

Formulation and Evaluation of Oral Reconstitutable Avipattikar Suspension

Alpana Kulkarni^{1*}, Dinesh Pandit¹, Sanket Walke¹, Ajit Kolatkar²

¹Alpana Kulkarni * MAEER'S Maharashtra Institute of Pharmacy, S. No. 124, MIT Campus, Paud Road, Kothrud, Pune-411038, Maharashtra, India

¹Dinesh Pandit MAEER'S Maharashtra Institute of Pharmacy, S. No. 124, MIT Campus, Paud Road, Kothrud, Pune-411038, Maharashtra, India

. 124, MIT Campus, Paud Road, Kothrud, Pune-411038, Maharashtra, India

²Ajit Kolatkar Practicing Ayurvedic Physician Shiv Teertha Nagar, Kothrud, Pune-411038, Maharashtra, India

* Corresponding Author: Alpana Kulkarni

Abstract: Avipattikar churna, a polyherbal Ayurvedic churna, is recommended for treatment of peptic ulcers and Functional Dyspepsia. The powders (churnas) are associated with limitations. The aim of the study was to develop a stable and palatable Avipattikar suspension consisting of a number of insoluble herbal powders. The study was also aimed at determination of acid neutralization capacity of Avipattikar suspension. Different batches of Avipattikar suspensions were prepared using the suspending agents namely, sodium carboxymethylcellulose, Aerosil® and Avicel® PH-101. Sodium citrate and mannitol were incorporated as the flocculating agent and taste masking agent respectively. The sedimentation volume, degree of flocculation, redispersibility and pH of the suspensions were evaluated. The suspending ability was in order of CMC > AR > AV. It was discovered that the higher the concentration of these suspending agents, the lower was the sedimentation volume and degree of flocculation. However, a lack of correlation was observed between the concentration of these suspending agents and the redispersibility. Avipattikar suspension consisting of CMC (0.5% w/v) exhibited best suspendability indices and palatability. The acid neutralization capacity of Avipattikar suspension was 24 times higher than that of the marketed antacid suspension. Avipattikar suspension may be a cheaper, safer and effective alternative for current antacids.

Keywords: Suspension, antacid, polyherbal, ayurvedic, acid neutralization capacity

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I. Introduction

Acid indigestion and heartburn affect a large number of global populations. Patients are prescribed antacids to relieve the symptoms caused by hyperacidity and/or peptic ulcers (acid indigestion) or Gastroesophageal Reflux Disease (GERD/ heartburn). Each year, people spend billions of dollars on antacids for relieving the symptoms of acid indigestion and heartburn. [1] Local and/ or systemic antacids are associated with limitations [2] namely, patient noncompliance due to unpleasant taste and high cost. Administration of sodium bicarbonate, a systemic antacid, may lead to systemic alkalization and sodium overload. Administration of calcium carbonate may induce hypercalcemia and rebound increase in gastric secretion. Use of magnesium hydroxide may produce osmotic diarrhea and renal failure. In addition, administration of antacids in high dose or long term treatment may be associated with gynecomastia. [3]

Herbal antacids are cheaper, safer and effective alternative for current antacids. In addition, the plant/s contain a number of phytoconstituents with antacid properties and can potentiate antacid activity. Hence herbal actives are preferred. [4]

Avipattikar churna, a polyherbal marketed Ayurvedic medicine, is used extensively for treatment of peptic ulcers. It contains thirteen herbs, namely shunthi (*Zingiber officinale*), maricha (*Piper nigrum*), pippali (*Piper longum*), haritaki (*Terminalia chebula*), vibhitaka (*Terminalia bellerica*), amalaki (*Embelia officinalis*), musta (*Cyperus rotundus*), nagarmotha (*Cyperus rotundus*) rhizomes powder, elaichi (*Elettaria cardamomum*), vidanga (*Embelia ribes*), patra (*Cinnamomum tamala*), lavanga (*Syzygium aromaticum*) and nishottar (*Operculina terpepethum*) root powder. All the herbal ingredients are present in 1 part except lavanga, trivrit and sugar candy, which are present in 11, 44 and 66 parts respectively. Therapeutic dose of Avipattikar churna, for treatment of peptic ulcers, is 3- 8 gm with water, before or after meals. [5]

