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Formulation and evaluation of Shankhpushpi pellets for worm manifestation in child

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ABSTRACT: Background: Shankhpushpi is a highly potent anthelmintic drug having bitter taste. In the formulation for pediatric and geriatric patients, the main challenge to the formulator is to mask the taste of obnoxious and bitter drugs without loss of optimal therapeutic activity of the formulation. **Aim:** The main objective of present study was the *in vitro* evaluation of the taste masking efficiency and anthelmintic activity of shankhpushpi formulation prepared by extrusion-spheronization. **Methods:** Pellets containing high shankhpushpi loadings in Eudragit L-100-55 were prepared by extruder and spheronizer. The taste masking of processed formulation was evaluated *in vitro* by dissolution method and chromatographic technique, while anthelmintic effect was evaluated by using six adult Indian earthworms and cattle worms. **Results:** The result of present study indicated that Shankhpushpi for few minutes began the paralysis of earthworm followed by death at the end of 375.5 min. The pellet formulation SP/I – 02 had better dissolution and taste masking profile. **Conclusion:** Thus, the present study demonstrated that formulated pellets of Shankhpushpi had potent anthelmintic activity and has commercial significance.

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INTRODUCTIONS:

Nature has provided a complete store house of remedies to cure all ailments of mankind and its related diseases. The human being appears to be affected with more diseases than other animal species. There can be little doubt that is sought out to alleviate human suffering from injury and diseases by taking advantage of plants of the surroundings. In the past, almost all the medicines used were extracted from the plants and the plant being man's chemist for ages [1].

In the recent years, the importance of herbal drugs in medicine has tremendously increased because of their

fewer side effects. Consequently, the demand for the herbal formulation is increasing day by day. The phytochemical constituents and their standardization are accelerated with the development of instrumental analysis and this field becomes important and new for investigation [2].

Infections with helminths are among the most widespread infections in humans and other domestic animals affecting a large number of world populations. The majority of these infections due to worms are generally restricted mainly to the tropical regions and the occurrence is accelerated due to unhygienic lifestyle and poverty also resulting in the development of symptoms like anaemia, eosinophilia and pneumonia.[2] These infections can affect most populations in endemic areas with major economic and social consequences. Because of limited availability and affordability of modern medicines most of the world's population depends to a greater extent on traditional medical remedies. The traditional medicines hold a great promise as source of easily available effective anthelmintic agents to the people, particularly in tropical developing countries, including India. Ideally an anthelmintic agent should have broad spectrum of action, high percentage of cure with a single dose, free from toxicity to the host and should cost effective. The origin of many effective drugs is found in the traditional medicine practices and in view of this several researchers have undertaken studies to evaluate medicinal plants for their proclaimed anthelmintic efficacy [3]. Natural anthelmintic includes- Moringaoleifera [4], Neem [5], Papaya seeds [6], Shankhpushpi [7], Wormwood [8], Clove [9], Garlic [1], Kalonji [10] and any others.

Shankhpushpi shows better anthelmintic activity. Shankhpushpi is a perennial herb that seems like morning glory. Its branches are spread on the ground and can be more than 30 cm long. The flowers are blue in colour (5mm) and the leaves, which are elliptic in shape (2 mm), are located at alternate positions with branches or flowers. Known as Aloe weed in English, the herb is commonly found in India, especially in the state of Bihar. All the parts of the herb are known to possess therapeutic benefits. It is believed to be the only herb that is capable of enhancing all the aspects related to brain power, such as learning, memory and the ability to recall. However, its popularity stems from its ability to treat insomnia and helmenthis effectively [11]. But its bitter taste leads to poor patient compliance in pediatric and geriatric population. Thus taste masking of these bitter drugs is one of the challenging task in front of manufacturing companies.

The taste masking of bitter APIs is a major challenge especially for the development of oral formulations in pharmaceutical industry. Several approaches have been reported which involve fluidized-bed coating, supercritical fluids and coacervation approaches where effective taste masking is achieved by applying polymeric coating layer to create a physical barrier around the drug [12]. Other alternatives involve the use of complexing agents (cylcodextrins, ion exchange resins) through the formation of inclusion complexes or resonates [13]. Recently, taste masking approaches have employed taste suppressants molecules by blocking the gap junction channels and hemi channels and thus suppressing the drugs taste [14,15]. However, there is an enormous need for more robust, cost effective and easy to scale-up taste masking technologies. Extrusion spheronization is a continuous, one step process that can be used for the preparation of taste masked pellets.

