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Formulation, Characterization and Development of Fast Dissolving Herbal Tablet for Hepatoprotective Activity

Abhishek Sahu*, B. K. Dubey, Deepak Kumar Basedia, Mukesh Kumar Patel and Sunil Shah

Technocrats Institute of Technology Pharmacy, Bhopal, (M.P.) – India

TIT College of Pharmacy, Bhopal, (M.P.) – India

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Abstract

Herbal medications are essential for treating a variety of liver disorders; the majority of them accelerate the liver's natural healing process. Both the Indian traditional medical system and ethnomedical practices use a variety of medicinal plants and their preparations to treat liver diseases. Coarsely ground shade-dried plant materials chosen for their hepatoprotective properties were extracted using several solvent systems in the current investigation. Following concentration, the extracts undergo first physical and phytochemical analysis to determine the type of active ingredients present and to evaluate the quality of the plant material. Numerous phytoconstituents, including glycosides, carbohydrates, proteins, amino acids, sterols, triterpenes, total phenolic compound, flavonoids, and saponin, were found in the results of the phytochemical analysis.

Key Words: Hepatoprotective activity, herbal tablets.

Introduction

In recent times natural products are becoming an integral part of human health care system, because there is a now popular concern over toxicity and side effects of modern drugs. There is also a realization that natural medicines are safer and allopathic drugs are often ineffective in several aliments. Medicinal plants existed even before human being made their appearance on the earth. Man's existence on this earth has been made possible only because of the vital role played by plant kingdom in sustaining his life.

***Corresponding Author**

Materials and Methods

Selection of the plant

The medicinal properties of plants have been investigated in the light of recent scientific developments throughout the world, due to their potent pharmacological activities. As per the information collected the present study dealt with the evaluation of hepatoprotective activity of leaves of Cyathea gigantea.

Collection and authentication of plant material

The leaves of the selected plant were collected from in and around the local area of Pachmarhi village in moist open area at altitude of above 600 m (M. P.) and was identified & authenticated.

Preparation of crude drug for extraction

The selected plant leaves were used for the preparation of the extract. The plants leaves were collected and dried under shade and then coarsely powdered with the help of mechanical grinder. The powder was passed

through sieve No. 40 and stored in an airtight container for the extraction **(Farnsworth et al., 1966).**

Extraction of dried leaves by using various solvents of increasing polarity:

The collected, cleaned and powdered leaves of plant were used for the extraction purpose. 500 gm of powdered material was evenly packed in the soxhlet apparatus. It was then extracted with various solvents from non-polar to polar such as petroleum ether, chloroform, acetone and ethanol. The solvents used were purified before use. The extraction method used was continuous hot percolation and carried out with various solvents, for 72 hrs. The aqueous extraction was carried out by cold-maceration process.

Formulation and Optimization:

Procurement of excipients:

The excipients, chemicals/ reagents and equipments used for various experiments areenlisted as follows:
Croscarmellose Sodium and Crospovidone were purchased from Yarrow chemicals Mumbai, Maharashtra and are of AR grade.

Preparation of Co-processed Superdisintegrants:

The co-processed superdisintegrants were prepared by solvent evaporation method. A blend of crospovidone and croscarmellose sodium (in the ratio of 1:1, 1:2 & 1:3) was added to 10 ml of ethanol. The contents of the beaker (250 ml capacity) were mixed thoroughly and stirring was continued till most of ethanol evaporated. The wet coherent mass was granulated through # 44-mesh sieve. The wet granules were dried in a hot air oven at 60º C for 20 minutes. The dried granules were sifted through # 44-mesh sieve and stored in airtight container till further use**. (Fu, Y et al,2004)**

Precompression Studies:

Various formulations and process variables were involved in mixing of ingredients and all these can affect the properties of the blends produced. Various evaluation parameters of blends tested are given below and data is represented in table.

Bulk densityMethod

The sample under test was screened through sieve no.20, the sample equivalent to 25 gm (50 cm^3) was accurately weighed and filled in a 100 ml graduated cylinder, the powder was leveled and the unsettled volume, V_o was noted.

Tapped DensityMethod

The sample under test was screened through sieve no.20 and the weight of sample equivalent to 25 g was filled in 100 ml graduated cylinder. The mechanical tapping of the cylinder was carried out using tapped density tester at a nominal rate of 300 drops per minute for 500 times initially and the tapped volume V_o was noted. Tapping was proceeding further for an additional tapping 750 times and tapped volume V_b was noted.

Compressibility Index

The bulk density and tapped density was measured and compressibility index was calculated using the formula.

Hausner ratioMethod

Tapped density and bulk density were measured and the Hausner ratio was calculatedusing the formula.