The churna/ powders are associated with limitations such as inconvenience in handling, in accuracy of dose, unpleasant taste. [6] Compression of such a large dose of herbal powders into a tablet would result in a

large size tablet. Swallowing of a large tablet is difficult for patients, especially pediatric and geriatric. An aqueous suspension is a suitable alternative. A pharmaceutical suspension is a coarse dispersion in which an internal phase is dispersed continuously through out the external phase. The internal phase consists of insoluble solid particles of specific particle size and the external phase is usually aqueous. In addition, liquid antacid suspensions are preferred to tablet or powders since they are absorbed more rapidly and have a greater ability to react with and neutralize gastric acid. [7]

However, a major challenge in the formulation of oral suspension is that of physical stability. On storage, the solid insoluble drug separates from the vehicle and settles to the bottom of the container. It is desirable that such formulations redispense easily upon shaking. The suspending agent/s is added to reduce the extent of sedimentation and to redispense the sediment in a suspension. [8]

The purpose of this research was to formulate oral Avipattikar suspension for overcoming the limitations of Avipattikar churna and to improve the palatability and the stability. Another objective of the study was to determine the effect of solids content on the settling behavior of the suspensions. The work was also aimed at determination of acid neutralization capacity of Avipattikar suspension.

II. Materials And Methods

Suntha rhizome powder, maricha fruit powder, pippali fruit powder, miri fruit powder, hirda fruit powder, behada fruit powder, amla fruit powder, nagarmutha rhizomes powder, elaichi seed powder, vidanga fruit powder, tamalpatra leaf powder, lavanga floral bud powder, nishottar root powder were procured from Shree Sai Enterprises, Pune-38. Aerosil® (AR) and Sodium carboxymethyl- cellulose (CMC) were purchased from Bhor tek Chemicals, Pune-21. Avicel® PH-101 (AV), Tween 80®, glycerin, methyl paraben, propyl paraben, disodium EDTA, sodium citrate, mannitol were supplied by Analab Fine Chemicals, Mumbai-53. Mucaine Gel Mint®, manufactured by Pfizer Ltd., was purchased from local market. All other chemicals were of analytical grade.

2.1 Characterization of Herbal Drugs

All the herbal drugs were subjected to appearance, organoleptic characters, determination of foreign organic matter, ethanol soluble extractive, water soluble extractive, ash content, acid insoluble ash, loss on drying, heavy metals, microbial contamination [9], pesticide residue. [10]

2.2 Study of Particle Size of Herbal Drugs

Herbal drug sample (10gm) was placed on top sieve, having the largest screen size, into the sieve shaker. The sieve shaker has 5 sieves varying from #12, #24, #44, #66, #80. After running the sieve shaker for 10min, herbal drug sample, retained on each sieve, was weighted. The percentage passed through the sieve was calculated as follows. [11]

$$\% \text{ Passed} = \frac{\text{Weight of herbal drug sample passed through the sieve}}{\text{Weight of total herbal drug sample}} \times 100$$

2.3 Formulation of Avipattikar Suspensions

Suspensions, containing 103 mg/ml or 3.1 gm/ 30 ml of herbal powders, were prepared. (Table 1) Initially, the herbal powders were weighed and mixed in geometrical proportion in the pestle-mortar. Tween 80® and glycerin were added to the powder mixture and triturated well. Methyl paraben, propyl paraben and disodium EDTA were added to the wet mixture followed by sodium CMC/ Aerosol®/ Avicel® PH-101 and triturated with water to form a smooth dispersion. Water was added gradually while triturating. The suspensions were stored in amber glass bottles at room temperature for future analysis.

Unfloculated Avipattikar suspension (U) was prepared in the absence of wetting agents and suspending agents using herbal drugs. (Table 1) The suspensions were stored in amber glass bottles at room temperature till future analysis.

2.4 Analysis of Organoleptic Characteristics and pH of Avipattikar Suspensions

The organoleptic properties such as the colour, odour, appearance were observed by sensory organs. The pH of the suspensions was measured using Digital pH meter. [12]

2.5 Analysis of Settling Behavior of Avipattikar Suspensions

The sedimentation volume, degree of flocculation, redispersibility and pH of the suspensions were evaluated as follows.

