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Design and development of polyherbal gel for alopecia and dandruff management

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ABSTRACT

Eight batches of Herbal Antidandruff gel were formulated. All the formulated gels were subjected to Physiochemical evaluations such as Clearance, pH, Homogeneity, Spreadability, Extrudability, Viscosity, Drug content was evaluated. Based on the physicochemical evaluations formulation F_5, F_6, F_7 and F_8 were selected as the optimized gel formulation. For the above selected formulations, i*n-vitro* release profiles were performed. The data obtained from *in vitro* release profile after 5 hours was fitted with various kinetic equations to determine the mechanism of active constituents release and release rate as indicated by higher correlation coefficients (r^2). The active constituents release from gel formulation follows zero order and non-fickian diffusion. Base on the i*n-vitro* release profile it was found that release of active constituents from prepared gels followed first order kinetics. The Antimicrobial screening result showed that the formulation F_8 was highly inhibited the fungi and bacterial growth around the patch. So F_8 was selected for further evaluations such as Skin irritation, *Ex- vivo* and stability studies. The stability studies were performed for the selected formulation (F_8) by both the technique as per the ICH guidelines.

KEYWORDS: Polyhedral, Gel, Alopecia, Herbal, Dandruff

INTRODUCTION

The term gel represents a physical state with properties intermediate between those of solid and liquids[1]. It is recommended that the term should be restricted to those systems have criteria[2] e.g. they are coherent colloidal system of at least two components (the gelling agent and a fluid component), exhibit mechanical properties characteristic of the solid state and each component is continuous throughout the system[3]. The term “gels” is

broad, encompassing semisolid of a wide range of characteristics from fairly rigid gelatin slabs, to suspensions of colloidal clays, to certain greases[4]. A gel can be looked upon as being composed of two interpenetrating phase (the gelling agent and a fluid component) [5]. Gels should possess properties like ideally, the gelling agent for pharmaceutical or cosmetic use should be inert, safe, and should not react with other formulation components[6]. The gelling agent included in the preparation should produce a reasonable solid-like nature during storage that can be easily broken when subjected to shear forces generated by shaking the bottle, squeezing the tube, or during topical application[7]. The gel should exhibit little viscosity change under the temperature variations of normal use and storage[9]. It should posses suitable anti-microbial to prevent from microbial attack[9].

The significance of Pharmaceutical Research and Development is on the creation of therapeutic, prophylactic and diagnostic substances with specific functions and minimum side effects in particular of being tools for modern medicine satisfying these conditions. Design and development of the polyhedral gel for alopecia and dandruff management

MATERIAL AND METHODS

Amla fruit, lemon fruit, Garlic, Ginger, Aloe vera Leaves were collected locally and processed. Carbapol, Triethanolamine, purchased from LOBA CHEMIE, Mumbai, Glycerin from Merk Limited, Mumbai, Polyethylene Glycol, Propyl Paraben, were purchased from Kemphasol, Mumbai. All chemicals and reagents were belongs to laboratory grade chemicals.

Collection of selected Herbs: *Emblica officinalis.* Gaertn, *Citrus limonum.* Risso, *Allium sativum.* Linn, and *Zingiber officinale.* Roscoe were collected from in and around Tiruchirappalli district, Tamilnadu. Collected herbs were authenticated by Botanist, Dept. of Botany, National College, Trichy.

Preparation of aqueous extract of selected Herbs: Collected and selected parts of herbs such as *Emblica officinalis.* Gaertn, *Citrus limonum.* Risso, *Allium sativum.* Linn, and *Zingiber officinale.* Roscoe were washed with distilled water and grinded individually by simple grinding. Then the extract was filtered, centrifuged and used for further studies.

***Maceration*:** Grinded drug material were placed inside a container, the menstruum was poured on top until completely covered the drug material. The container was then closed and kept for at least three days. The content was stirred periodically, and if placed inside bottle it should be shaken time to time to ensure complete extraction. At the end of extraction, the micelle was separated from marc by filtration or decantation. Subsequently, the micelle is then separated from the menstruum by evaporation in an oven or on top of water bath. This method is convenient and very suitable for thermolabile plant material.