Extrusion Spheronization has been employed as a novel technique for the formulation of oral solid dosage forms in pharmaceutical industries in the last decade. It was initially used in food and plastic industry but has attracted significant interest in pharmaceutical manufacturing for the development of robust formulations. Extrusion Spheronization can be used to develop various formulations such as sustained release Pellets [16,17]. It has been also introduced for taste masking purposes of bitter APIs by involving the use of taste masking polymers that prevent bitter drugs from coming in contact with the patient's taste buds [18].

Pellets are agglomerates of fine powders or granules of bulk drugs and excipients. They consist of small, free flowing spherical or semispherical solid units typically from about 0.5-2mm [19]. These are intended usually for oral administration. These are spheres of varying diameter depending on the application and the wish of the producer. Pellets are prepared using different technologies such as layering of the drug solution, suspension or powder on the inactive cores, extrusion, spheronization and agglomeration in roto-granulators or roto processors, compression, spray drying and spray congealing [20].

MATERIALS AND METHODS:

The plant material was purchased from Shivshankar Ayurvedic Agency Nagpur, Maharashtra, India. Eudragit

L-100-55 was purchased from Vikram Drugcoat. MCC PH 102 was purchased from Alka scientific Company. Triethyl citrate and PVP K-30 was purchased from Himedia Laboratories Pvt. Ltd. Mumbai, Maharashtra, India. All other reagents and chemicals were used of analytical grades and procured from authorized dealer.

Procedure for extraction:

Aerial parts of Shankhpushpi were shade dried at room temperature. The shade dried plant material was coarsely powdered and subjected to extraction by maceration method. In the extraction process, the 250 g of powdered material of the shankhpushpi was macerated with 500 ml of distilled water for 15 days. After complete extraction, the macerated material was filtered through the muslin cloth and concentrated on water bath.

Physical evaluation of Papaya extracts [20,21]:

The extract of papaya in powder for was evaluated for loss on drying, Ash value and Bitter calculation as per standard prescribed procedure of Pharmacopeia specification.

Phytochemical screening of papaya extracts [22]:

The extracts of papaya in powder for was evaluated for Alkaloids, Tannins, Amino acids, Proteins, Glycosides, Carbohydrates, Flavonoids, Phenols, Saponins, Phytosterols, Triterpenoids, Phlobatannins, Quinones and Oxalates.

UV spectrophotometric study on the drug preparing the tincture [23]:

Appropriate quantity of extract was dissolved in 100 ml distilled water and the resultant tincture was studied under UV-Visible Spectrophotometer.

Anthelmintic activity of extracts:

The *in vitro* anthelmintic activity of aqueous Shankhpushpi extract was evaluated on adult earthworms (*Pheretima posthuma)* as it is having anatomical and physiological resemblance with the intestinal round worm parasites of human beings. Earthworms were collected from moist soil and washed with normal water to remove all faecal matter were used for the anthelmintic study. The earthworms of 3-5 cm in length and 0.1-0.2 cm in width were used for all the experimental protocol [25]. While the cattle worms were collected from the cow dung and washed with normal water. The cattle worms of 0.5-1 cm in length were used for all experimental protocol [24-26]. Albendazole Tablet (Zim Laboratories) was used as standard anthelmintic drug during the experimental protocol. Seven groups were divided for both *P. posthuma* (n – 6). The group 1, 2, 3, 4, 5, 6 and 8 were treated with normal control; standard control (Albendazole 16 mg/ ml), extracts dose of aq. Shankhpushpi (0.02, 0.04, 0.08 and 0.1 ml/ ml) and marketed albendazole tablet (Albendazole 16 mg/ ml). Test samples of the extract were prepared in distilled water and worms of approximately equal size were placed in each nine cm petridish containing 25 ml of above test solution of extract. All the test solution and standard drug solution were prepared freshly before starting the experiments. Observations were made for the time taken for paralysis of individual worm. Time for death of worms were recorded after ascertaining that worms neither moved when shaken vigorously nor when dipped in warm water.

Pellet formulations of shankhpushpi extract:

Oral formulations are one of the most widely used and accepted dosage forms in medicine especially in herbal formulations. Considering its convenience and ability to mask unpleasant taste and odour of herbal extracts, pellet formulation is selected. Shankhpushpi exhibiting significant pharmacological anthelmintic activity were selected and formulated into oral pellets. Pellets were prepared by extrusion spheronization method. In pellet formulation triethyl citrate used as plasticizer, Polyvinyl Pyrrolidone (PVP) as binder and Eudragit L 100-55 as Coating Polymer [27].

