# Development of a Gastroretentive Polyherbal Formulation and its Standardization

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#### ABSTRACT

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Background: Phytopharmaceuticals within the shape of the entire herb, plant parts, or separated bioactive constituents have been utilized broadly in therapeutics since antiquated times till date. The appealing use of drugs of the natural root has driven the requirement for standardization as per the WHO guidelines. **Objectives:** The main aim of the existing study was to formulate polyherbal gastroretentive capsules by using Carbopol 934 and 971P in different concentration ranges to get desired buoyancy rate. Materials and Methods: The prepared formulation was characterized by physico-chemical parameters and pharmaceutical quality control tests. Standard procedures were used to estimate the organoleptic properties, extractive values, and ash values of the crude drugs used in formulations. Extraction was carried out using Soxhlation followed by preliminary phytochemical evaluation and HPTLC fingerprinting of the extracts. The extracts were formulated into a gastroretentive polyherbal capsule and assessed for physical parameters. Results: The phytochemical assessment established the presence of flavonoids, alkaloids, saponins, steroids, and glycosides. R, values obtained from the HPTLC studies of the extracts signified the presence of important phytoconstituents such as Shogaols, 6-Gingerol, 8-Gingerol, Glycyrrhizin, Andrographolides, Marmelosin, and Conessine. Percent Carr's consolidation index ranging from 8.111 ± 0.157 to 8.827  $\pm$  0.186, Hausner's ratio between 1.088  $\pm$  0.002 to 1.097  $\pm$  0.002, and angle of repose below 30 are indicative of excellent flow property of the granules. Conclusion: The gastroretentive capsules PHF4 containing granules formulated using 75 mg Carbopol 971P showed a buoyancy effect of more than 24 hr with desired structural integrity. Keywords: Extraction, HPTLC fingerprinting, Polyherbal formulation, Standardization.

# INTRODUCTION

The estimated use of plants in traditional medicine is as high as approximately 3,00,000 species. Entire herb or plant parts have been used since ancient days for the treatment of human ailments and continue to pave the new means for therapeutics at the global level.[1-3] Having application in pharmaceutical, nutritional and cosmetic areas, the attention to the use of plant material has immensely amplified. With the progression in the extraction technology, it is possible to extract and isolate the important bioactive constituents such as glycosides, alkaloids, tannins, steroids, volatile oils, fixed oils, phenols, flavonoids, and resins present in the various portions of the plants.<sup>[4]</sup> This has made it possible for increasing the use of drugs of natural origin which has been the mainstay in the treatment in recent years.<sup>[5]</sup> Polyherbalism has been inadvertently developed into an emerging therapeutic resource with the advantages of synergism, easy availability, economic, lack of side effects, and better pharmacokinetic and pharmacodynamic profile.[6-8] Out of nearby 7,50,000 prevailing species of plants only 10-15%

have been gaged for bioactive components. A promising number of scientific studies of medicinal plants have developed herbalism from traditional medical practice to modern herbal research.<sup>[3]</sup> The quality and quantity of these phytoconstituents determine the therapeutic efficacy of herbal drugs. These standards can be ensured by the systematic pharmacognostic evaluation of the medicinal plant.<sup>[8]</sup> The use of crude drugs obtained from medicinal plants needs to be collected timely, authenticated by an expert, dried, and ground. Further processes like extraction, fractionation, or isolation of the bioactive compounds may be done where applicable. Estimation and quantification of the bioactive substances present therein are performed to ensure the effectiveness of these processes.<sup>[7]</sup> The alluring use of drugs of natural origin has led to the need for standardization. World Health Organization (W.H.O.) has highlighted the need to warrant the quality control of drugs obtained from medicinal plants by utilizing modern techniques and standards.<sup>[1,9]</sup> Standardization of

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a crude drug involves evaluation of organoleptic characterization, macroscopic evaluation, microscopic valuation, powder characteristics, physico-chemical investigation, phytochemical analysis, fluorescence analysis, moisture content, ash values, extractive values, and chromatographic assessment.<sup>[8,10]</sup>

Sustained-release dosage forms have been devised to attain pharmacokinetic and pharmacodynamic benefits over conventional dosage forms. These include sustained therapeutic levels for prolonged periods and lessening of fluctuations in plasma concentrations.<sup>[11]</sup> The design of gastro-retentive dosage forms (GRDFs) to be retained within the stomach for an extended time and release the medication in a sustained manner has been gaining increasing attention in the past three decades.<sup>[12]</sup> Aspects affecting gastroretentive properties comprise the size and density of the dosage form, posture, appetite, and nature of meals. Several approaches to gastroretentive formulation include expandable, floating, high density, and mucoadhesive systems. Floating drug delivery systems are retained above the gastric contents unaffected by the peristalsis and hence delivering the drug to the upper GI tract in a sustained manner.<sup>[11,13]</sup> Floating effect can be obtained by incorporation of several polymers such as HPMC, CMC, Eudragit, Calcium alginate, Methocel K4M, Corbopols, and ethyl cellulose.<sup>[13]</sup> Incorporation of loosely crosslinked polymers such as Carbopols have been reported to show good drug entrapment, controlled drug release, and bioadhesive properties. Various grades of Carbopols such as 71G, 934, 971, 971P, 974, and 974P have been used to formulate a gastroretentive drug delivery system.[14]

The present study aims the preparation and standardization of a gastroretentive polyherbal formulation. The literature survey revealed that there is potential scope for using Carbopol as a polymer for the formulation of a polyherbal gastroretentive delivery system. The active constituents of polyherbal formulations were subjected to pharmacognostic evaluation. These constituents from crude drugs were extracted with a suitable solvent using the Soxhlet apparatus. The purity of obtained extracts was ascertained by HPTLC fingerprinting for the determination of specific phytoconstituents. The extracts were formulated into gastroretentive capsules, and the functionality of the same was assessed for floating and other physical properties.

# **MATERIALS AND METHODS**

# Plant Material Collection

The rhizomes of *Zingiber officinale*, the root of *Glycyrrhiza glabra*, whole herb of *Andrographis paniculata*, unripe fruits of *Aegle marmelos*, and stem of *Holarrhena antidysenterica* were collected from the Konkan region of Maharashtra and dried under shade. The dried plant parts were subjected to coarse grinding.