(a) Sedimentation volume: Avipattikar suspension was homogenized (by manual shaking) and transferred into a graduated Nessler's cylinder. The height of the sediment was observed daily till there was no change in the height of the sediment for three consecutive readings. Sedimentation volume (F) is defined as the ratio of the final settled volume V_u to the original volume V_o and was calculated using following Equation. [13]

$$\text{Sedimentation volume } F = V_u / V_o$$

Where, V_u = Final volume of the sediment, V_o = Initial volume of the sediment

(b) Degree of flocculation: It is the ratio of the sedimentation volume of the flocculated suspension (F) to the sedimentation volume of the deflocculated suspension (F_∞). Avipattikar suspensions A, B and C, containing a suspending agent, were flocculated suspensions whereas Avipattikar suspension U, without a suspending agent, was a deflocculated suspension. The degree of flocculation was calculated using following Equation. [13]

$$\text{Degree of flocculation } \beta = F / F_\infty$$

Where β is the degree of flocculation, and F and F_∞ are sedimentation volume of flocculated and deflocculated suspensions, respectively.

(c) Redispersibility: The redispersibility was determined by filling Avipattikar suspension in a glass vial and rotating the vial periodically around 360 degrees until thorough dispersion was achieved. The number of rotations (N) needed for complete redispersion was recorded. Redispersion was evaluated by visual observation. [14]

2.6 Effect of Solids Content on Settling Behavior of Avipattikar Suspensions

In the present study, the solids content of Avipattikar suspensions was varied purposely (25- 100 % w), and the suspensions were prepared with suspending agents namely, CMC (Table 2), AR (Table 3) and AV (Table 4). The total weight of active herbals was considered as the solids content of the suspensions. Avipattikar suspensions were prepared by the method described in section 2.3. The organoleptic characters and the settling behavior of Avipattikar suspensions was evaluated by method described in section 2.4 and 2.5.

2.7 Effect of Flocculating Agent on Settling Behavior of Avipattikar Suspensions

Sodium citrate, a flocculating agent, was incorporated in Avipattikar suspensions. Mannitol was added to flocculated Avipattikar suspensions for improving the taste of the suspension. (Table 5) Avipattikar suspensions were prepared and evaluated by method described in section 2.3 and 2.4, 2.5 respectively. The viscosity of the suspensions was determined using Brookfield viscometer. [15]

2.8 Formulation of Reconstitutable Avipattikar Suspension

The herbal powders/ solids were weighed and mixed in geometrical method into the pestle-mortar. (Table 6) Methyl paraben, propyl paraben and disodium EDTA were added to the mixture followed by sodium CMC and triturated with mannitol. The suspension was stored in amber glass bottles at room temperature till further analysis. Avipattikar suspension was reconstituted and evaluated by method described in section 2.4 and 2.5.

2.9 Evaluation of Antacid Capacity of Avipattikar Suspension and Marketed Antacid Suspension

Avipattikar suspension and marketed antacid suspension (5.0 g) was dispersed in 100ml of water, heated to 37° C, and mixed with 100.0ml of 0.1M hydrochloric acid previously heated to 37° C. The solution was stirred continuously, maintaining the temperature at 37° C. The pH of the solution was recorded at 37° C, after 10, 15 and 20 minutes, and the pH was not less than 1.8, 2.3 and 3.0 respectively and at no time the pH was more than 4.5. This was followed by addition of 10.0ml of 0.5 M hydrochloric acid previously heated to 37° C, continuous stirring for 1 hour while maintaining the temperature at 37° C. The solution was titrated with 0.1M sodium hydroxide till the pH of the solution was 3.5 and ml of sodium hydroxide was recorded. [16]

2.10 Sensory Evaluation of Reconstitutable Avipattikar Suspension

A sensory evaluation test was performed for confirmation of taste masking of Avipattikar suspension. Bitterness of Avipattikar suspension was measured by the taste panel of six healthy human volunteers from whom a written consent was obtained. The volunteers were instructed to keep 5 ml of Avipattikar suspension in the center of the tongue and not to swallow it. It was asked to retain in the mouth for 30 second, and then the mouth was thoroughly rinsed with distilled water. The response of the volunteers were recorded on the bitterness scale (0 =good, 1=tasteless, 2=slightly bitter, 3=bitter, 4=very bitter). [17]

III. Results And Discussion

3.1 Characterization of Herbal Drugs

The results indicated that *Embllica officinalis*, *Syzigium aromaticum*, *Terminalia bellerica*, *Terminalia chebula*, *Piper nigrum*, *Piper longum*, *Zingiber officinale*, *Tinospora cordifolia*, *Embelia ribes*, *Elettaria cardamomum* complied with pharmacopoeial specifications. [18] *Cinnamomum tamala* and *Cyperus rotundus* were neither described in IP nor in Ayurvedic Pharmacopoeia. However, we came across with research articles related to characterization of *Cinnamomum tamala* and *Cyperus rotundus*. Our results were supporting the results of Koppala et al. [19] and Anupama et al. [20].

