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Design and Development of Herbal Pediatric Edible Jelly for Anthelmintic Infections

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Abstract:

One of the striving problems in the pediatric therapy is the reluctance of children to a dosage regimen. Patient compliance and lack of ability of self-drug administration are two major factors underlining. Herbal dosage forms attained global importance because of the medicinal properties with less or no side effects, economical and Biocompatible too. The present work aims to formulate and evaluate the herbal edible jelly for the treatment of helminthiasis with the extracts of the plant *Moringa Oleifera*. *In vitro* drug release kinetics results indicated that the methanolic extract have better drug release kinetics. Anthelmintic activity was conducted with the help of equal sized earth worms (*Pheritima Postuma*). The time for paralysis and time taken till the death of the worm was measured. A commonly used anthelmintic drug i.e. piperazine citrate was prepared into jelly in the same manner to act as standard for the comparison. The results obtained for the methanolic extract *Moringa Oleifera* are better compared to that of the standard drug.

Key words: Anthelmintic, edible jelly, earth worms, herbal, moringa.

INTRODUCTION

The plant *Moringa oleifera* (ver: drumstick tree) belonging to the family Moringaceae can be called as “miracle tree” or “the tree of life” because all the parts of the plant have medicinal benefits[i], rich nutritive value and other uses like purification of the water[ii]. *M. oleifera* is a fast growing and drought resistant tree is believed to be originated from India, fruits and leaves of the tree were popular amongst the vegetables in the same subcontinent. The nutritive parts of *M. oleifera* (i.e, seeds, roots and leaves) reported showing anthelmintic activity[iii].

Soil transmitted helmenthic (STH) infections is one most common condition in the world. Transmission of the infections is by contaminated soil, eggs enters into the human body and grow to adult worms. These infections are manifested by diarrhoea, abdominal pain, general malaise, weakness and anaemia. Morbidity is directly propotional to the worm burden in the children of school age and immune-deficient individuals are particularly vulnerable to these parasitic helminth infestations. According to the estimates about 880 million children are indeed to be treated still. India alone contributes approximately 25% to the total global cases with 220.6 million children are in need of preventive medicine. WHO’s strategy for adressing the condition is to control morbidity through periodical treatment of population at hig-risk in endemic regions. WHO organises treatment with deworming medication to preschool-aged children, school-aged children and women of childbearing age (including pregnant women in the second and third trimesters and breastfeeding women) in prevalant regions. The global target is to eliminate morbidity of soil-transmitted helminthiases in children by 2020 which wil be achived by regular treating at least 75% of the children in endemic areas. In order to fullfill this target, it is in practice that, school children were been supplied with a dose of 400mg Albendazole chewable tablets one or twice a year by the authorities in developing countries.

Several researchers have reported anthelmintic activity earlier. Anthelmintic activity of M. oleifera seeds aqueous and ethanolic extract against *Haemonchus contortus* eggs and larve is reported by Delfin E. Cabardo Jr.[iv] in his study. Gertrude Mbogning Tayo et al. studied the anthelmintic activity in the leaves of M. oleifera in all four developmental stages of *Haemonchus contortus* collected from goat. Based on the study results extracts from the leaves show better activity in inhibiting the egg hatch and mortality of the larvae[v]. In another study lecithin from the seeds of the same plant is found to have nematicidal activity[vi]. The drumstick plant is proved to have better activity than horseshoe vitex plant on earthworms with piparazine citrate as standard[vii]. Although leaves and fruits are cooked food many children asusually be reluctant to eat food. It is a wise to prepare the herbal constituents in form of jellies, which unlike medication but like candies to kids.

Tablets besides being the most common and convinient dosage form, it is not much acceptable by children. ‘Dysphagia’(difficulty in swalowing)[viii] in taking tables is seen in most of the children. Eidble jellies are acceptable by children because of the organoleptic properties and they are candy like. To treat the condition naturally it is again a huge problem to make trageted population (children) consume a lot of vegitables. In a way to prevent that, but to treat the condition on herbal basis, through preferential route of administration i.e., oral route is solved by formulating an edible jelly with the herbal extract. Tushar V. Ahire et al[ix]., formulated Albendazole jellies and evaluated as jellies provide better patient complience and better taste masking ability than tablets.

MATERIALS AND METHODS

Leaves of the plant *Moringa oleifera* are collected directly from the plant in and around Guntur, Andhra Pradesh, India from July to September. The shade dried leaves were grounded into a coarse powder. Dr. Ammani, Head, Department of Botany, Acharya Nagarjuna University, Guntur, Andhra Pradesh, India, confirmed the authentication of the plant. Herbal drug extracts were prepared in the laboratory. Piparazine citrate from Dr.