# **Plant Authentication**

The plant material was authenticated by Dr. Sangram Keshari Das, Professor and HOD Dravyaguna at Gomantak Ayurved Mahavidyalaya and Research, Centre, Shiroda, Goa after submission of the herbarium.

# Pharmacognostic Studies

**Organoleptic properties:** Organoleptic properties aid in the determination of the purity as well as quality of the crude drugs. Color, odor, and taste were observed and recorded.

**Physico-chemical Studies:** Tests like pH, moisture content, ash values, and extractive values assist in the valuation of the purity and quality of the crude drug.<sup>[2]</sup>

**Loss on drying:** Accurately weighed 2 g of the pulverized crude drug was put in a preheated previously weighed porcelain dish. It was then

dried in a hot air oven at 105°C till consistent weight was obtained or till two successive weights differed by not more than 0.5 mg. The porcelain dish along with the residue was weighed after cooling in the desiccator.<sup>[6]</sup> **Total ash value:** The empty silica crucibles were weighed. Two grams each of the air-dried powdered crude drugs were added to these crucibles. The test sample was then ignited steadily in an electrical muffle furnace up to 450°C. The crucibles were cooled by placing them in a desiccator and the ultimate weight was recorded. The total ash values were recorded in terms of percentage with reference to the drug used.<sup>[15]</sup>

Acid insoluble ash value: To the crucibles containing the total ash 25 ml of dilute HCl was added. The crucibles were shielded with a watch glass and gently boiled for 5 min over a water bath. Five millilitres of hot water was used to wash the watch glass and the washings were poured into the crucibles containing the total ash. Through the ashless filter paper, the insoluble matter was filtered and washed using hot water till the filtrate was neutral. The filter paper holding the insoluble material was then transferred to the previously weighed crucibles, dried using a hotplate, and ignited till constant weight was obtained. The crucibles were cooled in a desiccator for 30 min and the final weight was recorded.

**Water-soluble ash value:** To the crucibles comprising total ash was added 25 ml of water. The contents were boiled for about 5 min and then filtered using ashless filter paper. The residue thus retained on the filter paper was washed using hot water. This residue along with the filter paper was transferred to previously weighed crucibles and ignited at a temperature not surpassing 500°C for 15 min. The crucibles were reweighed after cooling in a desiccator for about 30 min.<sup>[6]</sup>

Calculations for ash value:<sup>[16]</sup>

Weight of empty crucible = x Weight of sample = y Weight of ash + empty crucible = z Weight of ash generated = (z - x) g y g of sample yields (z - x) g of ash 100 g of sample yields  $(z - x) \times 100g$  of the ash y

Ash value = 
$$\frac{(z-x) \times 100}{y}$$
 %

**Determination of extractive values:** Estimation of water-soluble, and alcohol-soluble extractive values of crude drugs was carried out by following the procedures as below.<sup>[15]</sup>

**Determination of water and alcohol soluble extractive values by cold maceration:** Exactly 4 g of the coarsely powdered crude drug was transferred to a stoppered conical flask. To this was added 100 ml of the solvent (water/alcohol) and macerated with constant shaking for 6 h. The mixture was allowed to stand for 18 h. Post 24 h the mixture was filtered using Whatman filter paper. Twenty-five milliliters of the filtrate was transferred to a previously weighed porcelain dish and evaporated to dryness in a water bath. The residue thus obtained was dried for 6 hr at 105°C, cooled in a desiccator for 30 min, and instantly weighed. The weight of the collected residue was used to calculate the extractive value.<sup>[5]</sup>

Determination of water and alcohol-soluble extractive values by hot extraction: Exactly 4 g of the coarsely powdered crude drug was transferred to a conical flask. To this was added 100 ml of the solvent (water/alcohol) and the weight was recorded. The conical flask was stoppered, shaken well, and allowed to stand for one hour. The contents were refluxed for one hour. The mixture was cooled and reweighed. The weight was adjusted to the initial total weight with the solvent (water/ alcohol) used for extraction. The blend was shaken well and rapidly filtered through a dry filter paper. Twenty-five milliliters of the filtrate was transferred to a tared porcelain dish and evaporated to dryness in a water bath. The residue thus obtained was dried for 6 h at 105°C, cooled in a desiccator for 30 min, and weighed instantly. The weight of the dried residue was used to calculate the extractive value.<sup>[16]</sup>

#### Calculations for extractive values:<sup>[16]</sup>

25 ml of water extract = x g residue

100 ml of water extract =  $4 \times x$  g residue 4 g of sample yields  $4 \times x$  g residue

100 g of sample yields  $100 \times x$  g residue

Extractive value =  $100 \times x$  %

# Preliminary Phytochemical Screening

The existence of important constituents such as steroids, flavonoids, alkaloids, and saponins was determined by using various phytochemical tests.<sup>[3,9]</sup>

# Assessment of pH

One gram of the sample was added to a 100 ml volumetric flask to which distilled water was added up to the mark. The mixture was set aside for 4 h and filtered. With the calibrated pH meter, the pH of the filtrate was recorded using the standard solutions of pH 4, 7, and 9 (standard glass electrode).<sup>[15]</sup>

# **Extraction of Plant Material**

Soxhlet apparatus was used to carry out the extraction of crude drugs. A dried and coarsely ground crude drug was placed inside the thimble stitched of muslin cloth and closed tightly. A sufficient amount of extraction solvent (95 % ethanol) was poured into the bottom flask. Some amount of solvent was poured on the thimble to speed the onset of extraction. The solvent in the round bottom flask was then heated to boiling by optimizing the temperature of the heating mantle. The solvent vapors thus generated pass through the condenser, condense, and flow down to enter the extraction chamber. This hot solvent coming in contact with the crude drug extracts the constituents. As the level of solvent in the extraction chamber raises to the top of the siphon tube, the solvent containing the extracted constituents flows back into the round bottom flask.<sup>[7]</sup> The entire cycle was repeated continuously to ensure complete extraction of the phytoconstituents marked by a clear solvent emerging through the extraction chamber. After ensuring the completion of the extraction process the solvent collected in the round bottom flask with the constituents dissolved in it was recovered and subjected to evaporation using a rotary evaporator. Using a rotary evaporator (IKA RV 10), the surplus solvent was evaporated at 70°C under reduced pressure (- 760 mmHg) to obtain a sticky material.<sup>[2]</sup>

