

Formulation and development of Oral herbal liquid dosage form with its quality evaluation parameters

Research Article

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Abstract

The present work deals with the formulation and development of oral herbal liquid dosage and its comparative study with marketed dosage for quality evaluation parameters. We have used different Poly-herbs for the formulation of syrup because they expressed high effectiveness in a vast number of diseases. As aforementioned the therapeutic effect of herbal medicines is exerted due to the presence of different constituents and the effects are further potentiated when compatible herbals are formulated together in PHFs (Poly-herbal formulations). PHF show compatible effect with those of standard allopathic drugs. We had tested its Quality control pre and post-formulation evaluation parameters. The Quality control tests for developed herbal syrup include: Physical appearance (Color, Odor, and Taste), Clarity tests, solubility tests, pH, Density, Viscosity, Specific gravity, Refractive index, FTIR study of active constituent used in herbal syrup. This syrup is also tested for acute oral toxicity study (LD₅₀), Antioxidant activity by using Nitric oxide free radical scavenging method, and hepato-protective activity by using paracetamol-induced hepatotoxicity in rats. From the obtained results, we concluded that formulated poly-herbal syrup passed all quality control tests and also proved its effectiveness. The formulation F2 and F3 were the best poly-herbal formulation and it was selected for further study. In hepato-protective activity, F2 formulation when compared with the standard formulation of silymarin have shown good results.

Key Words: Poly-Herbal Formulation, Hepato-protective, Immuno-modulator, Scavenging activity, Anti-oxidant, Herbal.

Introduction

Drugs are given to a person in a variety of formulations. Drugs are rarely administered as pure chemical substances alone and are almost always given as formulated preparations or medicines (1). Formulations are made for particular applications and normally are more effective than their components when these are used singly (2). Formulations are commercially produced for drugs, cosmetics, foods, paints, coatings, cleaning agents, and for many other things. It can be solid, semisolid, or liquid formulations (3). The type of formulation given to a patient depends upon the type of patient and the condition of the patient (such as age, sex, and health condition) (4, 5). Also, the type of formulation is specific for particular routes of administration (6). Formulation studies involve developing

a preparation of the drug which is both stable and acceptable to the patient (7). The dosage forms are solid, Semi-solid, and liquid. Solid dosage forms are generally given orally and are used most commonly by patients. (**Examples:** Tablets, Enteric-coated tablets, Capsules, Sustained release preparations, Controlled release tablets) (8). Semisolid Dosage forms are easy to absorb as compared to solid formulations and can be administered via a variety of routes of administration. (**Examples:** Topical preparations- Drops, Creams and Ointments, Pastes, Gels and Lotions, Sublingual and Buccal administration, intranasal administration, Transdermal administration (9). Rectal administration Suppositories, Enemas, Vaginal administration- Pessaries). Liquid Dosage forms are essential pharmaceutical products that involve a mixture of active drug components and nondrug components (excipients) (10).

Liquid dosage forms are prepared by dissolving the active drug substance in an aqueous or non-aqueous (e.g. glycerin, ether, alcohol) solvent or by suspending the drug in an appropriate medium, or by incorporating the drug substance into an oil or water phase (11). Oral liquid dosage forms include solutions, syrups, suspensions, elixirs, and concentrates. The syrup is a concentrated or nearly saturated solution of sucrose in distilled water. The

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concentration of sugar in syrups is 66.7% w/w (IP). The syrup is sweet viscous preparation. The syrups which contain medicinal substances are called "medicated syrups". The syrups containing flavored substances are "flavored syrups" (11). They offer better patient compliance in people who find swallowing pills or capsules difficult, and more flexible dosage control than a fixed-dose tablet (12). However, particular issues arise in formulating and developing oral liquid dosages. These include the stability of the drug in solution, the solubility of the drug at the required concentration, and the acceptability of the taste (13).