Phytochemical studies: The aqueous extracts of *Emblica officinalis, Citrus limonum, Allium sativum,Zingiber officinalis* and *Aloe barbadensis* were subjected to the following preliminary phytochemical analysis.

Formulation of Herbal Antidandruff Gel

Table No. 1: Formulation of Herbal Antidandruff Gel

S. No.	Ingredients	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
1	*Emblica officinalis*	0.5ml	-	-	0.5ml	0.5ml	-	-	0.5ml
2	*Citrus limonum*	-	0.5ml	-	0.5ml	-	0.5ml	-	0.5ml
3	*Allium sativum*	-	-	0.5ml	0.5ml	-	-	0.5ml	0.5ml
4	*Zingiber officinalis*	-	-	0.5ml	0.5ml	-	-	0.5ml	0.5ml
5	*Aloe barbadensis*	-	-	0.5g	0.5g	-	-	0.5g	0.5g
6	Carbopol 940	0.30g	0.30g	0.30g	0.30g	-	-	-	-
7	Carbopol 934	-	-	-	-	0.30g	0.30g	0.30g	0.30g
8	Polyethylene Glycol	7g	7g	7g	7g	7g	7g	7g	7g
9	Triethanolamine	0.6g	0.6g	0.6g	0.6g	0.6g	0.6	0.6g	0.6g
10	Propyl Paraben	0.075g	0.075g	0.075g	0.075g	0.075g	0.075g	0.075g	0.075g
11	Glycerine	3ml	3ml	3ml	3ml	3ml	3ml	3ml	3ml
12	Water q.s	50ml	50ml	50ml	50ml	50ml	50ml	50ml	50ml

Procedure for preparation of Herbal Antidandruff Gel

- Measured quantity of propyl paraben, glycerine and weighed quantity of Polyethylene Glycol were dissolved in about 35 ml of water in beaker
- Then it was stirred at 100rpm using mechanical stirrer
- Carbopol 940 and 934 were added slowly to the respective beaker containing above liquid while stirring
- Triethanolamine (Neutralizing agent) was added slowly with stirring till to attain gelstructure
- Required proportions of aqueousextracts*Emblica officinalis, Citrus limonum, Allium sativum, Zingiber officinalis* and *Aloe barbadensis* were added to the prepared gel and stirred continuously to form proper gel

Physicochemical Evaluation of Herbal Antidandruff Gels: Gels were evaluated for their clarity, pH, homogeneity, spreadability, viscosity, drug content, extrudability, *in-vitro* diffusion studies, release kinetics, antimicrobial screening, skin irritation test and*ex-vivo* studies by using standard procedure. All studies were carried out in triplicate and average values were reported.

Screening of Antimicrobial activity of Herbal Antidandruff gel formulation: Discs impregnated with known concentration of antibiotics discs are placed on agar plate that has been inoculated (or) seeded uniformly over the entire plate with a culture of the bacterium to be tested. The plate is incubated for 18-24 hrs at 37oC. During this period, the antibacterial agent diffuses through the agar and may prevent the growth of organism.

Effectiveness of susceptibility is proportional to the diameter of inhibition of zone around the discs. Organisms which grow up to the edge of the disc are resistant.

Stability:

Stability is officially defined as the time lapse during which the drug product retains the same property and characteristics that it possessed at the time of manufacture. This process beings at early development phases. All the selected formulations were subjected to a stability testing for three months as per ICH norms at a temperature (40˚C ± 2˚C). All selected formulations were analyzed for the change in pH, spreadability, homogeneity or drug content by procedure statedearlier.

RESULTS AND DISCUSSION

Phytochemical studies: The phytochemical studies of *Emblica officinalis*, *Citrus limonum*, *Allium Sativum*, *Zingiber officinale*, *Aloe barbadensis* was done. The presence and absence of Phyto-constituents in the aqueous extract of the above sample was shown in Table.