# Preliminary phytochemical evaluation of the extracts

The hydroalcoholic extracts were subjected to preliminary phytochemical evaluation to confirm the extraction of important constituents for instance flavonoids, saponins, alkaloids, glycosides, and steroids.<sup>[3,9]</sup>

# **HPTLC Fingerprinting**

The sample was extracted in the respective solvents for the detection of the phytoconstituents in different extracts. The concentration of 10 mg/ml sample and AV Gastro extracts were prepared. On pre-coated silica gel  $F_{254}$  aluminum plates, 30 µL of these samples were spotted to a bandwidth of 7 mm using Camag Linomat 5 TLC applicator. Development of the plate was executed using an appropriate solvent system to resolve the different constituents. Following the derivatizations, the developed plates were scanned under 254 nm and 366 nm UV light with Camag TLC scanner 3.  $R_e$  values of the spots were documented.<sup>[17]</sup>

*Zingiber officinale:* The sample was further extracted with chloroform and concentrated. The concentrate thus obtained was dissolved in chloroform and applied to the TLC plate and developed using n-Hexane:diethyl ether (40:60) as a solvent system. The plate was sprayed with vanillin sulphuric acid for derivatization and visualized at 254 nm and 366 nm.<sup>[18]</sup>

*Glycyrrhiza glabra:* The TLC plate applied with the sample was developed in a twin trough chamber containing n-butanol:water:glacial acetic acid (7:2:1) as a solvent system. The developed plate was sprayed with vanillin sulphuric acid followed by heating at 105°C for 5 to 10 min for derivatization. The plate was scanned at 254 nm and 366 nm.<sup>[19]</sup>

*Andrographis paniculata:* After dissolving the extract in ethanol the TLC plate was charged with the sample and developed using Chloroform:ethanol (8:0.5) as a solvent system in a twin trough chamber. After having sprayed with vanillin sulphuric acid the plate was heated at 105°C till the colored spots were visible. The plate was visualized at 254 nm and 366 nm.<sup>[20]</sup>

*Aegle marmelos*: The extract was dissolved in ethanol and applied to the TLC plate. The plate was developed with Toluene:ethyl acetate (93:7) as a solvent system in the twin trough chamber. For derivatization, the plate was sprayed with Anisaldehyde sulphuric reagent and heated at 105°C for 5 to 10 min for visualization at 366 nm.<sup>[21]</sup>

*Holarrhena antidysenterica:* The extract was further extracted with a mixture of diethylether:chloroform (3:1) and 1 ml of 10 % ammonia and applied to the TLC plate. The development was carried out using Cyclohexane:chloroform:diethylamine (7:2:1) as a solvent system. Following the development, the plates were sprayed with Dragendorff's reagent for visualization at 254 nm.<sup>[22]</sup>

# Formulation of Polyherbal Capsules

The extracts were formulated into capsules as per the proportion specified in the marketed formulation of AV Gastro, by Amsarveda Pvt. Ltd., Goa. The wet granulation method was adopted to prepare the polyherbal granules containing extracts. The varying concentrations of two grades of Carbopol 971P and 934 were denoted as PHF1 to PHF4 and PHF5 to PHF8 formulations respectively (Table 16). Polyherbal extracts were blended uniformly with the polymer and diluent. To make a damp mass binder solution was used. Damp granules were attained by passing the mass through sieve 18#. After an hour of drying at 60°C, the granules were screened through a sieve 24# to yield granules of an unvarying dimensions. The dried granules were mixed with the glidant and lubricant followed by filling in two-piece empty capsule shells of cellulose.<sup>[23]</sup>

# Physical Characterizations of Granules and Capsules

The granules were analyzed for the physical parameters such as tapped density, bulk density, Carr's consolidation index, Hausner's ratio, and angle of repose. The formulated capsules were subjected to buoyancy testing, uniformity of weight, and disintegration test.<sup>[23,24]</sup>

Bulk and Tapped density: Exactly weighed 5 g of granules was transferred to the 25 ml cylinder and tapped twice gently to gather any granules adhering to the wall of the cylinder. The untapped initial volume  $V_o$  was noted. The cylinder was then tapped 100 times from the height of 2.5 cm using digital bulk density apparatus (Innovative). After ensuring the attainment of persistent volume, the final tapped volume,  $V_f$  was documented.

The bulk density  $D_o$  was calculated as  $D_o = \text{mass}/V_o$ 

The tapped density  $D_f$  was obtained by using the formula  $D_f = \text{mass}/V_f$ Carr's consolidation index and Hausner's ratio: The degree of flow properties of the granules was judged by calculating the Carr's consolidation index and Hausner's ratio as follows:

$$CI = (D_f - D_o) \times 100 / D_f$$
$$HR = D_f / D_o$$

**Angle of repose:** By applying the fixed height method, the angle of repose was determined by flowing the granules through the funnel which was fixed at the height of 2 cm from the plane surface. Having marked the base of the cone, the granules were poured off. After determining the average of two diameters, the radius *r* was calculated. The height *h* of the cone was determined. By substituting the values in the formula, the angle of repose  $\theta$  was obtained.

#### $\theta = tan^{-1}(h/r)^{[23]}$

**Buoyancy testing:** For the determination of buoyancy testing, the capsules were introduced in a 250 ml glass beaker holding 0.1 N HCl (pH 1.2). Time taken by all the granules to raise to the surface was taken as floating lag time (FLT) and the interval for which the granules persisted in the constant floating state was recorded as the total floating time.<sup>[24,25]</sup>

**Uniformity of weight:** Randomly selected twenty capsules were weighed individually using a digital electronic balance. After emptying each capsule carefully, the empty shell was weighed. The variance between the weights of the unbroken capsule and the empty capsule shell was recorded. The average weight of 20 capsules was documented.

**Disintegration test:** The disintegration time of the polyherbal capsules was estimated using the disintegration test apparatus. The experimental conditions used for the test were  $37^{\circ}C\pm 2^{\circ}C$  and the simulated medium used was 0.1 N HCl (pH 1.2). The disintegration of all 6 capsules leaving behind only the shell was considered the disintegration time.<sup>[23,26]</sup>

# **Statistical Analysis**

All the test results were recorded in triplicate and represented in the form of mean  $\pm$  SD. The statistical valuation of the data obtained was accomplished using MS Excel.