We have considered all these challenges to overcome through the effective use of excipients to modify the behaviors properties of the formulation without impeding the efficacy of the API (Active Pharmaceutical Ingredient). Liquid dosage forms are most commonly found in medicines for geriatric and pediatric patients (14). However, they have certain advantages, including fast efficacy due to the absence of dissolution time and more rapid absorption in the stomach and intestines than tablets (15).

Materials and Methods

The chemicals used for the research work are given as like API of some herbal extracts and products, clove oil, and Suddha Shilajit powder procured from Herbal Market of Karanja Lad, Dist-Washim, Maharashtra. Chemicals like Ethanol, Distilled water, Methyl paraben, propyl paraben, colorants, Sugar, Flavorings agents, Sodium nitroprusside, Gallic acid, Sulphanilamide, Phosphoric acid, Disodium hydrogen phosphate, Potassium dihydrogen phosphate, sodium chloride, diethyl ether, paracetamol, silymarin, glacial acetic acid were procured from Anuradha College of Pharmacy, chikhli. All the Instruments used for a study as mentioned here e.g UV Visible double beam, ELICO-SL 218, Electronic balance, Ostwald's U-tube Viscometer, Ultrasonic Sonicator, Hot water bath, Clarity test apparatus are of Dolphin make, Mumbai, Desiccator and Digital pH meter is of Equip-Tronics, Incubator and Pycnometer are of Lab Hosp, Mumbai, Refractometer is Metzer Make Optical Instrument, 2587.

Experimental method

A simple method of formulation of syrup was used for this poly-herbal formulation. A syrup with different ingredients in it was mentioned in below table 1.

Formulation of Syrups

Preparation of various formulae from **F1 to F6** for the poly-herbal formulation of syrups as mentioned in Table 1, Ingredients were used as like each 10ml of syrup contains

Evaluation tests

The physical appearance of syrup (Color, Odor, Taste) (16)

Color Examination

5 ml of final syrup was taken into watch glasses and placed against a white background in white tube light. It was observed for its color by the naked eye.

Odor Examination

2 ml of final syrup was smelled individually. The time interval among two smelling was kept at 2 minutes to nullify the effect of the previous smelling.

Taste Examination

A pinch of final syrup was taken and examined for its taste on the taste buds of the tongue.

Determination of pH

Placed an accurately measured amount of 10 ml of the final syrup in a 100 ml volumetric flask and made up the volume up to 100 ml with distilled water. The solution was sonicated for about 10 minutes. The pH was measured with the help of a digital pH meter (17).

Determination of Density

Density can be determined with the help of a density bottle (25ml). The density bottle (25ml capacity) was taken and the weight of the empty bottle was noted. The liquid whose density will be determined is filled in the bottle and weighed. Then both the weight of syrup is calculated by subtracting the weight of the empty bottle from the filled bottle. Then the density of syrup is calculated by using the formula (18)

$$\text{Density} = \text{Mass/Volume}$$

Determination of Viscosity

The viscosity of each formulation was determined by using Ostwald's U-tube Viscometer (19)

$$\eta^2 = \frac{t_2 \times \rho_2}{t_1 \times \rho_1} \times \eta_1$$

Where

η_2 :-Viscosity of sample

η_1 :-Viscosity of water

ρ_2 :-Density of sample

ρ_1 :-Density of water

t_2 :-Time required to flow sample

t_1 :-Time required to flow water.

Determination of Specific Gravity

Wash pycnometer thoroughly with water. Then rinse with acetone and let it be air dried. Weigh the empty pycnometer with a stopper. Fill the pycnometer with water and weigh it. Subtract the weight of the empty pycnometer from this reading to find the weight of water. Now fill the pycnometer with all assigned liquids one by one and weigh. Subtract the weight of the empty pycnometer from the reading to find the weight of each liquid. Determine the specific gravity of each liquid by using formula (20)

$$\text{Specific gravity} = \frac{\text{(weight of substance)}}{\text{(weight of equal volume of water)}}$$

Refractive index

It is measured by Refractometer. Place the apparatus in front of a proper light source. Clean the apparatus using a soft cloth and wipe the prism with a soft brush, if necessary, moistened with alcohol and then acetone. Place a drop of distilled water and adjust the instrument. Focus the telescope eyepiece on the

