depriving the host of food, causing blood loss, organ damage, intestinal or lymphatic obstruction, or by secreting toxins, they cause harm to the host. Though rarely lethal, helminthiasis is a significant contributor to sickness.

Anthelmintics are drugs that either kill (vermicide) or expel (vermifuge) infesting helminths. The choice of drug for each worm infestation is based not only on efficacy, but also on lack of side effects/toxicity, ease of administration (preferably single dose) and low cost. Development of resistance has not been a problem in the clinical use of anthelmintics.

Niclosamide was discovered in the early 1950s. It was initially employed as a molluscicide to kill snails. About a decade later, it was discovered to be effective against human tapeworm infection. Following FDA approval, it was first used to treat human tapeworm infections in 1982, and since then, it has been listed among the essential medications by the World Health Organization. Niclosamide belongs to salicylanilides- a large group of lipophilic, weaklyacidic molecules [30].

The drug acts by uncoupling of oxidative phosphorylation or stimulation of ATPase activity. Barring ova, adult worms are then partially digested in the intestine due to the action of the drug. Niclosamide is a highly effective drug against cestodes infesting man—*Taenia saginata, T. solium, Diphyllobothrium latum* and *Hymenolepis nana*, as well as pinworm.

The aim of present study is to design and formulate a chocolate formulation as a drug delivery system of an anthelmintic drug Niclosamide to improve patient compliance, palatability and to provide a basis for development of chocolate as a dosage form.

Materials and Methods: The following materials were use.

Table 1: Materials used

Sr. No.	Ingredients	Roles
1	Niclosamide	Anthelmintic
2.	Cocoa butter	Vehicle
3.	Carob powder	Diluent
4.	Milk powder	Flavourant
5.	Sugar	Sweetener
6.	Soya lecithin	Emulsifier
7.	Chocolate essence	Flavourant

Material sourcing

Table 2: Source of materials

Sr. No.	Drugs/excipient	Supplier/Gifted by
1.	Niclosamide	Raveez Pharma Pvt Ltd
2.	Cocoa Butter	Morde Foods Pvt Ltd
3.	Carob Powder	Sattvic Foods
4.	Milk Powder	Britannia Industries Ltd
5.	Sugar	Sugar (Food grade)
6.	Soya Lecithin	Research-Lab Fine Chem Industries
7.	Chocolate Essence	Papilon essences, Mfg by Magic Flairs

The method of preparation was as follows

1. Cocoa butter was accurately weighed as mentioned in the formulation table and transferred to a beaker.
2. This cocoa butter was heated on a water bath till it melted.
3. The temperature of the water bath should not exceed 40 °C.
4. To the above mixture, sugar was added as per the formulation table quantity.
5. To the melted cocoa butter 0.5g of API (Niclosamide) was added.
6. Above drug and butter mixture was stirred till the drug completed dissolved.
7. To this mixture weighed amount of powdered sugar (Quantity according to the formulation table) was added and the mixture was stirred till the sugar dissolved.
8. To the above mixture the given quantity of carob powder was added and stirred till a uniform mixture was formed.
9. To the above formed carob mixture weighed quantity of soy lecithin (food grade) was added.
10. The viscosity of the mixture increased due to soy lecithin's emulsification properties and an easily flowable chocolate mixture was obtained.
11. To this mixture 1-2 drops of chocolate essence were added and this was then poured into the silicon mould and kept further for deep freezing.

Five formulations were prepared using this method

Table 3: Formulations

Sr. No.		F1	F2	F3	F4	F5
	Ingredients	Per chocolate (grams)				
1.	Niclosamide	0.5	0.5	0.5	0.5	0.5
2.	Cocoa butter	3.5	3	4	4	3.5
3.	Carob powder	3	3	2	2	2
4.	Milk powder	0.5	0.5	0.5	-	-
5.	Sugar	1	1	1	1	1
6.	Soya lecithin	0.2	0.2	0.2	0.2	0.2
7.	Chocolate essence	1 drop	1 drop	1 drop	1 drop	1 drop

Solubility determination of Niclosamide

10mg drug was taken in three beakers. In the first beaker 5 ml water was added, in the second beaker 5 ml methanol was added and in the third beaker 5 ml ethanol was added. All three mixtures were stirred and shaken for 2hr and checked for saturation by observing for the presence of any undissolved particles. The solvent which completely solubilised the drug was taken and 10mg drug was dissolved in 100ml of solvent which was further diluted and the mixture was to be scanned to obtain the lambda max.

Standard curve was prepared by taking 10 mg Niclosamide which was dissolved in 100 mL ethanol. Further serial dilutions were performed and a UV spectrophotometer was used to measure the absorbance.

Evaluation parameters

Physical appearance: The formulation was tested for its surface texture in terms of its grittiness or stickiness. Formulation was inspected visually in terms of its look and colour. Its odour and colour was also evaluated.

Viscosity

A Brookfield Rotational digital viscometer was used to measure the viscosity of the chocolate base. 5 chocolates of

each formulation were melted in a beaker and the spindle was rotated at 20 rpm and checked for its viscosity.