Reddy's laboratories, Gelatin (edible) is purchased from Crown Jellos, Ethanol, Sodium hydroxide and Methyl paraben obtained from Merck Labs, Mumbai. Methanol, citric acid, Hydrochloric acid from Fisher scientific, Mumbai. Tween 80 and propylene glycol from Reachem, Mumbai and other ingredients are of pure and of analytical grade.

Extraction

The extraction is carried out in a Soxhlet extractor with the solvents water, ethanol, methanol and chloroform respectively. The extract was concentrated by distillation process. Then the extract is dried under the shade for further evaporation of the solvents. The dried extracts were labeled and are stored in desiccators for further use[x]. The extracts were represented as AQS, ETS, MTS, CHS for aqueous, ethanolic, methanolic and chloroform extracts. The extracts were tested for various phytochemical constituents and the data was given in Table 1.

Preparation of the jelly

Nine different formulations of jelly were prepared by using agar and gelatin as gelling agents in different concentrations as given in the Formula table 1. The gelling agents were tried initially at different concentrations to achieve desired appearance, stiffness and release. Citric acid is used to maintain the pH, propylene glycol incorporated to enhance the softness and slippery to the jelly. Organoleptic agents were added to improve the aesthetic value of the jelly. Sodium benzoate is used as preservative and honey and sugar were used as sweetening and bulking agents.

The jellies are prepared by taking agar/ gelatin, propylene glycol, citric acid in beaked and heated with continuous stirring to get solution form. In another beaker sugar solution is prepared and transfer into the first beaker. Sweetening and flavouring agent were added and mixed thoroughly. The dispersion was transferred in to molds to avoid exposure to outer environment. The formed jellies were wrapped in wax paper and stored in dry place. The formulae of edible jellies were shown in Table 2.

CHARACTERIZATION

Physical appearance : The prepared jellies were evaluated for physical appearance like clarity, colour, odour, texture, consistancy, stickiness and grittiness[xi]. These tests are important regarding the patient acceptance.

pH : pH of the formulation influences the stability. The pH of the soft edible jelly is measured by digital pH meter at room temparature. 0.5g of jelly (1%) is dispersed in 50ml of distilled water and measure the pH.

Viscosity : Viscosity of jelly was measured with a Brookfield® viscometer using spindle DV-E-64. Viscosity was measured for the fixed time of 2 minutes at the rotation of 1.5 RPM at room temperature (25ºC ± 5ºC). The viscosity measurements were made in triplicate using fresh sample each time[xii].

Content uniformity: The jellies were taken out of the molds in to beaker and dissolved in 0.1 N HCl to give 100 µg/ mL solution. The sample was analysed for drug content at 263 nm after filtering the sample through membrane filter of pore size 0.5 µm by using UV-Visible spectrophotometer[xiii]. The process was repeated for all the formulations to measure the drug content in triplicate.

***In vitro* drug release:** *In vitro* drug release study of jellies was carried out by using USP dissolution apparatus type II (paddle type). The dissolution test was carried out using 900 ml of 0.1 N HCl solution, at 37 ± 0.5^{o}C at 100 RPM. An aliquot of sample of the solution was withdrawn from the dissolution apparatus at 5, 10, 15, 20, 25, 30 min and replaced with equal volume of fresh dissolution media. The samples were passed through membrane filter of pore size 0.5 µm and were anlayzed by using UV-Vis Spectrophotometer at 263 nm. The process was carried out in triplicate.

Anti helmenthetic activity: The Antihelmintic activity was evaluated on adult earthworms *Pheretima posthuma* due to their anatomical and physiological resemblance with the intestinal round worms in human beings. The anthelmintic activity of the formulations were tested by taking six earthworms of equal size (8±1cm) in to the petridish contang 50ml of desired formation at room temperature.

Earthworms were divided into 10 groups. Each group was treated with one of the following: Vehicle (1%Tween 80 in normal saline solutiion), Piperazine citrate (15mg/ml), and extracts of 15, 30 and 50 mg/ml in normal saline containing 1%Tween 80. Observations were made for the time taken to paralysis and/or death of individual worms up to four hours of test period. The paralysis time and lethal time for each extract was recorded. Paralysis was said to occur when the worm did not revive even in normal saline. Death was concluded when the worms lost their motility followed by fading away of their body colour. The paralysis time and death time for the various formualtions were recorded. The process was carried out in triplicate.

Stability studies: Stability studies of prepared jellies were carried out by storing the jellies at room temperature (25°C ±5°C, 75%±5% RH) and at accelerated temprature (40°C ±5°C, 75%±5% RH) as per ICH guidelines. The stability studies are carried out for 3 months and the formulation being analyzed for the changes in the physical parameters like appearance, pH, sugar crystallization, stiffness and viscosity for every 30 days .