Table 1. Formulation composition of pellets by taste masking method.

Ingra dients	Pellet composition (% w/w)		
	SP/I-01	SP/I-02	SP/I-03
Drug (ml)	25 g of pellets contain 12.5 ml liquid Extract		
MCC (%)	50	40	45
EGL (%)	44	54	49
TEC (%)	11	11	11
PVP (%)	2	2	2
DW	q. s.	q. s.	q. s.

MCC – Microcrystalline cellulose, EDL – Eudragit, TEC – Triethyl citrate (Used 11 % of eudragit, PVP – Poly vinyl pyrrolidone, DW – Distilled water and q.s. – Quantity sufficient.

Taste masks formulations:

In the initial formulation study the pellets containing Eudragit and MCC in different ratio was prepared (SP/

01 to SP/03) as given in Table 1. Amongst the various ratio, the formulation SP/I- 02 was found to be suitable for further studies as it satisfy the properties of good pellets. SP/I-02 formulation was considered constant and the Shankhpushpi extract load was varied to prepare formulations SP/I-02a to SP/I-02d (Table 1 and 2). The extract was adsorbed in the MCC for 10 min. Then extract adsorbed MCC and Eudragit L 100-55 were mixed in a mortar pestle for 5 min. Triethyl citrate was added as a plasticizer, and the resultant mixture was triturated in a mortar for 5 min. Polyvinylpyrrolidone (PVP K-30) as a binder were added and mixed for 10 min in a mortar pestle. This mixture was granulated with distilled water in a mortar. To ensure uniform distribution of water during wetting phase, the material was repeatedly scrapped from the mixing mortar walls and later extruded at a screw speed of 40 rpm using a single screw extruder. Spheronization was carried out for 5 min at 550 rpm, followed by 15 min at 850 rpm. During the first 5 min period, 5% w/w of the total batch-size MCC PH 101 was sprinkled over the rotating extrudates to prevent the pellets from sticking. Pellets obtained were dried on tray dryer at 50 ^{0}C for 2 h.

Table 2. Formulation of pellets by taste masking method with different drug loading.

Ingradients	Pellet composition with different drug (Extract) loading (% v/w)			
	SP/02a	SP/02 b	SP/02 c	SP/02 d
Drug (ml)	5	10	12.5	15 m
MCC (%)	40	40	40	40
EGL (%)	54	54	54	54
TEC (%)	11	11	11	11
PVP (%)	2	2	2	2
DW	q. s.	q. s.	q. s.	q. s.

MCC – Microcrystalline cellulose, EDL – Eudragit, TEC – Triethyl citrate (Used 11 % of eudragit, PVP – Poly vinyl pyrrolidone, DW – Distilled water and q.s. – Quantity sufficient.

Characterisation of Pellets [26-28]:

In order to meet the requirements of pellet yield, size distribution, surface area, shape, surface roughness, density and friability, including the reproducibility of morphologic properties of the pellets, pellets were tested.

Pellet yield:

The coated pellets (20 g) were sieved for 5 min on sieve shaker equipped with series of sieves of pore opening as 1400, 1000, 710, 500 and 250 µm sieves (Sieve No. 12, 16, 22, 30 and 60 respectively). The pellet yield was calculated based on the pellet fraction between 710 and 1400 µm and presented as a percentage of the total pellet weight. This size fraction was used for all further measurements.

Size analysis:

The size of pellets was determined by sieving analysis. The average diameter is calculated using the equation;

Avg. Diameter = [Σ(% R)×(MA)]/100 …….. (1)

Where, R is retained and MA is mean aperture.

Shape analysis:

At least 20 pellets from each batch were randomly selected for shape analysis from fraction obtained after size analysis by sieving. The pellets were mounted on a surface of motic microscope, and the images of the pellets were captured. The area of the images and the maximum and minimum radii were calculated, and from these the various shape factors were calculated.

Flow properties:

The flow properties of prepared pellets was determined by calculating bulk density, true density, Hausner's ratio, Carr's Index and angle of repose.

Pellet Friability test:

The friability of pellets was determined by using Roche Friabilator. About 10 g of pellets (Fs) was placed in friability test apparatus together with 20 glass beads. The sample was subjected to falling shocks for 4 min at a rotational speed of 25 rpm and fines collected by sieving through 250 µm meshes. The weight difference was obtained and percentage loss was calculated.