Dimensions: The formulation thickness and dimension for 3 chocolates per formulation were calculated using a vernier calliper. The variation for limit for thickness is ±5% of the size of the formulation.

Hardness: Chocolate strength that is the force required for breaking the formulation was measured using a Monsanto hardness tester, the unit of measurement is kg/cm 2. For checking the hardness, the same strength chocolates (as per the formulation table) were prepared in a comparatively smaller mould allowing it to fit into the Monsanto tester and the hardness for that formulation was determined in triplicate per batch and the mean was calculated.

Weight variation: This study was performed according to USP. This test was carried out on 5 chocolates per formulation. Each formulation was weighed individually and average weight along with standard deviation was calculated in all the batches.

Loss on drying: This test is performed to evaluate the loss of weight in the formulation which is due to water or any other kind of volatile matter. This test is based on the thermogravimetric principle. The formulation was initially weighed in a porcelain dish and placed in a hot air oven for heating. After certain time intervals the formulation was weighed again until no more weight was lost.

Bloom test

Fat bloom: Fat bloom is caused due to two reasons- either recrystallization of a fat layer or migration of a filling fat to the surface. This layer causes the formation of a white layer on the chocolate surface thus making it lose its glossy appearance. This layer formation can be avoided by storing the chocolate at a constant temperature.

Sugar bloom

This is visible as an irregular layer on top of the formulation. It occurs due to condensation of moisture, mainly when the chocolate is removed from the refrigerator. This moisture disintegrates the sugar in the chocolate and crystallized sugar layer is formed on the surface giving the chocolate a non-appealing look. This test was done by visual inspection after storage for 24 hours at refrigerated conditions and room temperature.

Drug content determination: Drug content determination is determined using UV Spectrophotometer. In a beaker, the chocolate was first dissolved in 20 ml solvent (in this case ethanol), the chocolate was broken down and sonicated. This mixture was then centrifuged for 15 minutes at 2500 rpm. After centrifugation the supernatant liquid obtained was filtered and transferred to a test tube. This obtained liquid was then analysed in a UV spectrophotometer using ethanol as the blank at the lambda max of the API, that is, 243 nm.

Disintegration test: This test was performed using a USP Disintegration tester at 37±0.5 °C and 60rpm speed. 3 chocolates of a smaller size having the same concentration as each formulation was taken and transferred to the disintegration apparatus which was filled with distilled water and the test was run, the time in minutes for total disintegration was then recorded.

***In vitro* drug release:** This study was performed using USP II Apparatus. Saline phosphate buffer having pH 7.4 was chosen as the dissolution media. The basket was filled with 500mL of pH7.4 saline phosphate buffer and allowed to reach a temperature of 37±0.5ºC. The speed was kept at 100 rpm and this test was carried out for a period of 90 minutes. After the temperature has been reached the chocolate formulation was broken into two and placed in the basket. At a predetermined time, interval of 5 minutes, 5mL sample was withdrawn and this was replenished using the same amount of fresh medium. This withdrawn sample was filtered and analysed using a UV spectrophotometer, taking the buffer as a blank. The concentration of Niclosamide per withdrawn sample was calculated using cumulative percentage release.

Melting point: Formulation was taken in a porcelain dish and this dish is placed in a water bath. This water bath was placed on a tripod stand and heated. When the chocolate completely melted, a thermometer attached to the porcelain dish was checked for its melting point.

Results

Standard curve

Table 4: Standard curve readings

Sr. no.	Concentration (mg/ml)	Absorbance
1.	0.005	0.2263
2.	0.01	0.3972
3.	0.015	0.6515
4.	0.02	0.7597
5.	0.025	0.9913

Physical appearance

Table 5: Physical appearance

Sr. No.	Formulation	Colour	Odour	Taste	Texture
1.	F1	Dark brown	Chocolate like odour	Sweet and milky	Highly granular
2.	F2	Dark brown	Chocolate like odour	Sweet and milky	Highly viscous and then flaky
3.	F3	Dark brown	Chocolate like odour	Sweet and milky	Smooth and nongranular
4.	F4	Dark brown	Chocolate like odour	Sweet	Smooth and nongranular
5.	F5	Dark brown	Chocolate like odour	Sweet	Smooth and nongranular

The F1, F2 & F3 formulations were found to be pleasant milky in taste due to the presence of milk powder in it, whereas F4 and F5 lacked the property. Also, the F1 & F2 formulations were unable to freeze due to high granularity and high viscosity respectively.

Thickness

Table 6: Thickness

Sr. No.	Formulation	Thickness (cm)
1.	F1	-
2.	F2	-
3.	F3	10.7
4.	F4	10.83
5.	F5	8.76

The thickness of F5 formulation was the lowest and it was the highest for F4 formulation.

Hardness

Table 7: Hardness of formulations

Sr. No.	Formulation	Hardness (N)
1.	F1	-
2.	F2	-
3.	F3	3
4.	F4	3
5.	F5	4

The formulation batch F5 showed good hardness property than F3 and F4

Drug solubility: The drug showed excellent solubility in ethanol (left), whereas it was sparingly soluble in methanol (right) and the remaining drug settled at the bottom of the test tube.