# RESULTS

Authenticated crude drugs *Zingiber officinale, Glycyrrhiza glabra, Andrographis paniculata, Aegle marmelos,* and *Holarrhena antidysenterica* were subjected to preliminary physico-chemical evaluation by standardization parameters. The evaluation included the study of organoleptic properties, preliminary phytochemical evaluation, loss on drying, ash values, and extractive values. Extraction of the crude drugs was carried out. Further, the HPTLC fingerprinting of the extracts was executed to confirm the presence of specific phytoconstituents. The extracts were formulated into a gastroretentive polyherbal capsules and evaluated for various quality control tests to affirm the pharmaceutical excellence.

# Organoleptic properties and Preliminary phytochemical evaluation

The organoleptic properties of the crude drugs used for extraction are reported in Table 1 and Figure 1. The establishment of the profile of the crude drugs for their chemical composition was confirmed by the phytochemical assessment which confirmed the occurrence of flavonoids, alkaloids, and glycosides in *Zingiber officinale*. *Glycyrrhiza glabra* confirmed the presence of saponins and flavonoids. The presence of flavonoids and glycosides was seen in *Andrographis paniculata*. *Aegle marmelos* showed the occurrence of flavonoids and alkaloids, whereas, *Holarrhena antidysenterica* exhibited the presence of alkaloids and steroids (Table 2).

# Physico-chemical evaluation

The moisture content as indicated upon loss on drying varied from 0.093  $\pm$  0.007 to 0.174  $\pm$  0.006 (Table 3). The total ash values were recorded in the range of 7.427  $\pm$  0.058 to 32.780  $\pm$  0.098. Acid insoluble ash lies within the range of 0.843  $\pm$  0.033 to 7.813  $\pm$  0.069. Water-soluble ash value was exhibited in the range of 2.473  $\pm$  0.025 to 12.217  $\pm$  0.031 (Table 4). The extractive values of the crude drugs by cold maceration and hot maceration methods were determined. Alcohol soluble extractives by cold maceration method were documented in the array of 7.537  $\pm$  0.059 to 26.513  $\pm$  0.078, whereas the water-soluble extractives by cold maceration method were found to be in the range of 9.540  $\pm$  0.094 to 17.553  $\pm$  0.046. Using the hot maceration technique, the alcohol-soluble

#### Table 1: Organoleptic properties.

Sample	Color	Odor	Taste
Zingiber officinale	Yellowish-brown	Aromatic	Pungent
Glycyrrhiza glabra	Dull yellowish	Characteristic	Sweet
Andrographis paniculata	Dark green	Odorless	Bitter
Aegle marmelos	Orange-brown	Resinous aromatic	Acrid
Holarrhena antidysenterica	Buff	Odorless	Bitter



**Figure 1:** Crude powdered drugs: *Zingiber officinale* (A), *Glycyrrhiza glabra* (B), *Andrographis paniculata* (C), *Aegle marmelos* (D) and *Holarrhena antidysenterica* (E).

#### Table 2: Preliminary phytochemical evaluation.

Comple	Alkaloids	Flavonoids	Carbohydrates	Glycosides	Proteins	Tannins	Cononing	Steroids
Sample	Alkalolus	Flavonolus	Carbonyurates	diycosides	Proteins	Tannins	Saponins	Steroius
Zingiber officinale	+	+	+	+	-	-	-	-
Glycyrrhiza glabra	-	+	+	+	-	-	+	-
Andrographis paniculata	-	+	-	+	-	-	-	-
Aegle marmelos	+	+	+	-	+	+	-	-
Holarrhena antidysenterica	+	-	-	-	-	-	-	+

#### Table 3: Loss on drying.

Sample	Moisture content
Zingiber officinale	$0.138\pm0.013$
Glycyrrhiza glabra	$0.093\pm0.007$
Andrographis paniculata	$0.145\pm0.006$
Aegle marmelos	$0.126\pm0.002$
Holarrhena antidysenterica	$0.174\pm0.006$

The results are expressed as mean  $\pm$  SD of triplicate readings

#### Table 4: Ash value.

Sample	Total ash value	Acid insoluble ash value	Water soluble ash value
Zingiber officinale	$7.427\pm0.058$	$2.470\pm0.062$	$4.350\pm0.045$
Glycyrrhiza glabra	$13.937\pm0.053$	$3.853 \pm 0.092$	$3.58\pm0.057$
Andrographis paniculata	$11.163 \pm 0.084$	0.843 ± 0.033	$2.473 \pm 0.025$
Aegle marmelos	$32.780\pm0.098$	$7.813 \pm 0.069$	$12.217\pm0.031$
Holarrhena antidysenterica	$8.477\pm0.026$	$2.747\pm0.041$	$6.477\pm0.026$

The results are expressed as mean ± SD of triplicate readings

#### Table 5: Extractive value.

	Cold Maceration		Hot Maceration		
Sample	Alcohol- soluble extractives	Water-soluble extractives	Alcohol- soluble extractives	Water- soluble extractives	
Zingiber officinale	24.093 ± 0.025	$12.577 \pm 0.026$	11.137 ± 0.049	9.533 ± 0.079	
Glycyrrhiza glabra	$19.01 \pm 0.054$	17.553 ± 0.046	23.43 ± 0.036	$20.587 \pm 0.012$	
Andrographis paniculata	$18.847 \pm 0.068$	$14.377 \pm 0.061$	$16.417 \pm 0.085$	14.843 ± 0.049	
Aegle marmelos	26.513 ± 0.078	$16.470 \pm 0.067$	17.730 ± 0.079	$15.483 \pm 0.065$	
Holarrhena antidysenterica	7.537 ± 0.059	9.540 ± 0.094	$5.740 \pm 0.064$	$6.467 \pm 0.048$	

The results are expressed as mean  $\pm$  SD of triplicate readings

extractives were recorded in the array of  $5.740 \pm 0.064$  to  $23.43 \pm 0.036$ , and the water-soluble extractives were found to be in the range of  $6.467 \pm 0.048$  to  $20.587 \pm 0.012$  (Table 5).

# Soxhlet Extraction

Extraction of the crude drugs by the Soxhlet extraction technique using 95 % ethanol gave the % yield of various extracts in the range of 10.313  $\pm$  0.103 to 20.13  $\pm$  0.099 (Table 6). The phytochemical evaluation of the developed formulation confirmed the presence of alkaloids, flavonoids, glycosides, steroids, and saponins (Table 7).

