

FORMULATION, DEVELOPMENT AND EVALUATION OF *PANDANUS ODORATISSIMUS* EXTRACT CAPSULES DELIVERY SYSTEM AS AN ADVANCED PHYTOTHERAPY APPROACH FOR HEPATOPROTECTIVE**Prof. Dr. Mahmoud Mahyoub Alburyhi^{1*} and Prof. Dr. Amina El-Shaibany²**¹Professor Dr. of Pharmaceutics and Industrial Pharmacy, Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Sana'a University, Sana'a, Yemen.²Professor Dr. of Pharmacognosy, Department of Pharmacognosy, Faculty of Pharmacy, Sana'a University, Sana'a, Yemen.***Corresponding Author: Prof. Dr. Mahmoud Mahyoub Alburyhi**Professor Dr. of Pharmaceutics and Industrial Pharmacy, Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Sana'a University, Sana'a, Yemen. **Email ID:** alburyhi2020@gmail.com

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ABSTRACT

The *Pandanus Odoratissimus* is medicinal plant widely distributed in Yemen; the objective of the present study was to prepare the methanolic extract of *Pandanus Odoratissimus* flowers as capsules delivery system which used for hepatoprotective activity. Use of medicinal plants and their products are almost doubled over the last decade in developing countries and the present trend of wide spread interest in alternative therapies is well known. *Pandanus Odoratissimus* is used in traditional systems of medicine to hepatoprotective activity. It was concluded that among the all formulations the formulation F2 is the best results of *Pandanus Odoratissimus* extract medicinal herbs capsules delivery system as an advanced phytotherapy approach for hepatoprotective according to the drug release was found to be 82% within 60 minutes.

KEYWORDS: *Pandanus Odoratissimus*, Extract, Capsules, Medicinal herbs, Hepatoprotective activity, Phytotherapy.**INTRODUCTION**

Herbal medicine is the oldest form of health care known to mankind. It is an integral part of the development of modern civilization. The World Health Organization estimates that in some Asian and African countries 80% of the population depend on traditional medicine for primary health care; in many developed countries, 70% to 80% of the population has used some form of alternative or complementary medicine. The WHO recognizes the value of plant medicines in health care delivery and endorses the use of those which have been scientifically proven to be efficacious, safe for use and of good quality. Herbal medicines are in great demand in the developed world for primary health care because of their efficacy, safety and lesser side effects. A detailed investigation and documentation of plants used in health traditions and pharmacological evaluation of these plants and their taxonomical relatives can lead to the development of invaluable plant-based drugs for many dreaded diseases. A large number of plants and purified natural substances have been screened for liver disorders. *Pandanus Odoratissimus L.* is found widely forming thickets along roadsides, borders of agricultural fields, river banks and canals and on the seashore.^[1-4]

Previous studies showed that the herbal medicine plant-based formulations are used to alleviate the diseases. But the most important challenges faced by these formulations arise because of their lack of complete evaluation. So, evaluation is necessary to ensure quality and purity of the herbal product. The aqueous and methanolic extracts of *Pandanus Odoratissimus* were tested for hepatoprotective activity in carbon tetrachloride (CCl₄) induced liver damage of albino rats. Aqueous extract of *Pandanus Odoratissimus L.* is reported to possess promising activity as compared to methanolic extract.^[5-14]

***Pandanus Odoratissimus*^[9-30]**

Pandanus Odoratissimus is medicinal plant widely distributed in Yemen, as shown in Figure 1. The plant *Pandanus Odoratissimus* (synonyms: *Pandanus fascicularis Lam.*), belongs to the family Pandanaceae, *Pandanus Odoratissimus L.* known as Kathi in the South-West Asia (Yemen) and in the South of Arabic peninsular in Aseer and Theeffar. In Yemen Kathi is found widely in AL-Hodeidah (Tehama, Surdud Valley, Bura Valley), Taiz (Albarh, Alhujjareah), Abyan, and Lahaj. *Pandanus Odoratissimus L.* is a stout, branching, often multi-stemmed, large shrub or small tree (2-4), (14-