Table No. 2: Phytochemical studies

Phytoconstituents	Aqueous extracts				
	Emblica officinalis	***Citrus limonum***	***Allium sativum***	***Zingiber officinale***	***Aloe barbadensis***
Alkaloids	+	+	+	+	+
Glycosides	+	+	+	+	-
Saponins	-	-	+	+	+
Tannins	+	+	-	+	+
Phenols	+	+	+	+	-
Reducing sugars	+	+	+	+	+
Amino acids	+	+	+	+	+
Flavonoids	-	+	+	+	+
Terpenoids	-	+	_	+	+
Steroids	+	+	+	-	-

(+) Presence of phytoconstituents (-) Absence of phytoconstituents

UV Analysis: Absorption maxima (λ max) of Aqueous extract of*Emblica officinalis* Gaertn

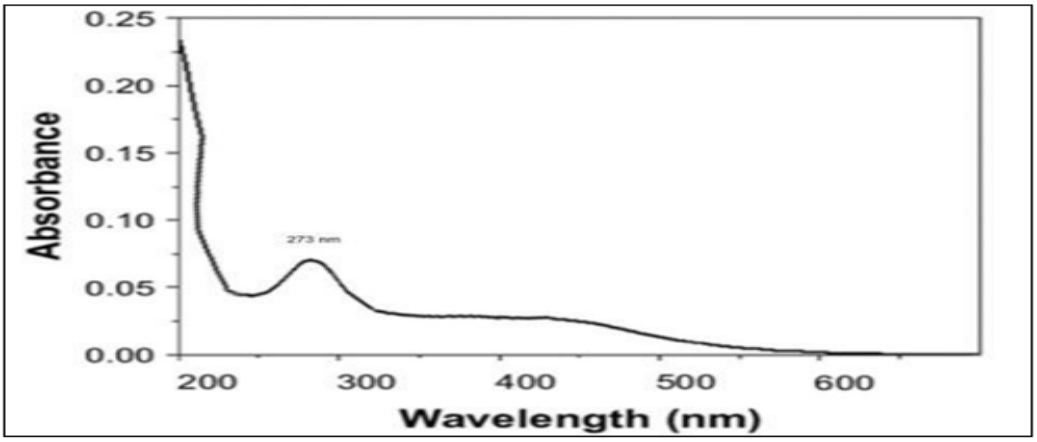

Figure 1: Absorption maxima (λ max) of Aqueous extract of *Emblica officinalis* Gaertn