Weight variation test

Table 8: Average weight variation

Sr. No.	Formulation	Average Weight deviation (%)
1.	F1	-
2.	F2	-
3.	F3	0.0077
4.	F4	0.0077
5.	F5	0.0041

The percentage deviation in weight was least for the formulation number F5.

Loss on drying

Table 9: Loss on drying

Sr. no.	Formulation	LOD (%)
1.	F1	-
2.	F2	-
3.	F3	1.63
4.	F4	0.57
5.	F5	1.17

Bloom test

Table 10: Bloom test

Sr. No.	Storage conditions	Fat bloom (appearance of white layer at the surface)	Sugar bloom (appearance of white crystalline dry layer at the surface)
1.	2-8°C for 24hours	No blooming seen	No blooming seen
2.	25°C for 24hours	No blooming seen	No blooming seen

Viscosity determination

The viscosity of chocolate base for batch F5 was found to be 2450 centipoise

Melting point

Table 11: Melting point

Sr. No.		Melting point (Degree Celsius)
1.	F5	59.336

Disintegration test

Table 12: Disintegration test

Sr. No.	Formulation	Disintegration time (min)
1.	F1	-
2.	F2	-
3.	F3	2.15
4.	F4	2.40
5.	F5	3.00

The disintegration time for F5 was the highest, i.e., 3min and lowest for F3, i.e., 2.15min

Drug content determination

Table 13: Drug content

Sr. No.	Formulation	Drug content (mg)
1.	F1	-
2.	F2	-
3.	F3	123.04
4.	F4	143.33
5.	F5	249.17

In-vitro drug release studies

Table 14: Drug release

Sr. No.	Formulation	% CDR at different time intervals (min)			
		30	60	90	120
1.	F1	-	-	-	-
2.	F2	-	-	-	-
3.	F3	5.49	6.88	6.52	8.33
4.	F4	2.64	3.27	4.08	7.37
5.	F5	4.72	6.35	8.14	10.49

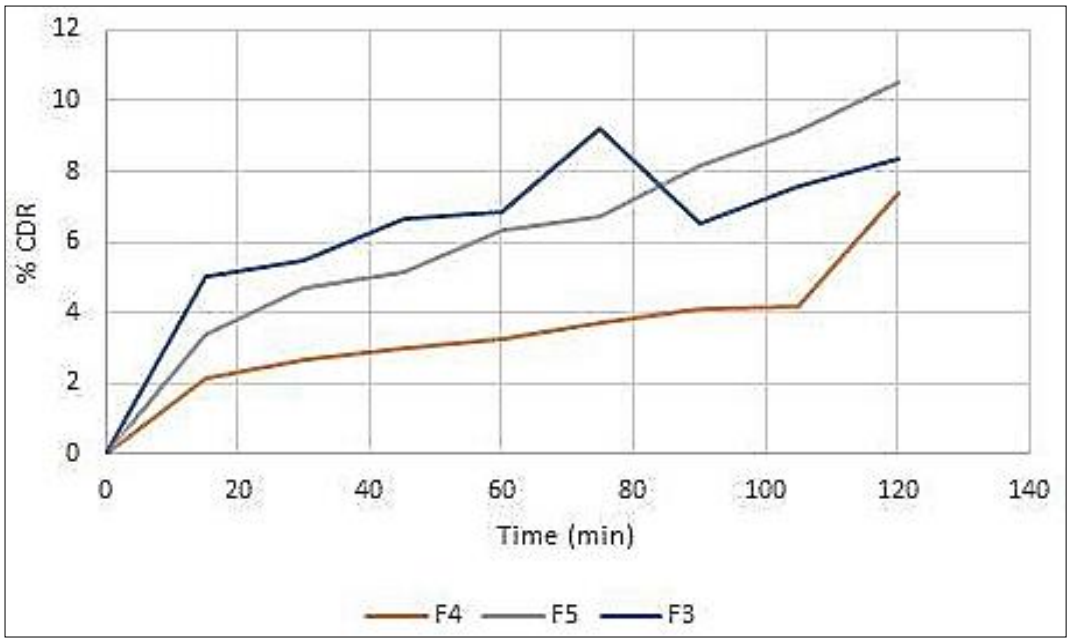

Fig 1: *In-vitro* drug release studies

The F3 formulation showed an abrupt release pattern due to an interference by the milk fats in the milk powder. So, the formulation F4 and F5 were optimised by eliminating milk powder from the excipients, which did not affect the other properties majorly. The F4 and F5 showed a good but very slow-release pattern that might extend for a few hours.

Conclusion

The formulations were made and optimised accordingly to get a patient - compliant and palatable formulation for the paediatric population with improved release profile. Five formulations were attempted to be formulated and evaluated for different evaluation parameters, like organoleptic parameters, thickness, hardness, loss on drying, Disintegration test, Drug content determination test and Dissolution test. The F5 formulation was found to be having optimum drug release and showed satisfactory results of other parameters. Hence was selected. To conclude, the formulation was a good attempt to construct an oral delivery system to give the required anthelmintic therapeutic effect.

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