Figure 1: Images of formulated edible jellies

Table 1: Preliminary qualitative investigation of *Moringa oleifera* leaves

Bioactive constituents	Ethanol	methanol	Chloroform	Aqueous
Alkaloids	+	+	+	_
Flavonoids	+	+	_	+
Carbohydrates	_	+	+	+
Glycosides	+	+	_	+
Sapponins	+	+	_	+
Steroids	+	-	-	-
Tannins	+	-	-	-
Triterpinoids	-	+	+	-

Table 2: Formulae of herbal edible jellies

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Herbal extract 0.5%	PPZ	AQS	CHS	ETS	MTS	AQS	CHS	ETS	MTS
Agar	-	2%	2%	2%	2%	-	-	-	-
Gelatine	4%	-	-	-	-	4%	4%	4%	4%
Citric acid	1%	1%	1%	1%	1%	1%	1%	1%	1%
Propylene Glycol	3%	3%	3%	3%	3%	3%	3%	3%	3%
Sugar syrup	60%	60%	60%	60%	60%	60%	60%	60%	60%
Methyl paraben	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%
Propyl paraben	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%
Flavouring agent	2ml	2 ml	2 ml	2ml	2ml	2ml	2ml	2ml	2ml
Honey	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Table 3: Physical properties of oral edible jelly

S.No	**Formulation code**	**Colour**	**Texture**	**pH**	**Stickiness**	**Viscosity (cps)**
1	F_1	Light green	Smooth	3.40±0.14	Non-sticky	56700
2	F_2	Dirty green	Smooth	3.45±0.18	Sticky	35472
3	F_3	Green	Smooth	3.43±0.1	Sticky	33624
4	F_4	Green	Smooth	.60±0.10	Sticky	36512
5	F_5	Green	Smooth	.60±0.10	Sticky	39875
6	F6	Dirty green	Smooth	3.35±0.11	Non-sticky	60600
7	F7	Green	Smooth	3.43±0.1	Non-sticky	59600
8	F8	Green	Smooth	.60±0.10	Non-sticky	61800
9	F9	Yellow Colour	Smooth	5.3±0.05	Non-sticky	55200

Table 4: Drug content and release data edible jellies

S.No	**Formulation code**	**% drug content**	**% drug released**
1	F_1	91.40±0.08	89.56±0.12
2	F_2	87.96±0.12	94.56±0.23
3	F_3	87.53±0.45	91.32±0.14
4	F_4	91.23±0.47	96.35±0.47
5	F_5	89.32±0.14	95.23±0.45
6	F6	92.31±0.45	95.24±0.25
7	F7	95.43±0.25	93.21±0.57
8	F8	94.23±0.13	99.87±0.37
9	F9	94.65±0.47	94.24±0.74

Table 4: Anthelmintic activity data of the edible jellies

Group	Treatment	Conc.(mg/ml)	Paralysis Time (P) in Min	Death Time (D) in Min
F4	Methanolic extract	15	40±3.5	80±5.5
		30	39±4.3	70±3.25
		50	25±2.6	40±5.57
F5	Piperazine citrate	15	18.73±1.78	44.43±4.03

All the values are express in Mean ± SD (n=6)

Table 4: Stability study data of the edible jellies

Formulation	Characteristics	30 days	60 days	90 days
F4	Appearance	Smooth	Smooth	Smooth
	pH	3.53±0.042	3.47±0.04	3.23±0.09
	Viscosity	60540	59600	58190
F5	Appearance	Smooth	Smooth	Smooth
	pH	3.6±0.08	3.4±0.06	3.63±0.07
	Viscosity	64130	62600	61840