Evaluation of taste masking of Papaya seed extract:

Gustatory sensation test for taste masking:

The gustatory sensation test was carried out in six healthy male volunteers. The taste masking efficiency of the used methods were analysed by gustatory sensation test where the level of taste masking was rated using a Hedonic Rating Scale for taste perception.

Taste masking test using dissolution method:

The pellet formulations SP/I-02 c and SP-09 were subjected to micro-dissolution method, using 20 ml of pH 6.8 phosphate buffer as a dissolution medium maintained at 37±1 ^{0}C. The stirring speed was kept

constant at 50 rpm. At predetermined intervals of study (1 to 5 min), 1 ml of sample was withdrawn and after every withdrawal 1ml of fresh dissolution medium was replaced. The samples were analysed either spectrophotometrically at 190-700 nm or was spotted for TLC analysis.

Table 3. Anthelmintic activity of Shankhpushpi extracts.

Sl. No.	Drug	Dose	*P. posthuma*	
			PT (min)	DT (min)
1	Control	-	-	-
2	ABZ	16 mg/ml	189.33	371.50
3	AE	0.02 ml/ml	255.30	442.50
		0.04 ml/ml	223.20	408.25
		0.08 ml/ml	198.54	385.51
		0.1 ml/ml	182.35	372.12
4	MAT	16 mg/ml	191.5	397.25

ABZ –Albendazole, AE – Aq. Extract and MAT – Marketed albendazole tablet.

Table 4. Evaluation results of taste masked pellet formulations.

FC	BD (X±S.D.)	TD (X±S.D.)	HR	CI
SP/I-01	0.70±0.10	0.784±0.08	1.11	10.6
SP/I-02	0.64±0.07	0.727±0.07	1.12	11.3
SP/I-03	0.69±0.07	0.769±0.11	1.11	10.4
SP/I-02a	0.63±0.09	0.701±0.04	1.10	9.5
SP/I-02b	0.67±0.11	0.740±0.08	1.09	8.5
SP/I-02c	0.64±0.07	0.727±0.07	1.12	11.3
SP/I-02d	0.69±0.09	0.754±0.05	1.09	8.6

Values are expresses as mean ± standard deviation (n = 3). FC – Formulation code, BD – Bulk density, TD – Tapped density, HR – Hausner ratio and CI – Carr's index.

Thin Layer Chromatography [28].

The extract was tested by thin-layer chromatography (TLC). Normal phase analytical TLC was performed on 3×5 cm silica gel (0.5 mm thickness) coated glass plates activated at 100-105 ^{0}C for 1 hr. Aq. Extract of shankhpushpi (as reference) was applied to the chromatographic plate (Silica gel G, Merck) beside the dissolution sample taken at the end of 5 min. The plates were eluted in solvent system Toluene: Ethanol (7: 3). The eluted plates were air dried and developed using vanillin: sulphuric acid (1g: 100 ml) reagent followed by heating at 100 °C for 10 min. The compounds were deleted by the characteristic colours of the spots and R_f values.

Table 5. Evaluation results of taste masked pellet formulations.

FC	AOR (°) (X±S.D.)	FBT (%)	AD («m)
SP/I -01	27.87±0.59	0.72	712.56
SP/I -02	26.98±0.62	0.64	740.32
SP/I -03	27.36±0.64	0.69	705.36
SP/I -02a	27.19±0.91	0.76	751.54
SP/I -02b	27.45±0.84	0.81	709.89
SP/I -02c	26.98±0.62	0.64	740.32
SP/I -02d	28.02±0.71	0.86	698.78

Values are expresses as mean ± standard deviation (n = 3). FC – Formulation code, AOR – Angle of Repose, FBD – Friability and AD – Avg. diameter.

Sectrophotometric evaluation (UV analysis):

The extract was tested by Spectrophotometric evaluation (UV analysis). The dissolution sample at predetermined interval of study (1 to 5 min), after every withdrawal the samples were analysed spectrophotometrically at 190-700 nm.

In vitro dissolution study of pelletst:

The ability of the enteric coated pellets of Shankhpushpi extract (SP/I-02 to remain intact and to release the active ingredient in the physiological environment of intestine was assessed by conducting *in vitro* drug release studies under conditions mimicking mouth to intestine. The drug release studies were carried out using USP standard dissolution apparatus-II (basket method) at stirring speed of 50 rpm at 37±1 ^{0}C in 900 ml of dissolution medium. Initially the pH of dissolution was kept 1.2 for 2 h using 0.1M HCl acid as the average gastric emptying time was estimated at 2 h. After 2 h, the pH of dissolution medium was adjusted to 6.8 using 1M NaOH solution and dissolution was continued. At predetermined intervals of study, 1 ml of sample was withdrawn at periodic

intervals and it was made up to 10 ml with buffer solution. After every withdrawal 1ml of fresh dissolution medium was replaced. The samples were analysed spectrophotometrically at 248 nm. The dissolution experiments were conducted in triplicate and the means of the absorbance were calculated.