Table no. 1: Ingredient table for poly-herbal formulations

A. Aqueous extracts derived from	Weight in mg					
	F1	F2	F3	F4	F5	F6
<i>Withania somnifera</i>	3	3.5	3.5	4	3	3
<i>Asparagus racemosus</i>	2	2.5	2.5	4	2	2
<i>Vitis Vinifera</i>	2.5	3	3.5	4	2.5	2.5
<i>Boerhaavia diffusa</i>	2	2.5	3	3	2	2
<i>Pueraria tuberosa</i>	2	2.5	3	3	2	2
<i>Ecliptaalba (L.) Hassk</i>	2	2.5	3	3	2	2
<i>Mucuna pruriens</i>	2	2.5	3	3	2	2
<i>Phyllanthus emblica</i>	2	2.5	3	3	2	2
<i>Triticum aestivum L</i>	2	2.5	2.5	3	2	2
<i>Rubia cordifolia</i>	1	1	1	1	1	1.5
<i>Aloe barbadensis miller</i>	1	1.5	1.5	3	1	1
<i>Dioscorea bulbifera</i>	1	1	1	1	1	1.5
<i>Glycine max</i>	1	1.5	2	2.5	1	1
<i>Tinospora cordifolia</i>	1	1.5	2	2.5	1	1
Fenugreek	1	1.5	1.5	2	1	1
<i>Hemidesmus indicus</i>	0.5	1	1.5	2	0.5	0.5
<i>Chlorophytum borivilianum</i>	0.5	1	1	1.5	0.5	0.5
Chickpea	0.5	1	1.5	2	0.5	0.5
common sunflower	0.5	1	1	1.5	0.5	0.5
<i>Phaselous vulgaris</i>	0.5	1	1	1.5	0.2	0.5
Flax	0.15	1	1	1.5	0.15	0.5
<i>Trapa natans</i>	0.15	0.15	0.15	0.15	0.15	0.65
<i>Terminalia chebula</i>	0.5	1	1.5	2	0.5	0.5
B. Fruit juices are derived from:						
<i>Carica papaya</i>	0.01	0.51	0.51	1.01	1.51	1.51
<i>Ananas comosus</i>	0.01	0.51	1.01	1.01	1.51	1.51
<i>Punica granatum</i>	0.01	0.01	0.51	1.01	1.51	1.51
C. Powders used						
Ashphaltum	0.5	1	1	1.5	0.5	0.5
D. Liquids liquid						
<i>Syzygium aromaticum</i>	2	2	2	2	2	2
Sugar syrup base	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Excipients	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.

cross-section of the instrument and rotate the index arm until a colored band or fringe has seemed through the telescope. Adjust the eyepiece on the movable arm to give a sharp focus on the scale and record the refractive index to the third place of decimal and for fourth place use a reading lens. Take at least three readings of each sample and its mean used for calculation. Open the prism by turning the lock nut and clean the face of the prism. Put a few drop test solutions on the prism and close it properly. Take three readings of each sample of liquid (21).

FTIR Spectroscopy

It is an analytical technique used to identify organic (and in some cases inorganic) materials. This technique measures the absorption of infrared radiation by the sample material versus wavelength. The infrared absorption bands identify molecular components and structures. The FTIR analysis method uses infrared light to scan test samples and observe chemical properties and Principle Component Analysis (PCA) (22)

Clarity test

It is measured by using clarity test apparatus. The purpose of this test is that the above-developed formulation is clean and clear with no solid particles (23)

In-Vitro evaluations

Acute toxicity study (LD₅₀)

Acute oral toxicity (LD₅₀) study of poly-herbal ayurvedic formulation was carried out using the Acute Toxic class method as per OECD guideline 425. The rat was fasted overnight and selected for acute toxicity study of Ayurvedic formulation was measured by using a group of rats by administrating a dose of 2000mg/kg orally. The control group received the vehicle. The groups were observed for behavioral changes for 24 hrs, and signs of toxicity (24). Institutional Animal Ethical committee approved the acute toxicity study with approval no. (IAEC/2018-19/1516).