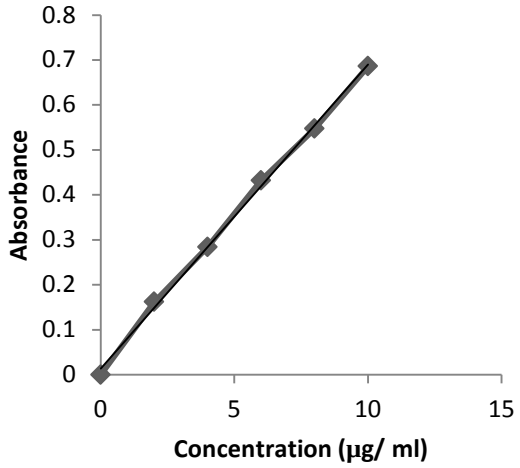

Figure 2: Calibration curve of the herbal extract at 263nm

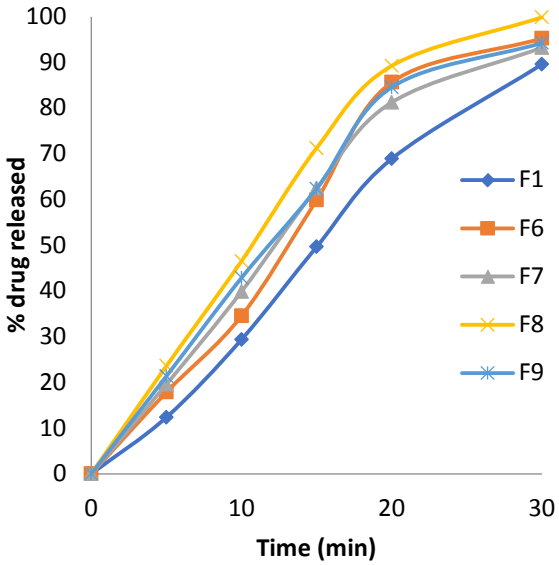

Figure 3: Drug release profile of the edible jellies

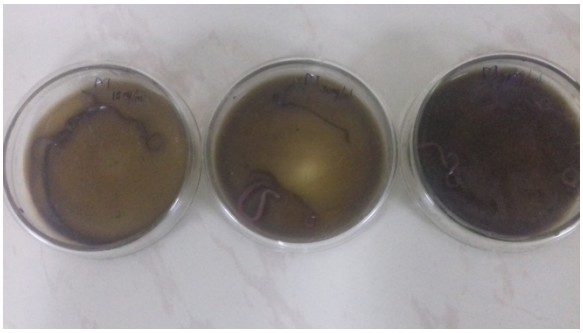

Figure 4: anthelmintic activity profile of edible jellies

RESULTS AND DISCUSSION

The dried leaves of *Moringa Oleifera* were extracted by soxhlation process by using various menstrum likes water, ethanol, methanol and chloroform. The extract was dried and tested for the phytochemical constituents. The results of the preliminary phytochemical screening revealed the presence of alkaloids, flavonoids, carbohydrates, glycosides, saponins, tannins and steroid. The results were shown in Table 1.

The edible jellies were prepared by using various extracts of *Moringa Oleifera* with gelatin and agar as jelling agents. The formulated jellies were shown in Figure 1. The jellies were inspected visually. The jellies formulated with agar as gelling agent are not that stiff and clear. They (F2-F5) converted into liquid state during the storage period. But the jellies prepared with gelatin (F6-F8) were stiff and transparent in nature and shown good appearance. The pH all the formulations were measured by using digital pH meter, all the formulations shown pH within the range of 3.4-5.3.

The viscosity of all the formulations were determined by using Brookfield Viscometer. The results indicated that the formulations F2-F5, having low viscosity and the formulations which are prepared with gelatin viz., F1, F6-F9 were found uniform in consistency. The results were shown in Table 3.

The drug content of prepared edible jellies of were estimated by using UV-Visible spectrophotometer. The medicament in the edible jellies was extracted by using 0.1 N HCl. The sample was estimated after filtration at 263nm. The data was shown in Table 4. The calibration curve data of herbal extract was shown in Figure 2. The amount of drug release from the jellies was carried by using dissolution apparatus Type I. The in vitro drug release from the jellies was estimated by using paddle apparatus. The amount of drug release was estimated. The F8 formulation shown highest drug release compared to other formulations. The data was depicted in Figure 2.

The anthelmintic activity was evaluated on adult Indian earthworms *Pheretima posthuma* due to its anatomical and physiological resemblance with the intestinal round worms in human beings. The formulations were evaluated for anthelmintic activity. The formulation F8 was compared with standard drug formulation (F1). The anthelmintic activity data of the formulation was given in Table 5.

The formulation which exhibited fast dissolution and effective anthelmintic activity was used to perform the stability studies. The stability studies of the formulated jellies were stored in a controlled environment condition for 3 months. The jellies checked periodically for every 30

days for change in appearance, pH and viscosity. The data was shown in Table 5. The data revealed that the optimized formulation not shown any change in appearance, pH and viscosity.

CONCLUSION:

In the present investigation, the edible jellies loaded with various extracts of Moringa olefiera were formulated successfully by using agar and gelatin as gelling agent. the edible jellies made up of gelatin were stiff with good appearance. The optimized formulation F8 showed acceptable physico-chemical properties and good stability. The formulation exhibited good anthelmintic activity which is suitable to administered to children as an alternative to oral solid dosage forms.

Conflict Of Interest: The author declares no conflict of intrest.

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