18) m in height, with about the same canopy spread. Plants of spiny trunks. Wild seedling - derived plants often have a single bole or trunk for 4-8m before forking. Maximum stem diameter is 12-25 cm. In Yemeni traditional medicine, the fresh floral axis (peduncle) is used to treat *Nocturnal Enuresis* in children. The Anti-diuretic activity of Aqueous and Ethanolic extracts of prop roots of *Pandanus Fascicularis Lam.* It was studied and found that the Ethanolic extract of prop roots of *Pandanus Fascicularis* has beneficial effects as anti-diuretic activity for treatment of polyuria in diabetes Insipidus. *Pandanus Odoratissimus L* peduncle showed no toxic effect with a predicted lethal dose >16g/kg. The findings indicate the peduncle extracts increase the capacity of the bladder which is an indicator of muscle relaxation with no direct effect on the muscle of dissected bladders. The methanolic extract of the peduncle decrease the urine volume both at 24hrs. and days) with no effect on its electrolytes.



Fig. 1: *Pandanus Odoratissimus* Flowers.

Liver Disorders^[31-42]

Liver Disorders One way to classify liver disorders is by their duration. A chronic disorder lasts for more than 6 months; a subacute disorder lasts for 3 to 6 months; while an acute disorder occurs over a period less than 3 months. A very severe disorder that leads to liver failure within 6 weeks is termed fulminant. Hepatitis: Hepatitis (plural hepatitis) is a medical condition defined by the inflammation of the liver and characterized by the presence of inflammatory cells in the tissue of the organ. The condition can be self-limiting (healing on its own) or can progress to fibrosis (scarring) and cirrhosis.

Liver Cirrhosis: The term cirrhosis is used to describe the orange or tawny surface of the liver. Chronic hepatitis C infection can lead to liver damage through the development of fibrosis (scarring) tissue in the liver. After years or decades of infection liver fibrosis can become so extensive that the architecture of the liver is altered as a result of excessive scarring, development of small nodules, and changes in liver tissue this is called cirrhosis. As cirrhosis further develops, scar tissue replaces healthy liver cells and the ability of the liver to perform its many functions is impaired.

Jaundice Is yellowing of the skin, eyes, and other tissues due to excess circulating bilirubin. Fatty liver Fatty liver is the accumulation of lipid within hepatocytes. It is the commonest cause of elevated liver enzymes. Some

patients will have excess alcohol intake as the underlying cause but there are a significant and growing number of patients with non-alcohol-related fatty liver. Non-alcoholic fatty liver disease, (NAFLD) is a term used for a group of inter-related chronic liver disorders causing a wide spectrum of liver damage associated with increased fat content in the liver in the absence of increased alcohol intake. The spectrum of potentially progressive liver damage can include: Simple (hepatic) steatosis (fatty accumulation in the liver, also known as fatty liver) NASH, advanced fibrosis, cirrhosis, hepatocellular carcinoma (HCC), hepatoma and liver cancer. The term 'NASH' is sometimes used to describe the three subsequent stages after hepatic Steatosis. Non-alcoholic fatty liver disease (NAFLD) comprises a morphological spectrum of liver lesions, closely resembling those seen in alcoholic liver disease (ALD), but developing in individuals who do not consume excessive amounts of alcohol.

Liver is the most important organ where drugs are structurally altered; resulting biologically inactive or active metabolites and some of these are toxic. Liver diseases are mainly caused by toxic chemicals, excess consumption of alcohol, infections and autoimmune disorder. Most of the hepatotoxic chemicals damage liver cells mainly by lipid peroxidation and other oxidative damages. Liver is also exposed to drugs in higher concentration as whole of the drug pass through liver to reach systemic circulation. Thus, the liver is a vulnerable target of injury from various chemicals and drugs and disordered hepatic function is an important cause of abnormal drug handling. If not treated early such injuries can lead to chronic liver disorders. A number of herbal formulations have been claimed to be effective in managing liver disorders. To enhance the acceptability of the Herbal Medicine by consumers, many of the herbs have been converted into conventional dosage forms such as tablets, capsules, suspensions, solutions and powders. So, it is necessary to formulate the medicinal product into the dosage forms that are practical to use in order to gain the patient compliance and to meet the prescribed medicine delivery requirement while manufacturing is capable. These criteria are the challenge for most researcher and formulation scientist.^[5-14]

Capsules are the common dosage form considered for many oral drugs that perceive good patient compliance and more simply to manufacture with less cost compare to the manufacturing of tablet. There is a considerable need to dry the extracted plant prior to the capsule filling process in order to eliminate the moisture content. Thus, drying of the extracted plant to obtain semisolid powder, a free flowing, nonadherent, crumbly look powder form of semisolid medication, is a challenging option.