Table 6. Anthelmintic activity of bitter herb pellet formulations.

Groups	Dose mg/ml	*P. posthuma*	
		PT (min)	DT (min)
DW	-	-	-
ABZ	16	189.33	371.50
SP/I–01	500	202.45	399.00
	600	195.23	368.25
SP/I–02	500	191.20	375.5
	600	183.52	364.2
SP/I–03	500	235.58	412.36
	600	209.00	398.30

DW- Distilled water, ABZ –Albendazole and MAT – Marketed albendazole tablet. Pellets dose are expressed as mg of pellets/ 25 ml.

Anthelmintic screening of formulations:

For screening of anthelmintic activity, 500 mg of pellets (containing Shankhpushpi extract) were crushed and to it 25 ml of distilled water was added. This mixture was added into a petridish containing 6 equal size earthworms of 3-5 cm in length and 0.1-0.2 cm in width to observe the paralysis and death time. Four groups were divided for both *P. posthuma* (n – 6). The group 1, 2, 3 and 4 were treated with normal control; standard control (Albendazole 16 mg/ 25 ml), SP/I-02 of 500 and 600 mg pellets/ 25 ml respectively.

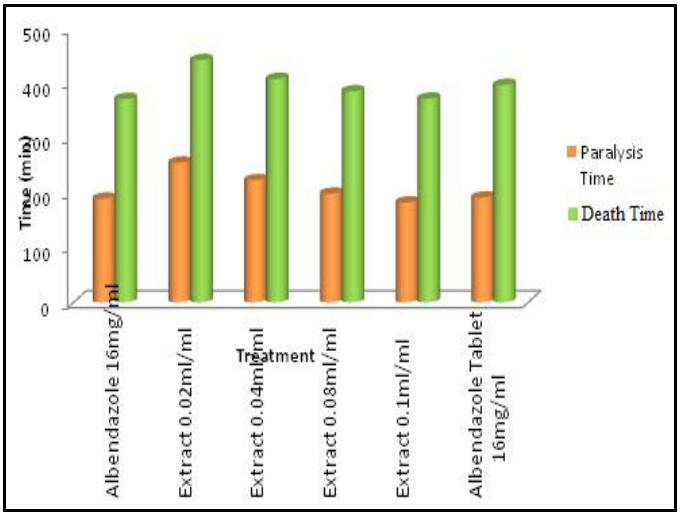

Fig 1. Anthelmintic activity of Shankhpushpi extract.

RESULT AND DISCUSSION:

The physical evaluation result of papaya extract showed that the loss on drying, ash values and total bitter were 3.23, 8.63 and 3.61 % respectively. The Shankhpushpi extract contained Alkaloids, Tannins, amino acids, Proteins, Carbohydrates, Flavonoids, Phenols, phytosterol and Saponins as phytochemicals.

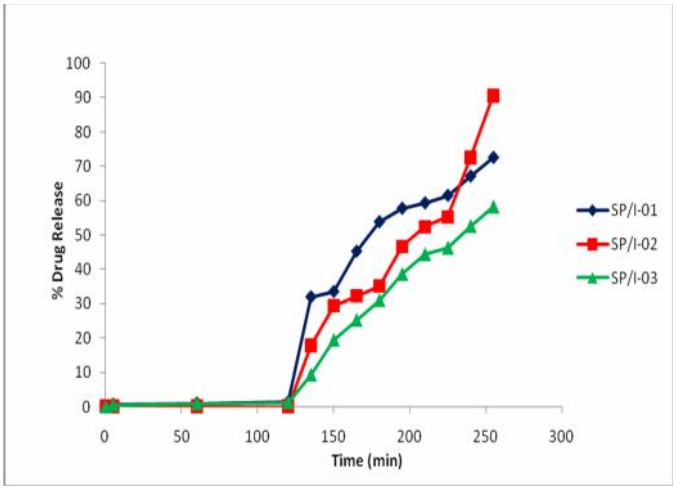

Fig 2. The percentage release of Shankhpushpi extract pellet formulations.