# HPTLC Fingerprinting

HPTLC fingerprinting for the extracts was performed as per the standard procedure to detect the important constituents. *Zingiber officinale* extract

indicated the detection of 12 peaks for the sample extract and 13 peaks for the AV Gastro extract at 254 nm (Table 8 and Figure 2). Whereas 12 peaks were seen in both the sample and AV Gastro extract at 366 nm (Table 9 and Figure 3). The prominent peak at R, value 0.66 indicates the presence of Shogaols, at 0.40 indicated 6-Gingerol, and at 0.44 indicated 8-Gingerol (Table 8 and 9; Figures 2, 3, and 4). Glycyrrhiza glabra showed 12 and 15 peaks for the sample and AV Gastro extracts respectively at 254 nm (Table 10 and Figure 5). However, 15 and 14 peaks were detected at 366 nm for the sample and AV Gastro extracts respectively (Table 11 and Figure 6). Peaks at R<sub>e</sub> values of 0.25 and 0.24 indicate the existence of Glycyrrhizin (Table 10 and 11; Figures 5, 6, and 7). Andrographis paniculata assessed at 254 nm recorded 20 peaks with the sample drug extract and 21 peaks with the AV Gastro extract (Table 12, Figure 8). While 20 and 21 peaks were recorded for the sample and AV Gastro extracts respectively at 366 nm (Table 13 and Figure 9) The peaks at R value of 0.24 suggests the presence of Andrographolides (Table 12 and 13; Figures 8, 9, and 10). Aegle marmelos exhibited 26 peaks for sample drug extract and 23 peaks for AV Gastro extract at 366 nm (Table 14 and Figure 11). Peaks corresponding to R, value 0.63 indicates the presence of Marmelosin (Table 14; Figures 11 and 12). The sample drug extract of Holarrhena antidysenterica displayed 10 and 12 peaks at 254 nm for the sample and AV Gastro extracts respectively (Table 15 and Figure 13). R, value of 0.77 and 0.81 corresponds to the presence of Conessine (Table 15; Figures 13 and 14).

# Physical Evaluation of Capsules

The extracts obtained were formulated into eight gastroretentive capsule formulations, PHF1 to PHF8 by using Carbopol 934 and 971P in varying concentrations (Table 16 and Figure 15). These formulations were examined for physical assessment parameters like tapped density, bulk density, and angle of repose. Using the data of bulk and tapped densities, Carr's consolidation index and Hausner's ratio were computed. The values of bulk density and tapped density varied from  $0.406 \pm 0.008$  to  $0.441 \pm 0.01$  and  $0.441 \pm 0.009$  to  $0.484 \pm 0.011$ , respectively. Percent Carr's consolidation index ranged from  $8.111 \pm 0.157$  to  $8.827 \pm 0.186$  and Hausner's ratio lay between  $1.088 \pm 0.002$  to  $1.097 \pm 0.002$  which signifies that the granules have excellent flow properties. The angle of repose was estimated to be below 30 for all the formulations, which showed that the flow properties of the granules were excellent (Table 17).

#### Table 6: Soxhlet extraction of plant material.

Sample	% Yield
Zingiber officinale	$12.347 \pm 0.090$
Glycyrrhiza glabra	$20.13\pm0.099$
Andrographis paniculata	$16.687 \pm 0.165$
Aegle marmelos	$19.447\pm0.068$
Holarrhena antidysenterica	$10.313 \pm 0.103$

The results are expressed as mean  $\pm$  SD of triplicate readings

#### Table 7: Phytochemical evaluation of the developed formulation.



+ = present; - = absent

#### Table 8: HPTLC fingerprinting of extracts of Zingiber officinale at 254 nm.

		-	-	
Peak No.	Zingiber offic	<i>cinale</i> sample	Zingiber offic	cinale AV Gastro
Peak NO.	R <sub>f</sub> value	% area	R <sub>f</sub> value	% area
1	0.02	24.38	0.02	28.05
2	0.13	2.92	0.07	19.18
3	0.19	6.44	0.11	2.95
4	0.25	4.09	0.18	6.52
5	0.31	4.86	0.25	2.22
6	0.36	2.80	0.28	1.04
7	0.40	3.69	0.33	3.63
8	0.56	0.63	0.43	1.00
9	0.66	23.14	0.44	0.98
10	0.71	16.09	0.55	0.56
11	0.80	3.95	0.66	19.39
12	0.92	7.00	0.70	8.23
13	-	-	0.91	6.24



**Figure 2:** HPTLC fingerprinting peaks of sample (A) and AV Gastro (B) extracts for *Zingiber officinale* at 254 nm.

#### Table 9: HPTLC fingerprinting of extracts of Zingiber officinale at 366 nm.

Peak	Zingiber offic	inale sample	Zingiber officin	ale AV Gastro
No.	R <sub>,</sub> value	% area	R <sub>f</sub> value	% area
1	0.01	2.38	0.03	11.82
2	0.03	2.16	0.10	4.80
3	0.05	2.72	0.15	4.31
4	0.10	2.48	0.20	2.08
5	0.19	2.78	0.30	5.43
6	0.26	3.26	0.37	5.48
7	0.32	1.71	0.46	4.01
8	0.35	2.49	0.62	33.97
9	0.44	2.32	0.68	12.42
10	0.62	44.92	0.75	12.55
11	0.68	30.10	0.88	1.02
12	0.87	2.67	0.91	2.11

# **Buoyancy Testing**

The capsules were evaluated for the physical parameters to determine whether the formulation passes the testing limits. The buoyancy testing of the prepared granules showed the best floating efficiency with Carbopol 971P. Evaluation of buoyancy testing for the PHF1 to PHF4 prepared by using Carbopol 971P yielded the floating lag time in the range of 14.833  $\pm$  0.236 to 29.000  $\pm$  0.816 and a total floating time from 8.167  $\pm$  0.236 to >24 hrs. PHF5 to PHF8 prepared by using Carbopol 934 showed the floating lag time in the range of 17.167  $\pm$  0.624 to 31.167  $\pm$ 



**Figure 3:** HPTLC fingerprinting peaks of sample (A) and AV Gastro (B) extracts for *Zingiber officinale* at 366 nm.





Figure 4: HPTLC fingerprinting TLC plates of AV Gastro and sample extracts for *Zingiber officinale* at 254 (A) and 366 (B) nm.