Determination of Antioxidant activity

Nitric oxide scavenging activity was measured spectrophotometrically. Take 2ml of sodium

Nitroprusside in 0.5ml phosphate buffer saline. Then it is mixed with 0.5ml of the sample at various concentrations (0.2-0.8mg/ml). The mixture is then incubated at 25 °C. After 150 minutes of incubation 0.5ml of the incubated solution is withdrawn and mixed with 0.5ml Griess reagent (1ml of sulfanilic acid reagent (0.33% in 20% glacial acetic acid at R.T. for 5 minutes with 1ml of naphthyl ethylene diamine dichloride.1%w/v). The mixture is then incubated at R.T. for 30 minutes and its absorbance pouring into a cuvette is measured at 546nm. The amount of nitric oxide radical inhibition is calculated following this equation (25)

$$\% \text{ inhibition} = \frac{\text{Control} - \text{Test}}{\text{Control}} \times 100$$

Determination of Hepato-protective activity

Administration of Paracetamol per se at a dose of 2g/kg, P.O., showed centrilobular necrosis in histopathological studies in animals and its association with the elevation of serum biomarkers for liver functions such as SGOT, SGPT, ALP, and total bilirubin. Pretreatment with polyherbal extract at 100mg/kg and 200mg/kg, P.O., for 7 days offered

significant protection against paracetamol-induced hepatic damage by maintaining the serum biochemical parameter (SGOT, SGPT, ALP, and total bilirubin). Polyherbal extract showed dose-dependent protection against paracetamol-induced hepatic damage and the protective effect of extract 200mg/kg, P.O., was comparable with silymarin 100mg/kg, P.O.²⁶

Comparison study

Comparison of hepato-protective and antioxidant activity of poly-herbal syrup with the marketed formulation.

Results and Discussion

The results were obtained by the above-developed oral herbal liquid dosage form with its quality evaluation parameters are explained below

Results of Physicochemical evaluation

The physical appearance of prepared different F1 to F6 Poly-herbal Formulations

It involves evaluation of color, odor, and taste and is mentioned in table 2.

Table 2: Physicochemical evaluation of poly-herbal formulations

Sr no.	Formulations	Color	Odor	Taste	Indication
1	F1	Yellowish Orange	Pleasant	Sweet	Acceptable
2	F2	Reddish Yellow	Pleasant	Sweet	Acceptable
3	F3	Yellowish Orange	Pleasant	Sweet	Acceptable
4	F4	Yellowish Orange	Pleasant	Sweet	Acceptable
5	F5	Yellowish Orange	Pleasant	Sweet	Acceptable
6	F6	Reddish Yellow	Pleasant	Sweet	Acceptable

Table 2 shows the results obtained for color, odor, and taste of formulated batches of syrups. The color of the formulation was found to be Yellowish orange except for F2 and F6 batches. The color of the formulation ranges from Reddish-yellow to Yellowish orange for F1 to F6 batches. It also shows the results

obtained for the odor of formulated batches of syrups. The odor of the formulation was pleasant for F1 to F6 batches. This table also indicated the results obtained for the taste of formulated batches of syrups. The taste of the formulation was sweet for F1 to F6 batches.

Chemical evaluation tests of developed F1 to F6 Poly-herbal Formulations with standard formulation

Table no. 3: pH, density, viscosity, Refractive index, and specific gravity of developed Poly-herbal formulation

Sr.No.	Formulations	pH	Density	Viscosity	Sp. Gravity	R.I.
1	Standard	6.11	1.21g/ml	8.988p	1.22	1.443
2	F1	6.62	1.13g/ml	2.421p	1.14	1.443
3	F2	6.97	1.19g/ml	3.655p	1.15	1.445
4	F3	6.91	1.22g/ml	3.485p	1.18	1.443
5	F4	6.73	1.18g/ml	3.329p	1.14	1.443
6	F5	6.68	1.14g/ml	3.094p	1.15	1.447
7	F6	6.71	1.13g/ml	2.784p	1.14	1.443