In the present study the *Pandanus Odoratissimus* flowers freeze -dried extract powder solid dosage form capsules

delivery system was prepared and evaluated as an advanced phytotherapy approach for hepatoprotective.

MATERIALS AND METHODS

Pandanus Odoratissimus flowers extract prepared and gift from (Prof Dr. Amina El-Shaibany, Professor Dr. of Pharmacognosy, Department of Pharmacognosy, Faculty of Pharmacy, Sana'a University, Sana'a, Yemen). Hard Gelatin Capsules (Size 00), Crospovidone, Microcrystalline Cellulose, Magnesium Stearate, Methyl Paraben, Sodium Starch Glycolate, 0.1N HCl Buffer, Potassium Dihydrogen, Disodium Hydrogen Phosphate and Sodium Hydroxide, gift from (Shaphaco Pharmaceutical Industry Company-Yemen).

Formulation and Evaluation of *Pandanus Odoratissimus* Extract^[43-71] Determination of The Organoleptic Properties of Extract

The following organoleptic properties of the extract were

assessed: physical appearance, odor and taste. For these samples of *Pandanus Odoratissimus* extract was inspected and assessed using the natural senses (e.g. eyes, nose, mouth).

Determination of The Solubility of Extract

The solubility of a substance fundamentally depends on the solvent used as well as on temperature and pressure. The extent of solubility of a substance in a specific solvent is measured as the saturation concentration where adding more solute does not increase its concentration in the solution. Oral ingestion is the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, cost-effectiveness, and flexibility in the design of dosage form. As a result, many of the generic drug companies are inclined more to produce bioequivalent oral drug products. So, the solubility application according to standard parameters of solubility as shown in Table 1.

Table 1: Standard Parameters of The Solubility.

Description	Part of The Solvent Required Per Part of Solute
Very Soluble	Less than 1
Freely Soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly Soluble	From 30 to 100
Slightly Soluble	From 100 to 1000
Very Slightly Soluble	From 1000 to 10,000
Practically Insoluble	More than 10,000

Determination of The Density of Extract

Preformulation parameters like bulk density, tap density, carr's index, and angle of repose. A known quantity of powder was poured into the measuring cylinder carefully level the powder without compacting, if necessary and read the unsettled apparent volume, V_o , to the nearest graduated unit as shown in Table 2.

Calculate the bulk density, in gm per ml, by the formula.

Bulk density = Bulk Mass/ Bulk Volume

Carr's compressibility index:

Carr's index (%) = (Tapped density - Poured density) / Tapped density

Table 2: Carr's Index of Powder Flowability.

Carr's Index%	Type of Flow
5 -15	Excellent
12 - 16	Good
18 - 21	Fair to Passable
23 - 35	Poor
33 - 38	Very Poor
>40	Extremely Poor

Formulation of *Pandanus Odoratissimus* Extract Capsules^[43-71]

A uniform powder is obtained by mixing the *Pandanus Odoratissimus* extract of with the appropriate adsorbent microcrystalline cellulose, disintegrate as sodium starch glycolate, crospovidone, lubricant as mg stearate, and preservative as methyl paraben, the materials filled into the capsules as shown in Table 3.

Table 3: Composition of *Pandanus Odoratissimus* Extract Capsules.

Ingredients	Quantity Per Capsule (mg)		
	Formulation Code		
	F1	F2	F3
<i>Pandanus Odoratissimus</i> Extract	50%	50%	50%
Crospovidone	10%	---	5%
Sodium Starch Glycolate	5%	15%	10%
Avicel PH102	33.9%	33.9%	33.9%

Magnesium Stearate	1%	1%	1%
Methyl Paraben	0.1%	0.1%	0.1%

Evaluation of *Pandanus Odoratissimus* Extract Capsules^[43-71]

Determination of Moisture Content of *Pandanus Odoratissimus* Extract

There are numerous methods for water content analysis (e.g. oven method, infrared drying method, microwave drying method, titration methods, chemical extraction of water, refraction method, and electrolytic method, etc.). For this study, the shell of the capsules was removed and the moisture level of the contents of the capsules determined by using the moisture content analyzer.