# Table 10: HPTLC fingerprinting of extracts of *Glycyrrhiza glabra* at 254 nm.

Peak No.	Glycyrrhiza g	labra sample	Glycyrrhiza glabra AV Gastro		
reak NO.	R <sub>f</sub> value	% area	R <sub>f</sub> value	% area	
1	0.02	4.16	0.02	1.66	
2	0.07	1.21	0.10	2.37	
3	0.09	2.77	0.17	3.75	
4	0.25	25.18	0.22	6.98	
5	0.30	24.63	0.26	8.07	
6	0.36	3.44	0.30	19.22	
7	0.41	6.87	0.37	3.01	
8	0.52	3.22	0.41	5.59	
9	0.54	1.89	0.49	4.21	
10	0.56	3.73	0.52	2.59	
11	0.70	15.36	0.58	2.67	
12	0.88	7.54	0.61	0.81	
13	-	-	0.72	18.45	
14	-	-	0.83	11.86	
15	-	-	0.88	8.75	

0.624 and a total floating time between 7.167  $\pm$  0.236 to 11.833  $\pm$  0.624 (Table 18; Figures 16 and 17). Out of all the formulated preparations, PHF 4 showed the highest floating efficiency of more than 24 hours, this may be due to lower cross-linking densities and higher molecular weight between adjacent cross-links. Moreover, maintenance of the structural integrity of the granules was observed over the period of 24 hours. Weight variation parameters arrayed from 399.65  $\pm$  0.910 to 399.9  $\pm$  0.889 for all the developed formulations. The capsule disintegration time varied from 6.533  $\pm$  0.302 to 7.510  $\pm$  0.376, which was found to be within the limits (Table 18 and Figure 18C).

# DISCUSSION

One of the preliminary steps in the identification of the possibility of the adulteration of crude drugs is the assessment of their organoleptic properties by the sensory perception of features for example color, odor, and taste.<sup>[2]</sup> Several preliminary detection tests are performed

Table 11: HPTLC fingerprinting of extracts of Glycyrrhiza glabra at 366 nm.

Peak No.	Glycyrrhiza g	labra sample	Glycyrrhiza glo	abra AV Gastro
Peak NO.	R <sub>f</sub> value	% area	R <sub>f</sub> value	% area
1	-0.01	0.27	0.06	4.28
2	0.05	6.02	0.10	7.23
3	0.11	4.96	0.15	3.68
4	0.12	3.02	0.18	2.61
5	0.15	4.61	0.25	8.29
6	0.19	1.61	0.31	10.67
7	0.24	6.59	0.37	5.86
8	0.30	19.08	0.45	10.25
9	0.37	5.09	0.56	5.71
10	0.45	3.93	0.63	5.34
11	0.49	4.25	0.68	5.87
12	0.53	3.74	0.81	10.94
13	0.67	12.02	0.86	10.13
14	0.86	22.73	0.88	9.13
15	0.90	2.09	-	-



**Figure 5:** HPTLC fingerprinting peaks of sample (A) and AV Gastro (B) extracts for *Glycyrrhiza glabra* at 254 nm.



**Figure 6:** HPTLC fingerprinting peaks of sample (A) and AV Gastro (B) extracts for *Glycyrrhiza glabra* at 366 nm.



Figure 7: HPTLC fingerprinting TLC plates of AV Gastro and sample extracts for *Glycyrrhiza glabra* at 254 (A) and 366 (B) nm.

Table 12: HPTLC fingerprinting of extracts of Andrographis paniculata at
254.

Peak No.	Andrographis paniculata sample		Andrographis paniculata AV Gastro	
-	R <sub>f</sub> value	% area	R <sub>f</sub> value	% area
1	0.03	22.92	0.02	26.54
2	0.10	8.35	0.10	7.48
3	0.16	3.13	0.15	3.96
4	0.18	2.10	0.17	2.33
5	0.20	1.80	0.22	8.85
6	0.24	7.27	0.25	5.26
7	0.26	2.24	0.32	4.51
8	0.29	5.42	0.37	0.69
9	0.35	5.52	0.39	0.90
10	0.50	22.12	0.44	20.46
11	0.60	2.42	0.55	1.74
12	0.65	1.69	0.60	1.05
13	0.75	1.54	0.65	0.57
14	0.91	13.48	0.69	1.09
15	-	-	0.91	14.57

to unveil the existence of primary as well as secondary metabolites in the crude drugs and their extracts.<sup>[7]</sup> The adulteration, superiority, and purity of the crude drugs can be ascertained by performing the physico-chemical evaluation such as pH analysis, loss on drying (LOD), total ash value, water-soluble ash value, acid-insoluble ash value, and extractive values.<sup>[2,10]</sup>

Many active components such as steroids, flavonoids, alkaloids, glycosides, tannins, fixed oils, volatile oils, phenols, and resins are disseminated in several portions of the plants namely flowers, leaves,



Figure 8: HPTLC fingerprinting peaks of sample (A) and AV Gastro (B) extracts for Andrographis paniculata at 254 nm.

Table 13: HPTLC fingerprinting of extracts of Andrographis paniculata at	
366.	

Peak No.		<i>is paniculata</i> 1ple	Andrographi AV Ga	
	R <sub>f</sub> value	% area	R <sub>f</sub> value	% area
1	0.01	0.81	0.01	2.26
2	0.05	9.08	0.05	8.46
3	0.10	5.09	0.09	5.15
4	0.12	3.85	0.12	3.52
5	0.16	3.28	0.15	3.24
6	0.20	6.23	0.19	7.52
7	0.24	6.94	0.22	5.67
8	0.31	11.04	0.25	3.31
9	0.38	3.44	0.28	4.86
10	0.45	14.29	0.31	3.24
11	0.51	1.43	0.34	2.92
12	0.54	5.83	0.39	13.63
13	0.62	2.45	0.46	2.08
14	0.65	1.76	0.49	4.84
15	0.72	2.41	0.57	3.64
16	0.78	3.09	0.62	3.50
17	0.84	3.02	0.78	2.47
18	0.90	4.45	0.85	4.35
19	0.93	7.38	0.90	2.08
20	0.96	4.12	0.94	7.90
21	-	-	0.96	5.38



**Figure 9:** HPTLC fingerprinting peaks of sample (A) and AV Gastro (B) extracts for *Andrographis paniculata* at 366 nm.

fruits, seeds, bark, and roots. The usefulness of bioactive components present therein is known since a long time ago. The existence of several extraction techniques including conventional and new methods has made it possible to extract important therapeutic constituents rather than using crude herbs for the treatment of ailments.<sup>[4]</sup> The term extraction can be expressed as the critical isolation of active phytoconstituents from the plant material or animal tissues by utilizing the appropriate



Figure 10: HPTLC fingerprinting TLC plates of AV Gastro and sample extracts for *Andrographis paniculata* at 254 (A) and 366(B) nm.