Table 3 shows the results obtained for pH, Density, Viscosity, Specific gravity, and Refractive index of formulated batches of syrups. The value was found to be in the range of 6.1-6.9 for all six batches and the standard formulation value was (6.1). **A known standard formulation Silymarin syrup was taken for comparison with our developed formulation.** It also shows the density of formulated batches of syrups. The value was found to be in the range of 1.13-1.22g/ml

for all six batches and standard (1.21 gm/ml). The results obtained for the viscosity of formulated batches of syrups were found to be in the range of 2.42-3.65p for all six batches and for standard formulations it was (8.98p). The specific gravity of formulation was found to be in the range of 1.14-1.18 for all six batches and for standard formulation it was (1.22). The refractive index of the formulation was found to be in the range of 1.443-1.447 for all six batches and standard (1.443).

Results for evaluation of Clarity tests and solubility of developed F1 to F6 Poly-herbal formulations: Table 4: Evaluation of Clarity tests of developed Poly-herbal formulations

Sr. no.	Formulations	Clarity	Solubility
1	Standard	Clean and clear with no solid particles	Soluble in water
2	F1	Clean and clear with no solid particles	Soluble in water
3	F2	Clean and clear with no solid particles	Soluble in water
4	F3	Clean and clear with no solid particles	Soluble in water
5	F4	Clean and clear with no solid particles	Soluble in water
6	F5	Clean and clear with no solid particles	Soluble in water
7	F6	Clean and clear with no solid particles	Soluble in water

Table 4 showed and indicated the results obtained for clarity and solubility tests of formulated batches of syrups. The formulated poly-herbal syrup was found to be clean and clear with no solid particles for all F1 to F6 batches and standard as well as the formulated poly-herbal syrup was found to be soluble in water for all F1 to F6 batches and standard. **A known standard formulation Silymarin syrup was taken for comparison with our developed formulation.**

Results for FT-IR Spectra of developed Poly-herbal formulations

<p>Figure 1: FTIR spectra of <i>Phyllanthus emblica</i></p>	<p>Figure 2: FTIR spectra of <i>Hemidesmus indicus</i></p>	<p>Figure 3: FTIR Spectra of <i>Withania somnifera</i></p>
<p><i>Phyllanthus emblica</i>: O-H (stretch)-3400-3600, Aro C-H stretch-3140.11, Ali C-H stretch 2947-2746, C=O stretch- 1774.51, C-O-C bend-1300-1100, O-H bend-1234 was found in Figure 1.</p>	<p>Anantmul: O-H stretch-3583.74-3437.35, Aro C-H stretch 3100-2900, Ali C-H stretch 2900-2700, C=O stretch 1732.08, C-O-C stretch 1600-1400, O-H bend 1300-1100.</p>	<p><i>Withania somnifera</i>: O-H stretch 3510.45-3309.85, Aro C-H stretch 3047.53-2939.52, Ali C-H stretch 2889.37-2750.49, C=O stretch 1647.21, C-O-C stretch 1600-1400, C-O bend 1300-1100.</p>
<p>Figure 4: FTIR Spectra of <i>Eclipta alba (L.) Hassk</i></p>	<p>Figure 5: FTIR Spectra of <i>Terminalia chebula</i></p>	<p>Figure 6: FTIR Spectra of <i>Mucuna pruriens</i></p>
<p><i>Ecliptaalba (L.) Hassk</i>: O-H stretch 3618.46, Aro C-H stretch 2943.37, Ali C-H stretch 2846.93, C=O stretch 1732.08, C-O-C stretch 1600-1400, C-O bend 1454.</p>	<p><i>Terminalia chebula</i>: O-H stretch 3522.02, Aro C-H stretch 3170.97, Ali C-H stretch 2947.23, Aro C=C stretch 2400-2200, C=O stretch 1750, O-H bend 1307.74, C-O-C stretch 1600-1400.</p>	<p><i>Mucuna pruriens</i>: O-H stretch 3437.15-3375.43, N-H stretch- 3305.99, Aro C-H stretch 3047.53, Ali C-H stretch 2877.79-2754.35, C=O stretch 1651.07, C-N stretch 1300-1100, O-H bend 1458.18</p>