Angle of repose

Angle of repose indicates the frictional forces in a loose powder. It can be defined as the maximum angle between the slope of pile of powder and its base. The Angle of repose was determined using funnel method, designed by Newmann. The blend was poured through a funnel that could be raised vertically until a specified cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose (θ) was calculated using the formula.

Preparation of fast dissolving tablets by direct compression method:

Fast dissolving tablets of herbal extract were prepared by direct compression. All the ingredients (except granular directly compressible excipients) were passed through # 60- mesh separately. Then the ingredients were weighed and mixed in geometrical order. Powder blend was evaluated for bulk density, tapped density, Carr's index and Hauser's ratio. Compressed into tablets of 150mg using 8mm round flat punches on 10-station rotary tablet machine (Clit).(Gohel MC et al,2007)

Table 1: Formula for different batches of Plant extract tablets

Ingredients	CF F1	PM F2	PM F3	PM F4	CP F5	CP F6	CP F7
Plant Extract	200	200	200	200	200	200	200
Mannitol	16	6	6	6	6	6	6
Superdisintegrants (CP+CCS)	-	10	10	10	10	10	10
Aerosil	30	30	30	30	30	30	30
Pre-gelatinised	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Starch							
Menthol	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Magnesium stearate	1.0	1.0	1.0	1.0	1.0	1.0	1.0

PM(F2,F3,F4) - Physical Mixture of crospovidone and croscarmellose sodium in different Ratios (1:1, 1:2, 1:3), CP(F5,F6,F7) -Co-processed Superdisintegrants of crospovidone and croscarmellose sodium in different Ratios (1:1,1:2, 1:3), CF,F1-Control formulation (without superdisintegrants), CP – Crospovidone, CCS –Croscarmellose sodium

Evaluation of Formulated fast dissolving Tablet:

Hardnes:. Hardnes is amount of strength of tablet to withstand mechanical shocks of handling in manufacture, packaging and shipping and tablet should be ableto withstand reasonable abuse when in the hand of consumer. Hardness of tablet was evaluated by **Monsanto hardness tester or Pfizer tester.** Hardness was measured in kg/cm^2 and for tablet it is above 4-6 kg/cm^2.

Friability: This test is applicable to compressed tablets and is intended to determine the physical strength of tablets. It was evaluated by Roche Friabilator with100 revolution rotating 25 per minute for 4 min by using 6 tablets. According to USPtablet should have limit < 1%. for acceptance Following formula was used to calculate the friability.

%F=1- (loss in weight/initial weight)100

Weight variation: Weight variation was calculated as per method describe in USP.20 tablets was weighed individually and the average wias calculated.The requirements are met if the weight of not more then 2 of tablets differ by more then percentage listed in the tablet and no tablets differ by in weight by more then double that percentage.

Table No. 2 Percentage weight variation of tablet (I.P)

S.No	Avg. weight of individual tablet	Limits (%)
1	< 130	10
2	130-324	7.5
3	> 324	5

Disintegration test

Disintegration test was measured using disintegration test apparatus. One tablet was placed in each of the six tubes of disintegration test apparatus.

Thickness variation

Ten tablets from each formulation were taken randomly and their thickness was measuredwith a micrometer screw gauge.

Results and Discussion

Selection of the plant

On the basis of literature review and discussion with the traditional medical practitioners of the Rewa, ujjain and Bhopal (MP), India, leaves of Cyathea gigantean was selected for evaluation of the hepatoprotective activity.

Preliminary Phytochemical Analysis

The phytoconstituents were identified by chemical tests, which showed the presence of various constituents in the different extracts. The results shown that the acetone, ethanol and aqueous extracts of leaves of Cyathea gigantean contain almost same and maximum number of pharmacologically active constituents. The results are shown in **Table . 3.**

Table 3: Preliminary phytochemical studies of various extracts of dried leaves of *Cyathea gigantean*

Sl.No.	Constituents	Tests	Pet.ether extract	CHCl3 extract	Acetone extract	Ethanolic extract	Aqueous extract
1.	CARBOHYDRATES	Molisch's test	-	-	-	+	+
		Fehling's test	-	-	-	+	+
2.	GLYCOSIDES	Legal's test	-	-	-	-	-
		Borntrager's test	-	-	-	-	-
		Baljet test	-	-	-	-	-
3.	FIXED OIL AND FATS	Spot test	+	+	+	-	-
		Saponification test	+	+	+	-	-
		Millon's test	-	+	-	+	+
4.	PROTEINS& AMINO ACIDS	Ninhydrin test	-	+	-	+	+
		Biuret test	-	+	-	+	+
5.	SAPONINS	Foam test	-	-	-	+	+
6.	PHENOLIC COMP. AND TANNINS	FeCl3 test	-	-	+	+	+
		Lead acetate test	-	-	+	+	+
7.	PHYTOSTEROLS	Salkowski test	+	-	+	-	-
		Libermann-bucchardtest	+	-	+	-	--
8.	ALKALOIDS	Dragendorff's test	-	-	-	-	-
		Mayer's test	-	-	-	-	-