3.2 Study of Particle Size of Herbal Drugs

Antacids belong to the class of drugs that are able to neutralize body fluids. [21] As the majority of the antacid materials are poorly water soluble, they depend upon a small particle size to increase the rate of reaction with gastric acids. Consequently, a more rapid and reproducible effect is observed with the finely divided suspensions. [22] The efficacy of an antacid varies directly with the particle size of insoluble drug. [2] Besides, the physical stability of suspensions, is governed by the particle size of insoluble solids. The particle size of the insoluble solids should be as small as possible. [23]

All the herbal drugs were fine powders. A powder is a fine powder when all the particles pass through a sieve with nominal mesh aperture of 180 μm and not more than 40 per cent by weight pass through a sieve with a nominal mesh aperture of 125 μm . (Results not revealed.) Nominal mesh size of # 80 is 180 μm and Nominal mesh size of # 112 is 125 μm . The particle size of *Terminalia chebula* and *Terminalia bellerica* was large as compared to other powders and they were moderately coarse powders. [24] Avipattikar suspension consisting of the poorly soluble herbal drugs and having fine particle size, has a potential to be used as antacid.

3.3 Screening of Suspending Agent

The present study was aimed to develop oral suspensions in which a number of insoluble herbal powders were included. The suspensions were prepared using water as a vehicle. Various suspending agents were used in the development of Avipattikar suspension such as Aerosil® (2 -4 % w/w), sodium CMC (0.1 -1 % w/w), Avicel® PH-101 (0.6 - 1.5% w/w). [25] Other excipients such as Tween 80® (wetting agent that reduces interfacial tension), glycerin (wetting agent and viscosity imparting agent), and disodium EDTA (stabilizing agent) were incorporated for formulating a stable and palatable suspension. Oral liquid formulations, are highly prone to invasion by microorganisms. Among oral liquid formulations, antacid suspensions favor microbial growth since their susceptibility to bacteria and fungi is greater due to their alkalinity and basic pH. [26,27,28] Methyl and propyl paraben were incorporated as preservatives.

3.4 Analysis of Organoleptic Characteristics and pH of Avipattikar Suspensions

The suspensions showed flavour and colour characteristics of herbal powders, i.e., brownish, cloudy appearance, agreeable odour, and homogeneous dispersion of powders in the vehicle. (Table 7) The suspensions showed a pH value of 4.46 to 5.17. (Table 7) Use of different suspending agents did not result in any significant changes in this property.

3.5 Analysis of Settling Behavior of Avipattikar Suspensions

Liquid suspensions are associated with phase instability problems namely, sedimentation/ settling of solids in the container under the gravitational force of earth, dispersion of insoluble drugs in water for a sufficient period of time. Poorly formulated suspensions show rapid settling of drug particles, formation of a hard cake and difficulty in redispersion of the cake. It affects administration of the drug from the suspension and may result in under dosing or overdosing. [29] Hence the settling behaviour of the suspensions must be studied. "Stable suspension" is one in which the dispersed phase (herbal powders) and the aqueous phase do not separate for sufficient time after preparation, or if separation occurs, the suspending agent may readily redisperse the herbal powders with gentle agitation. [30] It was predetermined at the initial phases of development that the Avipattikar suspensions of this invention should be stable as made/ on the day of preparation. They should be stable for at least three hours after preparation, preferably stable for at least one day after preparation, and most preferably stable for at least fifteen days after preparation.

It is reported that sodium CMC is stable over pH 5-10 and is used in 0.1-5% w/v concentration as the suspending agent. [31] Aerosil®, colloidal silicone dioxide, is stable over pH 0-7.5 and is used in 2-4% w/v concentration as the suspending agent. [32] Avicel® PH-101 is microcrystalline cellulose (MCC). It is stable over pH 1-11 and is used in 0.6-1.5% w/v concentration as the suspending agent. [31]

Suspension U revealed least sedimentation volume and redispersibility and was attributed to absence of any suspending agent in it. Suspension A consisting of sodium CMC (0.5% w/v) depicted highest sedimentation volume after two weeks of preparation. Suspension C consisting of AV (1 % w/v) depicted lowest sedimentation volume after two weeks of preparation. (Table 7, Figure 1)