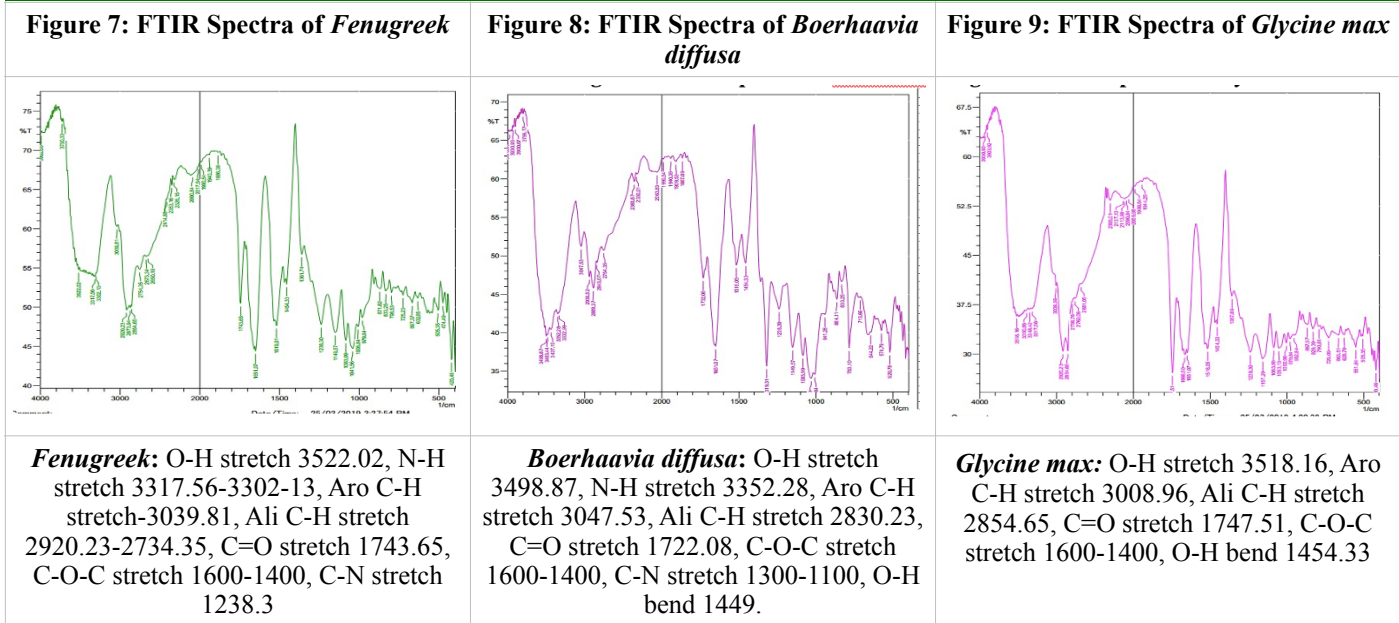