	Aegle marmelos sample		e Aegle marmelos AV Gas	
Peak No.	R <sub>f</sub> value	% area	R <sub>f</sub> value	% area
1	-0.00	15.53	0.01	30.64
2	0.02	17.53	0.10	3.63
3	0.04	15.45	0.13	3.29
4	0.11	3.73	0.16	2.39
5	0.13	4.15	0.18	1.43
6	0.17	3.26	0.19	1.70
7	0.19	2.15	0.22	0.35
8	0.24	0.27	0.26	1.13
9	0.25	0.48	0.32	2.07
10	0.33	3.67	0.34	1.56
11	0.40	24.22	0.40	30.10
12	0.46	0.26	0.55	1.49
13	0.48	0.46	0.59	2.03
14	0.51	0.22	0.60	1.12
15	0.56	0.60	0.62	1.03
16	0.63	0.30	0.63	1.89
17	0.66	0.71	0.75	1.10
18	0.71	0.31	0.82	1.95
19	0.73	0.30	0.83	3.20
20	0.75	0.25	0.88	2.53
21	0.83	2.31	0.89	3.13
22	0.90	2.36	0.94	1.54
23	0.94	0.74	0.95	0.73
24	0.95	0.21	-	-
25	0.96	0.41	-	-
26	0.99	0.11	-	-



**Figure 11:** HPTLC fingerprinting peaks of sample (A) and AV Gastro (B) extracts for *Aegle marmelos* at 366 nm.



(A)

**Figure 12:** HPTLC fingerprinting TLC plates of AV Gastro and sample extracts for *Aegle marmelos* at 366.

Table 15: HPTLC fingerprinting of extracts of *Holarrhena antidysenterica* at 254.

Peak	Holarrhena antidysenterica sample		Holarrhena ar AV G	· · · · · · · · · · · · · · · · · · ·	
No.	R <sub>r</sub> value	% area	R <sub>f</sub> value	% area	
1	-0.00	20.39	0.00	37.66	
2	0.01	39.04	0.12	7.25	
3	0.11	1.19	0.16	0.95	
4	0.17	1.57	0.19	0.96	
5	0.19	1.10	0.30	15.36	
6	0.50	1.82	0.37	18.14	
7	0.72	4.41	0.50	3.35	
8	0.77	3.14	0.58	3.72	
9	0.87	21.04	0.68	0.76	
10	0.89	6.30	0.81	2.01	
11	-	-	0.87	9.51	
12	-	-	0.92	0.33	

solvent or azeotropic mixture of solvents and standard procedures.<sup>[1,7,27]</sup> The selection of a suitable extraction method determines the correctness of qualitative and quantitative assessments of the biologically active components present in the plant sample under study.<sup>[4]</sup>

Presently widespread research is being carried out on diverse plant species and their bioactive components.<sup>[28]</sup> Fingerprinting involves the characterization of pharmacologically active constituents extracted from a crude drug of natural origin using chromatographic



**Figure 13:** HPTLC fingerprinting peaks of sample (A) and AV Gastro (B) extracts for *Holarrhena antidysenterica* at 254 nm.



(A)

Figure 14: HPTLC fingerprinting TLC plates of AV Gastro and sample extracts for *Holarrhena antidysenterica* at 540.

techniques, identification measures, and chemical investigation.<sup>[7,28]</sup> Chromatographic and fingerprint investigation plays an imperative part in the qualitative and quantitative valuation of these intricate herbal remedies. It is now possible to obtain a densitogram and an electronic photocopy of the chromatographic fingerprint to spot the occurrence of marker substances in a test sample by High-performance thin-layer chromatography.<sup>[28]</sup> The examination of herbal drugs utilizes the preparative and analytical HPTLC owing to its high separation ability. Almost all the phytoconstituents of the herbal products can be analyzed provided that the optimization of the procedure is done including optimization of the stationary phase and mobile phase along with other chromatographic aspects. Determination of the number of peaks or  $R_f$  value or area of peaks. Any deviation from the standard indicates contamination or deterioration of the drug.<sup>[29]</sup>

Carr's consolidation index and Hausner's ratio assist in predicting the affluence of flow of the material.<sup>[30]</sup> Excellent flow property is depicted by the material showing Carr's index in the range of 1-10 and Hausner's ratio varying from 1-1.11.<sup>[31]</sup> The angle formed by the heap of solid material relative to the horizontal surface represents the angle of repose. High values of this parameter indicate poor flow property. The determinants of the angle of repose include the shapes of the particles, surface area, density, and the coefficient of friction of the substance.<sup>[32]</sup> Values ranging from 25-30 are indicative of excellent flow properties.<sup>[31]</sup>

The drawback of loss of the effect too quickly due to gastric emptying led to the development of floating or mucoadhesive systems. The advantages of uniform distribution in the gastric content and gradual exit from the stomach have resulted in their prolonged effects and low interindividual differences.<sup>[33]</sup> Several polymers are available that increase the floating efficiency of the dosage forms. These include HPMC, CMC, Eudragit S, and Carbopol.<sup>[13]</sup> One of the widely used polymers to increase the buoyancy effect of the dosage form include Carbopol which is available

#### Table 16: Composition of gastroretentive capsule.

	Formulation code							
Ingredients (mg per capsule)	PHF1	PHF2	PHF3	PHF4	PHF5	PHF6	PHF7	PHF8
Extracts	225	225	225	225	225	225	225	225
Carbopol 971P	45	55	65	75	-	-	-	-
Carbopol 934	-	-	-	-	45	55	65	75
Lactose	122	112	102	92	122	112	102	92
PVP K30	4	4	4	4	4	4	4	4
Mg stearate	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2



Figure 15: PHF4 capsules.