Degree of flocculation, in ascending order was Suspension C consisting of AV \leq Suspension B consisting of AR \leq Suspension A consisting of CMC. (Table 7)

Redispersibility is commonly used for evaluation of the acceptability of suspension. (United States Pharmacopoeia-National Formulary, 2007) Regarding the ease of redispersion of cake, Suspension A consisting of CMC, was easily redispersible than suspension C, consisting of AV, than suspension B, consisting of AR. (Table 7)

When Aerosil/ colloidal silicon dioxide, is dispersed in water, the insoluble particles form a 3 dimensional inter particle network in the liquid. It helps in stabilization of dispersions. The dispersed drug particles are embedded in the network and the settling of solids is reduced. Stability is determined by the type of carboxymethylcellulose as well as the concentration of carboxymethylcellulose. CMC is adsorbed on the surface of drug particles and forms bridging. It also contributes to smooth flow of the suspension.[33]

3.6 Effect of Solids Content on Settling Behavior of Avipattikar Suspensions

The objective was to study the effect of amount of solids on the settling behavior of the suspensions. Hence the solids content was varied from 3.1 gm to 0.775 gm in suspensions A1 to A4 and B1 to B4. The solids content was 100 % w/v, when 3.1 gm herbal powder was suspended in the suspensor vehicle. The solids content was 75 % w/v, when 2.33 gm herbal powder was suspended in the suspensor vehicle. (Table 8)The solids content was 50 % w/v, when 1.61 gm herbal powder was employed for making the suspension. (Table 8) The solids content was 25 % w/v, when 0.775 gm herbal powder was employed for making the suspension. (Table 8)

Optimum masking of the taste of the solid pharmaceutical active in the suspension can be achieved by limiting the amount of water in the suspension. Irrespective of minimum amount, water, present in the suspension, should hydrate the suspending agent as well as should impart the desirable flow properties. [29]For taste-masking of herbal actives and for imparting desirable flow properties, the total amount of water was varied from 10 to 35 mL in the suspensions. (Table 2, 3, 4) The settling behaviour of the suspensions was studied.

(a) Sedimentation volume: The sedimentation volume varied directly with the solids content of the suspension. (Table 8) The suspension A1 containing 0.33% of sodium CMC had the highest volume of sedimentation and also its degree of flocculation was high. When the volume of water/ suspension was less, the sedimentation volume was lower. Avipattikar suspensions, containing different concentrations of the same suspending agent, showed no significant change in sedimentation volume. However, the sedimentation volume of the suspensions varied considerably with the suspending agent. These results confirmed that the physical stability of the suspensions depends on the types of suspending agents rather than the physical properties of the drug/s. [31] Sedimentation volume (Table 8) indicated that A1 suspension having 0.33 % w/v concentration of sodium CMC, B1 suspension having 1.6% w/v concentration of Aerosil® and C1 suspension having 0.2% w/v concentration of Avicel® PH-101 were stable after 15 days of preparation. (Figure 2, 3, 4)

(b)Degree of Flocculation: The degree of flocculation increased from 1.12 to 0.83 in A1, A2, A3, A4 suspensions. (Table 8) The degree of flocculation increased from 1.03 to 0.80 in B1, B2, B3 and B4 suspensions. (Table 8) The incremental increase in degree of flocculation is an indicator of formation of a stable suspension. The higher values of degree of flocculation, associated with AR and CMC, indicated that they are better suspending agents. [23]

(c)Redispersibility: Avipattikar suspensions, containing different suspending agents, showed no significant change in their ease of redispersion. The redispersion behavior was dependent on the concentration of the suspending agent. (Table 8) The longest time for redispersion was observed in suspension A3 containing 0.5% of sodium CMC. The redispersibility of Avipattikar suspensions with AV was higher than that with AR or CMC.

Avipattikar suspensions, formulated with CMC and AR, revealed maximum sedimentation volume and degree of flocculation. CMC and AR were employed for further experimentation.