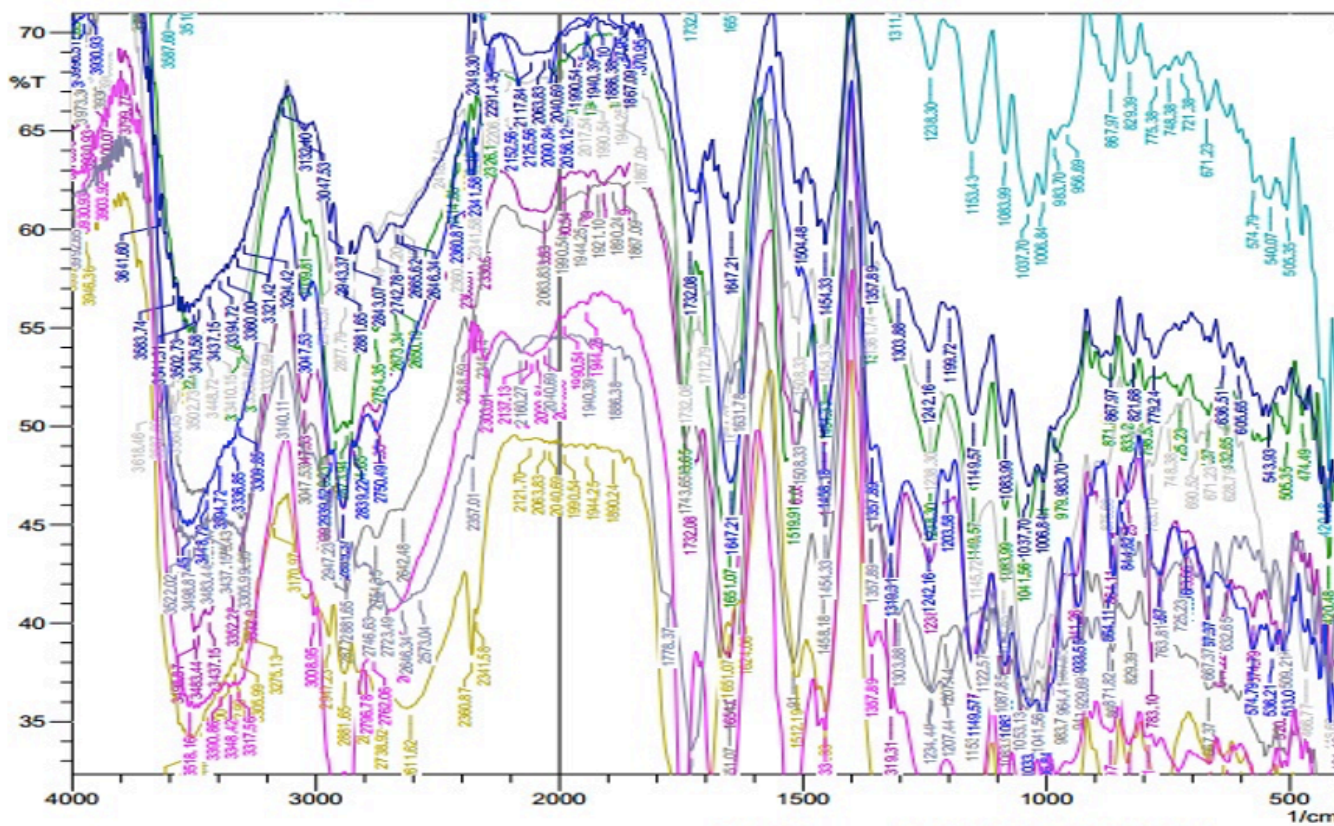