The Organoleptic Properties of *Pandanus Odoratissimus* Extract

The manufactured *Pandanus odoratissimus* capsules were stored at room temperature, 4 weeks storage period and every week, samples of capsules were taken from each site and assessed for organoleptic properties (i.e. gross physical nature, color and odor of the powder content and overall size, shape and appearance of the capsules).

Determination of Uniformity of Weight and The Amount of *Pandanus Odoratissimus* Extract Capsules

For the determination of the uniformity of weight, the British Pharmacopoeia method was used. Twenty of the *Pandanus Odoratissimus* capsules prepared were taken at random, their contents individually weighed and the average weight (mass) of the content determined. Not more than two of the individual weights (masses) had to deviate from the average weight (mass) by more than 7.5% and none of the deviates by more than twice that percentage. The amount of powder actually filled into the capsules was also compared with the desired quantity and the difference between the desired and actual quantity calculated. The formulation, 500mg of *Pandanus Odoratissimus* extract was to be filled in one capsule. Twenty capsules were thus randomly chosen, their contents weighed, the percentage difference between this and the desired weight calculated and averaged for the 20 capsules to assess the accuracy of the filling process.

In-Vitro Dissolution Studies of *Pandanus Odoratissimus* Extract Capsules

The dissolution test measures the rate at which a drug is released into solution from a dosage form and is used as an indication of the bioavailability of a pharmaceutical product and of product quality. In this study the paddle method was used. The quantitation of the amount of extract dissolved was measured based on UV absorbance measured at 410nm, the wavelengths for maximum UV absorbance of solutions of the *Pandanus Odoratissimus* extract determined by using a UV-Vis Spectrophotometer. For the dissolution study the following requirements and procedure were used:

Apparatus: Paddle. Medium: 0.1N HCl. Volume of medium: 900ml. Temperature: 37±0.5°C. Rotation speed: 50 rpm. Dissolution time: 15, 30, 45, and 60 minutes.

RESULTS AND DISCUSSION

The Organoleptic Properties of The Freeze -Dried of *Pandanus Odoratissimus* Extract

As shown in Table 4, the organoleptic properties of the freeze -dried extract.

Table 4: The Organoleptic Properties of *Pandanus Odoratissimus* Extract.

Proprieties	<i>Pandanus Odoratissimus</i> Extract
Physical Appearance	Free-Flowing, Small Particulate Powder
Taste	Bitter
Odor	Honey Odor

The Solubility of The Freeze -Dried of *Pandanus Odoratissimus* Extract

The results obtained in the solubility testing of the extract *Pandanus Odoratissimus* show that the extract is soluble in water as shown in Table 5.

Table 5: The Solubility Evaluation in Different pH.

Type of Solvent	Solubility of Extract
Water	Soluble
HCl (0.1N)	Very Soluble
NaOH (0.1N)	Freely Soluble

The Flowability of *Pandanus Odoratissimus* Extract

The *Pandanus Odoratissimus* extract powders have angles of repose is 11.9° and the carr's index of compressibility for *Pandanus Odoratissimus* extract is 13.3% can be categorized as having excellent flow properties this implicated that the *Pandanus Odoratissimus* extract powders possessed appropriate flowability for the manufacture of capsule dosage form as shown in Table 7.

Moisture Content of *Pandanus Odoratissimus* Extract

Moisture content is an important parameter for capsule dosage form and it is also important for herbal medicines, which are hygroscopic. The percentage of moisture content of *Pandanus Odoratissimus* was 3.17 % as shown in Table 6.

Table 6: The Results of Evaluation Parameters of *Pandanus Odoratissimus* Extract.

Test	<i>Pandanus Odoratissimus</i> Extract
Drying	Freeze Dryer System
The Solubility of Extract(g/ml)	19.75g/10ml of Water
Carr's Index%	13.3%
Angle of Repose	11.9°
Particle size	0.16mm
Percentage of Moisture Content	3.17%

The Microbial Contamination Testing of *Pandanus Odoratissimus* Extract

The results of the microbial contamination of the extract are shown in Table 7, it was found to be no growth.

Table 7: The Results of Microbial Contamination Testing of *Pandanus Odoratissimus* Extract.