		Wagner's test	-	-	-	-	-
		Hager's test	-	-	-	-	-
9.	GUMS&MUCILAGE	Froth test	+	-	-	-	+
		Alcoholic test	+	-	-	-	+
10.	FLAVONOIDS	Lead acetate test	-	-	+	+	+
		Con. H_2SO_4 test	-	-	+	+	+
		$FeCl_3$ test	-	-	+	+	+

Precompression Studies:

Co-processed superdisintegrants were prepared by solvent evaporation using crospovidone and croscarmellose sodium in different ratios (1:1, 1:2. & 1:3). The co- processed superdisintegrants were evaluated for their flow and compression properties in comparison with physical mixture of superdisintegrants. The angle of repose of co- processed superdisintegrants was found to be <25° which indicate excellent flow in comparison to physical mixture of superdisintegrants (>30°) due to granule formation, Carr's index in the range of 10-15% and Hausner's ratio in the range of 1.10-1.14 (Table 4).

Table 4: Pre-compression Parameters of Co-processed Superdisintegrants and Physical Mixture of Superdisintegrants

S. No.	Parameters	Formulation Code					
		PM1	**PM2**	**PM3**	**CP1**	**CP2**	**CP3**
1.	Bulk density (g/cc)	0.38	0.37	0.42	0.23	0.25	0.28
2.	Tappeddensity (g/cc)	0.47	0.43	0.49	0.26	0.27	0.30
3.	Angle ofrepose (degree)	32	30	36	24	26	24
4.	Carr's index (percent)	14	16	14	12	13	11
5.	Hausner'sRatio	1.15	1.15	1.16	1.14	1.12	1.10

Table 5: Pre-compression Parameters of Herbal FDT Formulations to be Prepared by Direct Compression Method

S. No.	Parameters	Formulation Code						
		CP F1	PMF2	PMF3	PMF4	CPF5	CPF6	CPF7
1.	Bulk density (g/cc)	0.56	0.54	0.53	0.54	0.51	0.53	0.52
2.	Tappeddensity (g/cc)	0.61	0.60	0.63	0.63	0.57	0.58	0.59
3.	Angle ofrepose (degree)	31.27	29.21	30.3	29.35	28.83	28.62	28.97
4.	Carr's index (percent)	17	14	13	13	12.3	11.58	12.8
5.	Hausner's Ratio	1.08	1.15	1.14	1.13	1.13	1.12	1.14

Evaluation of Formulated fast dissolving Tablet:
Fast dissolving tablets were prepared using co-processed superdisintegrants and physical mixture of superdisintegrants. Directly compressible mannitol (Pearlitol SD 200) was used as a diluent to enhance mouth feel. A total of six formulations and control formulation CP0 (without superdisintegrant) were designed. As the blends were free flowing (angle of repose $<30^0$ and Carr's index <15% Table 6.8), tablets obtained were of uniform weight (due to uniform die fill), with acceptable variation as per IP specification i.e., below 7.5%. Hardness of the tablets was found to be in the range of 2.96-3.13 kg/cm^2. Friability below 1% was an indication of good mechanical resistance of the tablets. Among all the designed formulations, formulation, CPF5 was found to be promising and displayed an in vitro dispersion time of 22 sec, which facilitates their faster dispersion in the mouth.
Overall, the formulation CPF5 containing 4% w/w of co-processed superdisintegrant (1:1 mixture of crospovidone and croscarmellose sodium) was found to be promising and has shown an in vitro dispersion time of 22 sec, when compared to the formulation PMF2 containing 4% w/w of Physical mixture of superdisintegrant (1:1 mixture of crospovidone and croscarmellose sodium) which shows 36sec, 38 sec and control formulation (CPF1) which shows 99 sec, 106 sec values respectively for the aboveparameters (Table 6).