Figure 10: An overlay comparison study of the observed spectrum peak region of *Phyllanthus emblica*, *Withania somnifera*, *Ecliptaalba* (L.) Hassk, *Fenugreek*, *Boerhaavia diffusa*, *Terminalia chebula*, *Hemidesmus indicus*, *Mucuna pruriens*, and *Glycine max*.



All data shown here are the overlay results obtained for FTIR observed peak region for active ingredients of formulated batches of syrups. The infrared absorption bands identify principal molecular components of herbal drugs like polyphenol, Flavonoids, Saponins, and alkaloids as mentioned in many literature searches. And there are also no specific intermolecular incompatibilities in the selected procured extracts for formulation. **For FT-IR spectra some**

active specific drugs were taken as it contains larger contribution of more phenolic, saponin, alkaloidal and favonoidal content in it. There may be chances of interaction within different molecules that may lead to produce drug-drug interaction or chemical incompatibilities or specific intra or Intermolecular interaction. This possibility was checked by overlay or comparison study carried out using FT-IR spectroscopy.

Pharmacological Evaluation

Acute Toxicity Study (LD₅₀)

Acute oral toxicity (LD₅₀) study of polyherbal Ayurvedic formulation was carried out using the Acute

Toxic class method as per OECD guideline 425. It was employed to record for signs of toxicity, no toxicity was found for the 2000mg/kg dose of the drug.

Results for Evaluation of *In-vitro* Antioxidant activity of developed Poly-herbal Formulations

Table 5: Nitric Oxide Scavenging Activity of Poly-herbal Formulations

Sample (µl)	Absorbance (546nm)	% inhibition
Control	1.648	-
Standard	0.622	62.25
F1	0.236	85.67
F2	0.172	89.56
F3	0.185	88.77
F4	0.380	76.94
F5	0.592	64.07
F6	0.331	79.91

Table 5 shows the results obtained for *In-vitro* Antioxidant activity of formulated batches of syrups. The nitric oxide scavenging activity of formulation was found to be in the range of 64.25-89.56 for all six batches and for standard it was found to be 62.25%. From all the above parameters tested for the formulated formulation, we considered the optimized final formulation as with batch F2, and the result for an antioxidant activity for this was found to be 89.56% inhibition. **A solution without active ingredients was taken as a Control contains distilled water and a known standard formulation Silymarin syrup was taken for comparison with our developed formulation.**

Results for Evaluation of Hepato-protective activity of developed optimized Polyherbal formulations

Table 6: Paracetamol-induced liver Toxicity in Rats

Groups	Liver enzymes			Bilirubin (mg/dl)		
	SGPT(U/L)	SGOT(U/L)	SAP(IU/L)	Total	Direct	Indirect
Control	27	31	105	0.55	0.43	0.5
Paracetamol	130	169	268	1.06	0.63	0.88
Poly-herbal Extract (Batch F2)	50	62	128	1.1	0.4	0.7
Silymarin	41	54	99	0.61	0.37	0.36

Table 6 shows the results obtained for the Hepato-protective activity of formulated batches of syrups. Swiss albino rats from the pharmacology laboratory of Anuradha College of Pharmacy were used for this study. The hepato-protective activity of formulation was determined by using a biochemical study that includes liver enzymes such as SGOT, SGPT, ALP, and total bilirubin. In the paracetamol-induced animals, liver enzymes like SGOT, SGPT, ALP, and bilirubin concentrations increased significantly. The pre-treatment with poly-herbal extract contains active constituents significantly to prevent acute hepatotoxicity in animals because the SGOT, SGPT, ALP, and bilirubin were maintained at near normal levels as compared to paracetamol-induced groups. Thus, this indicates batch F2 shows a significant hepato-protective activity. **A solution without active ingredients was taken as a Control contains distilled water and a known standard formulation Silymarin syrup was taken for comparison with our developed formulation.** It shows a good result when compared with ayurvedic poly-herbal formulations.

Conclusion

Poly-herbal medicines are still the mainstay of about 75-80% of the world population mainly in developed countries for primary health care because of better cultural acceptability, better compatibility with the human body, and lesser side effect. From this study, we concluded that the poly-herbal formulations containing herbal extracts, herbal forms, and products possess Antioxidant and Hepato-protective activity as it was also claimed in the literature survey. From the above result, it was concluded that the formulated herbal syrup was found to be clean and clear with no solid particles. According to post-formulation studies, the herbal syrup possesses a sweet taste hence palatable too. There was no change in either color or odor of the formulated syrup. The pH of F2 and F3 was found to be 6.9, The Density of F2 and F3 were found to be 1.19 and 1.22, The Viscosity of F2 and F3 were found to be 3.65 and 3.48, and The Specific gravity of F2 and F3 was found to be 1.15 and 1.18, The R. I. of F2 and F3 were found to be 1.445 and 1.443. Hence from the result, we concluded formulation F2 and F3 were the best poly-herbal formulation and it was selected for further

detailed study. In hepato-protective activity F2 formulation when compared with the standard formulation of silymarin have shown good result and further study on chronic toxicity and accelerated stability study needs to be carried out in the future.

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