# Table 17: Physical evaluation parameters of granules

Formulation code	Bulk density (g/ml)	Tap density (g/ml)	Carr's consolidation index (%)	Hausner's ratio	Angle of repose ( $\theta$ )
PHF1	$0.441\pm0.01$	$0.484 \pm 0.011$	$8.827\pm0.186$	$1.097\pm0.002$	$27.655 \pm 0.136$
PHF2	$0.423 \pm 0.009$	$0.462\pm0.010$	$8.454\pm0.171$	$1.092\pm0.002$	$29.271\pm0.382$
PHF3	$0.411 \pm 0.008$	$0.448 \pm 0.009$	$8.222\pm0.157$	$1.090\pm0.002$	$28.808\pm0.471$
PHF4	$0.406 \pm 0.008$	$0.441 \pm 0.009$	$8.111 \pm 0.157$	$1.088\pm0.002$	$27.601 \pm 0.176$
PHF5	$0.429 \pm 0.018$	$0.470\pm0.021$	$8.586 \pm 0.357$	$1.094\pm0.004$	$29.853\pm0.490$
PHF6	$0.412\pm0.016$	$0.449 \pm 0.020$	$8.232\pm0.328$	$1.090\pm0.004$	$28.766\pm0.316$
PHF7	$0.429 \pm 0.019$	$0.470\pm0.021$	$8.586 \pm 0.357$	$1.094\pm0.004$	$29.340\pm0.406$
PHF8	$0.441 \pm 0.009$	$0.484 \pm 0.011$	$8.827 \pm 0.186$	$1.097\pm0.002$	$27.538 \pm 0.412$

The results are expressed as mean  $\pm$  SD of triplicate readings

#### Table 18: Results for capsule evaluation parameters.

•	•			
Formulation code	Floating lag time (min)	Total floating time (Hrs)	% Weight variation	Disintegration time (min)
PHF1	$14.833 \pm 0.236$	$8.167\pm0.236$	$399.9\pm0.889$	$6.793 \pm 0.464$
PHF2	$20.333 \pm 0.471$	$10.833 \pm 0.471$	$399.65 \pm 0.910$	$7.323 \pm 0.381$
PHF3	$24.167 \pm 0.236$	$14.300 \pm 0.216$	$399.55 \pm 0.805$	$6.533 \pm 0.302$
PHF4	$29.000 \pm 0.816$	$24.000 \pm 0.000$	$399.85 \pm 0.910$	$6.587 \pm 0.376$
PHF5	$17.167 \pm 0.624$	$7.167 \pm 0.236$	399.8 ± 0.812	$7.230 \pm 0.169$
PHF6	$21.000 \pm 0.816$	$8.500 \pm 0.408$	$399.85 \pm 0.910$	$6.827 \pm 0.347$
PHF7	$25.500 \pm 0.408$	$10.333 \pm 0.236$	$399.7 \pm 0.954$	$7.250 \pm 0.204$
PHF8	$31.167 \pm 0.624$	$11.833 \pm 0.624$	$399.9\pm0.889$	$7.510 \pm 0.376$

The results are expressed as mean  $\pm$  SD of triplicate readings.





Figure 16: Floating lag time.

Figure 17: Total floating time.



**Figure 18:** Evaluation of physical parameters of the developed formulation: Floating granules at 20 min (A), Floating granules at 24 hrs (B), and Disintegration test (C).

in various grades such as 71G, 934, 934P, 971, 971P, 974, and 974P. Hydrogels formed from Carbopol are highly permeable to various drugs and tend to swell thereby releasing the entrapped drug through cross-linkages. Being a lightly crosslinked polymer, Carbopol 971P is more efficient in controlling the release of the entrapped drug.<sup>[34]</sup> Carbopol 971P has lower cross-linker densities and higher molecular weight amid adjacent cross-links than Carbopol 934. The cross-linked polymers have total molecular weight reported values of about 1.25x10<sup>6</sup> for Carbopol 971P and  $3 \times 10^6$  for Carbopol 934.<sup>[35]</sup> Another advantage of low molecular weight polymer is that the bioadhesive property is high due to the availability of a great number of -COOH groups for hydrogen bonding.<sup>[34]</sup>

# CONCLUSION

We have successfully developed a gastroretentive polyherbal formulation using Carbopol 971P and 934 in varying concentrations to obtain floating granules. The optimized formulation PHF4 with loosely cross-linked and low molecular weight polymer Carbopol 971P at the concentration of 75 mg yielded the granules with effectual floating properties and structural integrity over 24 h. The granules also possessed excellent flow properties suitable to be encapsulated within the capsule shells. Development of the capsule also aided in the concealing of the bitter and acrid taste of the component extracts which would enhance patient compliance. However, pharmacological confirmation of the formulation to increase therapeutic efficiency in gastric disorders needs to be estimated.

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# **CONFLICT OF INTEREST**

The authors declare no conflict of interest.

# ABBREVIATIONS

W.H.O.: World Health Organization; GRDFs: Gastro-retentive dosage forms; HPMC: Hydroxypropyl methylcellulose; CMC: Carboxymethyl cellulose; HPTLC: High-performance thin-layer chromatography; TLC: Thin layer chromatography; FLT: Floating lag time; TFT: Total floating time; PHF: Polyherbal formulation.

# Authors' Contribution

The study was designed by Manish Kumar Gupta, Medha Amol Khade, and Prashant Basappa Gurav. The extraction and pharmacognostic evaluation were carried out by Medha Amol Khade. The HPTLC fingerprinting was determined by Supriya Rajesh Hyam. Development and assessment of the formulation were executed by Medha Amol Khade and Prashant Basappa Gurav. Medha Amol Khade carried out the statistical analysis. The manuscript was written by Medha Amol Khade and Prashant Basappa Gurav. Birendra Srivastava critically analyzed and contributed valuable suggestions toward the improvement of the manuscript. The final draft was thoroughly read and approved by all the authors.

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#### **GRAPHICAL ABSTRACT**

#### SUMMARY

Crude drugs have been used for therapeutic benefits since ancient times. However, regulatory requirements have been made stringent only recently by WHO. The present study focuses on the development of a standardized gastroretentive polyherbal formulation with significant buoyancy using suitable Carbopol. Various pharmacognostic and pharmaceutical evaluation parameters have been assessed to affirm the purity and quality of the formulation.

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