Standard curve of Aqueous extract of *Emblica officinalis* Gaertn

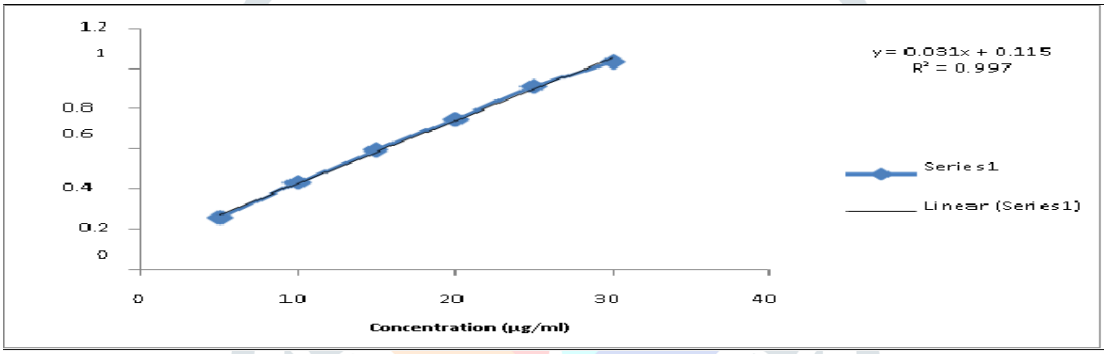

Figure 2: Standard curve of Aqueous extract of *Emblica officinalis* Gaertn

Standard curve of Aqueous extract of *Citruslimonum*. Risso

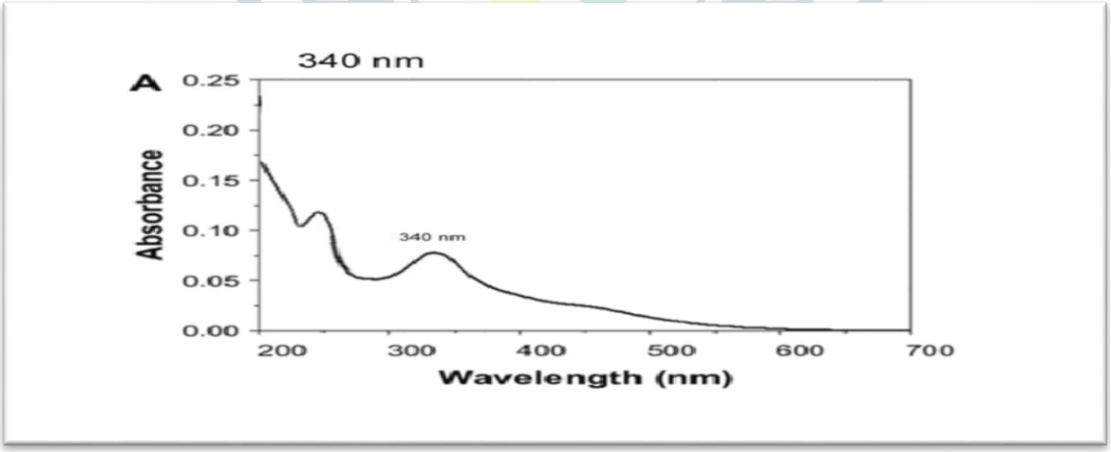

Figure 3: Standard curve of Aqueous extract of *Citruslimonum*

Absorption maxima (λ max) of Aqueous extract of *Citrus limonum*. Risso

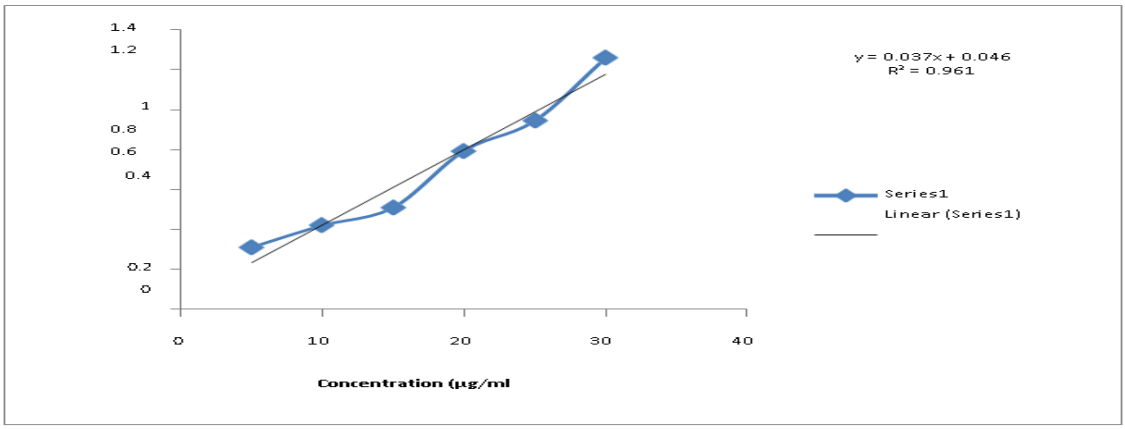

Figure 4: Absorption maxima (λ max) of Aqueous extract of *Citrus limonum*

Physico chemical evaluation of Herbal Antidandruff Gel

Table No. 3: Physico chemical evaluation of Herbal Antidandruff Gel

Formulations	Clarity	pH	Homogeneity	Spreadability (g.cm/sec)	Extrudability	Viscosity (cps)	% Drug Content
F1	Turbid	6.9	Not Good	10.08	+	8823	70.92
F2	Turbid	6.8	Not Good	12.89	+	8818	75.30
F3	Turbid	6.7	Not Good	12.27	+	8951	68.53
F4	Turbid	6.9	Not Good	13.86	+	8890	72.95
F5	Clear	7.1	Good	18.75	+ +	9632	79.82
F6	Clear	6.9	Good	20.55	+ +	9826	83.02
F7	Clear	7.0	Good	22.39	+ +	9142	78.92
F8	Clear	7.2	Good	18.07	++	9122	85.46

+ Satisfactory, ++ Excellent

Eight batches of Herbal Antidandruff Gel formulations were prepared by using Carbopol 940 and Carbopol 934 were subjected to various physicochemical evaluations. Based on the clarity, pH, homogeneity, spreadability, viscosity, percentage drugcontent and extrudability formulations F_5, F_6,F_7,F_8 were selected for further studies.