Table 6: Evaluation of herbal FDT Formulations

Parameters	Formulation Code						
	CP0	PMF2	PM F3	PM F4	CP F5	CP F6	CP F7
Hardness (kg/cm2) * ±SD	2.96±0.05	2.9±0.1	2.83±1.4	3.26±0.05	3.13±0.04	3.23±0.05	3.25±0.03
Thicknes s* (mm)	2.23±0.02	2.17±0.02	2.26±0.05	3.0±0.01	2.11±0.02	2.21±0.01	2.12±0.01

In vitro Dispersion time (s)* ±SD	98±2	36.31±1.52	41.13±0.77	41.36±2.52	22±2	31.33±3.41	39±2.0
Weight Variation(%)	146-159 mg (IP limits ± 7.5%)						

Every year 18,000 people are reported to die due to liver cirrhosis caused by hepatitis. Traditional systems of medicine, especially Ayurveda contains number of preparations for treating liver & GIT disorders. Modern medicine provides only symptomatic relief with side effects in the treatment of liver disease. Herbal drugs,used in Indian System of Medicine are however claimed to be effective and safe in such ailments. Polyherbal preparations are considered safe & effective products consisting of multiple extracts active principles from medicinal plants with additive or synergistic benefit. By considering the above aspects, the present proposal of study is designed for the development and evaluation for effective management of liver diseases using some of the indigenous plants.

In the present study, coarsely powdered shade dried plant materials selected for the hepatoprotective acivity were subjected for extraction with different solvent system. The extracts after concentration is first subjected for preliminary physical and phytochemical investigation to assess the quality of plant material and understand the nature of active constituents present.

Results of phytochemical investigation revealed the presence of various phytoconstituents like glycosides, carbohydrates, proteins, amino acids, sterols, triterpenes, total phenolic compound, flavonoids and saponin.

In the present research work an attempt has been made to optimize, formulate and characterize fast dissolving tablet. Co-processed superdisitegrants consisting of crospovidone and croscarmellose sodium exhibited good flow and compression characteristics.

Cyathea gigantean plant extract tablets containing co-processed superdisintegrants exhibited quick disintegration and improved drug dissolution.. The tablets disintegrated within 60 sec under experimental in vitro laboratory conditions. It can be concluded from the present work that co-processed superdisintegrants of crospovidone and croscarmellose are superior to physical mixture of crospovidone and croscarmellose used in herbal fast dissolving tablets.

Conclusion

The tablets of aqueous extracts of Cyathea gigantea plant is disintegrated within 60 sec under experimental in vitro laboratory conditions.

After thorough analysis of the results obtained from the study, following conclusions were drawn;

- Herbal therapy provides rational means for the treatment of many internal diseases and the plant products are harmless or have least side effects than synthetic drugs.
- Herbal formulations have reached widespread acceptability as therapeutic agents in India and abroad. Some of the indigenous plants available in India found to significant hepatoprotective activity.
- Fast dissolving tablet was prepared and evaluated from these extracts. The result indicated the ability of improving the dissolution profile was increase by using co-processed superdisintegrants of crospovidone and croscarmellose.

It is the given that numerous studies have been demonstrated that SARS-CoV-2 shares many biological features with SARS-Cove, our knowledge of the path physiological mechanisms underlying SARS can be used to understand the disease processes involved in COVID-19. Mechanistically, the interaction between the S protein and ACE2 is likely to have a central role in disease pathogenesis, especially in cardiovascular manifestations of this disease, and this interaction is a potential target for the prevention and treatment of COVID-19.

Several hurdles need to be overcome in the study of the mechanisms underlying COVID-19. First, biological experiments using SARS-CoV-2 can be performed only in laboratories with a bio safety

level 3 rating. Second, the use of animal models to mimic the disease process is associated with numerous challenges. Given that cellular or tissue tropism is likely to be an important factor contributing to the diverse phenotypes of COVID-19 mouse or rat models are not ideal to study host tropism because they are not as susceptible to SARS-CoV-2 as humans owing to differences in the amino acid sequence of ACE2. To use mice or rats, human *ACE2* needs to be introduced artificially. Transgenic mice expressing *ACE2* infected with SARS-CoV-2 have been reported to show signs of pneumonia, but the overall symptoms experienced by these mice are much milder than those in humans. Therefore, alternative platforms might involve genome-edited mouse or rat models in which *Ace2* is replaced by human *ACE2*, other animal species that are naturally susceptible to SARS-CoV-2 infection (such as ferrets, hamsters and non-human primates) or in vitro models such as induced pluripotent stem cells and or ganoids

The COVID-19 pandemic is changing our lives in unprecedented ways. Given the lack of safe and effective vaccines or proven treatments for COVID-19, our main strategy to combat the pandemic is social distancing. The capacity of health-care systems globally has been severely tested (and in some countries completely overwhelmed), and the effect of this pandemic on social interactions, health-care delivery and the global economy continues to mount. Reduced physical activity owing to lockdown measures might also contribute to poor control of cardiovascular risk factors. Vaccine development is expected to take 12–18 months. To meet the urgent need for effective treatment and preventative strategies, a concerted effort must be made by researchers globally to investigate and integrate biological and clinical findings related to COVID-19.

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