The UV spectrophotometric study showed that a very dilute solution of shankhpushpi extract in water (about 50 µg/ml) shows absorption maxima at 248 nm. The Anthelmintic activity was carried out and compared with standard drug Albendazole. On screening of prepared extract, the anthelmintic activity was observed on 0.1ml/ml as similar to the activity as that of Albendazole. The anthelmintic effect of aqueous extract of shankhpushpi on the survival of earthworms (Table 3) was time and dose dependent. The higher doses of extract resulted in an early onset of activity and higher number of death of earthworms occurred compared with lower doses (Fig 1). The aqueous extract of shankhpushpi at 10 mg/ml exhibited paralysis of earthworms on 182.35 min after exposure and death on 372.12 min of exposure. All the earthworms exposed to Albendazole solution were found to be paralyzed at 189.33 min and their death at 371.5 min (Fig 1), whereas, none of the earthworms was found dead or paralyzed in distilled water and the solution of marketed tablet of Albendazole also exhibited significant activity. The aqueous extract was selected for further experiment because its total bitter value was more and optimum anthelmintic activity. All pellet formulations were prepared using aq. extract. Almost all pellet formulations exhibited good flow properties (Table 4 and 5). The

Shankhpushpi extract pellet formulations showed minimum size and good friability (Table 5). The taste perception studies revealed that the rating of pellet formulations SP/I-01 to 03, SP/I-02a to 02d were 5, 6, 4, 6, 6, 6 and 5 respectively. In the taste masking pellet composition SP/I-02 was efficiently taste masked based on values. Chromatographic (TLC) evaluation of extracts showed no spot for sample, where as reference shows two spot having different R_f values. The chromatographic evaluation shows that the Pellet formulation was taste masked since no bitter was released within 5 min period.

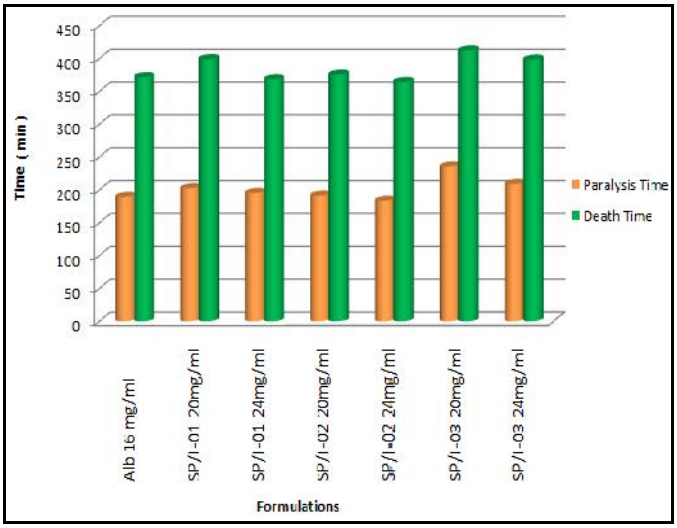

Fig 3. Anthelmintic activity of bitter herb pellet formulations.

The pellets were subjected to micro-dissolution test and the absorption spectrum of taste masking pellet formulation does not show any absorbance it may be concluded that the bitter taste would be masked *in vivo*. The *in vitro* dissolution study resulted that the percentage of shankhpushpi extract released for first 2 h from the above formulations in pH 6.8 and pH 1.2 was negligible. In the pH 6.8 drugs started to release from all the batches of pellet formulations. The total amount of drug release from SP/I-01, SP/I-02 and SP/I-03 was found to be 72.65, 90.68 and 58.24 % after 255 min respectively. The maximum percentage of drug release was observed from formulation SP/I – 02 (Fig 2). The results of the dissolution studies indicates that the optimized pellet formulation SP/I – 02 has better dissolution profile as compared to SP/I-01 and Sp/I-03. Anthelmintic activity of formulation and comparison with standard (Albendazole) indicated that, optimized formulation exhibited comparable and significant activity (Table 6). From the study it can be concluded that, the taste masking formulation SP/I-02 showed highest activity (Fig 3).

CONCLUSION

Based on dissolution and the chromatographic data, the taste masking efficiency of pellets was found to be satisfactory. The Shankhpushpi seed extract pellet exhibited significant anthelmintic activity with good commercial properties. The pellet formulation SP/I – 02 had better dissolution and taste masking profile. Thus Shankhpushpi pellet could be use for safe and successful management of worm infection in child. Shankhpushpi pellets were proposed as alternatives to tablets breaking, as they offer more flexibility for dose adaptation to a child's body weight.

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