Sample Type	Environments	Test Type	Bact. Count
<i>Pandanus Odoratissimus</i>	CLED Environment	Escherichia coli	No Growth
		Salmonella	No Growth
		Enterobacteriaceae	No Growth
		Yeast & Mould	No Growth
	Chocolate Environment	Escherichia Coli	No Growth
		Salmonella	No Growth
		Enterobacteriaceae	No Growth
		Yeast & Mould	No Growth
	Blood Environment	Escherichia Coli	No Growth
		Salmonella	No Growth
		Enterobacteriaceae	No Growth
		Yeast & Mould	No Growth

Evaluation of *Pandanus Odoratissimus* Extract Capsules**The Organoleptic Properties of *Pandanus Odoratissimus* Extract Capsules**

The organoleptic properties during storage of *Pandanus Odoratissimus* capsules at room temperature for over 4 weeks period as shown in Table 8.

Table 8: Organoleptic Properties of Stored *Pandanus Odoratissimus* Extract Capsules.

Week	Size, Shape of Capsule	Powder in Capsule	Color of Powder	Odor of Powder
0	Regular "00" Size & Shape	Powder	Yellowish Brown	No Change
1	No Change	Powder	Yellowish Brown	No Change
2	No Change	Powder	Yellowish Brown	No Change
3	No Change	Powder	Yellowish Brown	No Change
4	No Change	Powder	Yellowish Brown	No Change

Uniformity of Weight and Content of *Pandanus Odoratissimus* Extract Capsules

The results of the uniformity of weight and content of the *Pandanus Odoratissimus* capsules were calculated. The average deviation in weight from average for *Pandanus Odoratissimus* capsules were 0.1% and the average total content per capsule 92.72% within the limit on the acceptable deviation in weight average for capsules is $\pm 7.5\%$ and within the limit on the amount of content in the capsules 90% to 110%. The results indicated that the *Pandanus Odoratissimus* capsules within the limit of British Pharmacopoeia specifications.

In-Vitro Dissolution Studies

The results of *in-vitro* dissolution of formulations in buffer 0.1NHCl at time interval (15, 30, 45 and 60 minutes) by using digital dissolution tester at $(37 \pm 0.5^\circ\text{C})$.

Table 9: The Drug Release Percentage of *Pandanus Odoratissimus* Extract Capsules.

NO	Drug Release %											
	Formulation Code											
	F1				F2				F3			
	Time(min)				Time(min)				Time(min)			
	15	30	45	60	15	30	45	60	15	30	45	60
1	40.5	52.4	58.9	59.9	44.5	52.2	59.9	74.9	40.3	48.4	56.8	57.9
2	45.6	54.8	68.9	68.9	47.6	57.4	68.9	75.8	44.9	50.6	66.9	67.9
3	47.3	56.9	75.4	80.3	48.3	60.2	81.3	80.6	46.3	51.3	68.7	76.3
4	50.6	59.7	79.9	86.7	55.6	63.6	86.7	87.7	49.9	57.2	77.5	82.9
5	55.3	67.9	88.8	94.2	59.3	68.7	94.2	93.9	50.3	57.2	84.7	90.9
Average	47.8	58	74	77	51	60.4	78	82	46.9	54.1	70.9	75

The *in-vitro* dissolution of *Pandanus Odoratissimus* extract capsules is one important of the results of dissolved active ingredient *Pandanus Odoratissimus* extract, as shown in Table 9. The results of formulations have shown that the drug release of F2 was found to be 82% within 60 minutes. In addition, the average drug release of F1, F2 and F3 were found to be 47.8%, 44.5%, 40.3% within 15 minutes. The drug release of F1, F2 and F3 were found to be 58%, 60.4%, 54.1% within 30 minutes. The drug release of F1, F2 and F3 were found to be 74%, 78%, 70.9% within 45 minutes. The drug release of F1, F2 and F3 were found to be 77%, 82%, 75% within 60 minutes. it was concluded that formulation of *Pandanus Odoratissimus* extract capsules F2 can be taken as an optimized capsules for drug release 82% within 60 minutes. So, it was found to be among the all formulations F2 was the best formulation.

CONCLUSION

It was concluded that among the all formulations the formulation F2 is the best results of *Pandanus Odoratissimus* extract medicinal herbs capsules delivery system as an advanced phytotherapy approach for hepatoprotective according to the drug release was found to be 82% within 60 minutes.

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