3.7 Effect of Flocculating Agent on Settling Behavior of Avipattikar Suspensions

A suspension should be uniform and any sedimentation, which occurs during storage, should be easily redispersed on agitation. In flocculated suspensions, floccules settle rapidly to form a large, loose and easily dispersible sediment. Sodium citrate was incorporated in Avipattikar suspensions F1 to F5 to achieve controlled flocculation. [14] Use of different concentrations of flocculating agent was associated with absence of any significant changes in either pH or sedimentation volume of Avipattikar suspensions. Since sedimentation volume gives only a qualitative assessment of flocculation[11], the degree of flocculation (β) is more important parameter in pharmaceutical suspensions. [34] The degree of flocculation of Avipattikar suspensions F1, F2, F3 and F4 was closer to 1 and it indicated the improvement in physical stability. (Table 9) A good suspension

should exhibit ready redispersibility (that is lower redispersibility number) so as to ensure uniformity of administered doses of medicament upon shaking.[35] All the formulations exhibited low redispersibility number, especially suspension F5. (Table 9)

Mannitol was incorporated for improving the palatability of Avipattikar suspension. It is about half as sweet as sucrose and, when taken orally, has a cooling effect which is considered desirable in masking bitter taste. It is an isomer of sorbitol and is soluble in water.[36]

Avipattikar suspensions, F3 revealed maximum sedimentation volume and degree of flocculation. The redispersibility of F3 suspension was the least. Hence suspension F3 were employed for further experimentation.

3.8 Formulation of Reconstitutable Avipattikar Suspension

It was decided to prepare dry powder of Avipattikar suspension to reduce the bulk and to extend the shelf life. The suspension would be reconstituted just before administration by adding sufficient water to dry powder and shaking the suspension. Patients are advised to drink 30 ml of this suspension, before/ after the meals to get relief from heartburn and gastrointestinal reflux disorder (GERD). The characteristics of liquid Avipattikar suspension and reconstituted Avipattikar suspension were similar. (Table 10)

3.9 Evaluation of Antacid Capacity of Avipattikar Suspension and Marketed Antacid Suspension

Antacids are widely used in the treatment of various gastrointestinal disorders such as peptic ulcers and gastritis. Antacids are also used for the relief of acid indigestion, heartburn, dyspepsia, sour stomach, reflux esophagitis and GERD. Gastric antacids are agents that neutralize or remove acid from the gastric contents. The clinical use of antacids is based on their ability to neutralize stomach acid and increase the pH of gastric secretions. Accordingly, it is desirable that an antacid possesses high acid neutralization capacity and a rapid rate of gastric acid neutralization. Although antacids do not neutralize all gastric acid, increasing gastric pH from 1.3 to 2.3 neutralizes 90% and increasing pH to 3.3 neutralizes 99% of gastric acid. For optimal healing of peptic ulcers, most clinicians believe that gastric pH should be maintained at about 3-3.5.[37]

The pH of Avipattikar suspension A (consisting of CMC as the suspending agent) at 10, 15 and 20 min after addition of 100.0ml of 0.1 M HCl was similar to the pH of Avipattikar suspension U (suspending agent was not added). Both Avipattikar suspension A (consisting of CMC as the suspending agent) and Avipattikar suspension U needed same volume of 0.1M sodium hydroxide during titration. (Table 1) These results indicated that the suspending agent was possessing insignificant gastric acid neutralization activity.

After addition of 100.0ml of 0.1 M hydrochloric acid, the pH of Avipattikar suspension, was higher (3.7) than the pH of marketed suspension (2.1). (Table 11) The acid neutralization equivalent of Avipattikar suspension, was 24 times higher (2.906 mMol of H⁺/ gm) than the acid neutralization equivalent of marketed suspension (0.12 mMol of H⁺/ gm). (Table 11) It revealed the higher antacid potential of Avipattikar suspension as compared to the marketed antacid suspension.

3.10 Sensory Evaluation of Reconstitutable Avipattikar Suspensions

When reconstitutable Avipattikar Suspension was subjected to sensory evaluation by human volunteers, the volunteers did not feel any bitter taste after keeping the suspension in mouth for 30 seconds, which confirmed that bitter taste of herbal drugs was masked successfully. (Table 12) [17]

IV. Conclusion

Avipattikar suspension consisting of CMC (0.5% w/v) exhibited best suspendability indices. It indicated masking of the bitter taste of the herbal drugs. The study revealed the higher antacid potential of Avipattikar suspension. The physical stability of Avipattikar suspensions is governed by the nature of the suspending agent rather than the physical properties of the drug/s. The study indicated a direct relation between solids content and sedimentation volume. The present study successfully demonstrated formulation of stable Avipattikar suspension from Avipattikar churna.

V. Declaration

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