Optimized formula of Herbal Antidandruff Gel

Table No. 4: Optimized formula of Herbal Antidandruff Gel

S. No.	Ingredients	F_5	F_6	F_7	F_8
1.	*Emblica officinalis*	0.5ml	-	-	0.5ml
2.	*Citrus limonum*	-	0.5ml	-	0.5ml
3.	*Allium sativum*	-	-	0.5ml	0.5ml
4.	*Zingiber officinalis*	-	-	0.5ml	0.5ml
5.	*Aloe barbadensis*	-	-	0.5g	0.5g
6.	Carbopol 934	0.30g	0.30g	0.30g	0.30g

7.	Polyethylene Glycol	7g	7g	7g	7g
8.	Triethanolamine	0.6g	0.6	0.6g	0.6g
9.	Propyl Paraben	0.075g	0.075g	0.075g	0.075g
10.	Glycerine	3ml	3ml	3ml	3ml
11.	Water q.s	50ml	50ml	50ml	50ml

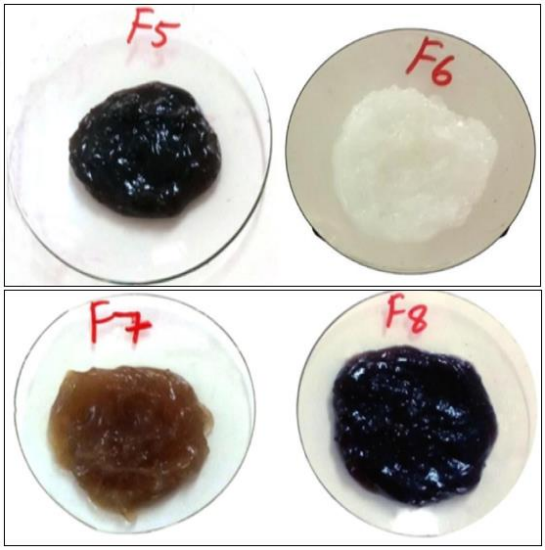

Figure 5: different prepared Formulation F_5, F_6, F_7 and F_8

Physiochemical Evaluation of Best Four formulations

Table No. 5: Physiochemical Evaluation

Formulations	Clarity	pH	Homogeneity	Spreadability	Extrudability	Viscosity	Drug content
F_5	Clear	7.1	Good	18.75	79.82	9632	79.82
F_6	Clear	6.9	Good	20.55	83.02	9826	83.02
F_7	Clear	7.0	Good	22.39	78.92	9142	78.92
F_8	Clear	7.2	Good	18.07	85.46	9122	85.46

Screening of Antimicrobial activity of Optimized Gel formulation

The anti-microbial activity for the given sample was carried out by Disc Diffusion Technique (Indian Pharmacopoeia 1996, Vol II A-105). The test microorganism of *Malassezia furfur* was obtained from Institute of Microbial technology, Chandigar and other test organisms *Candida albicans Staphylococcus aureus, Escherichia coli, Klebsiella aerogenes* were obtained from National Chemical Laboratory (NCL) Pune and maintained by periodical sub culturing on Nutrient agar and Sabouraud dextrose agar medium for bacteria and Fungi respectively. The effect produced by the sample was compared with the effect produced by the positive control (Reference standard Ciprofloxacin 5 µg/disc for bacteria; Nystatin 100 Units/disc for *Candida albicans and* Ketoconazole 100 units/disc *Malassezia furfur*).

For Fungi: After 72h the plates were observed. The zone of inhibition was calculated by measuring the minimum dimension of the zone of no fungal growth around the patch.

For Bacteria: After 24h the plates were observed. The zone of inhibition was calculated by measuring the minimum dimension of the zone of no bacterial growth around the patch.

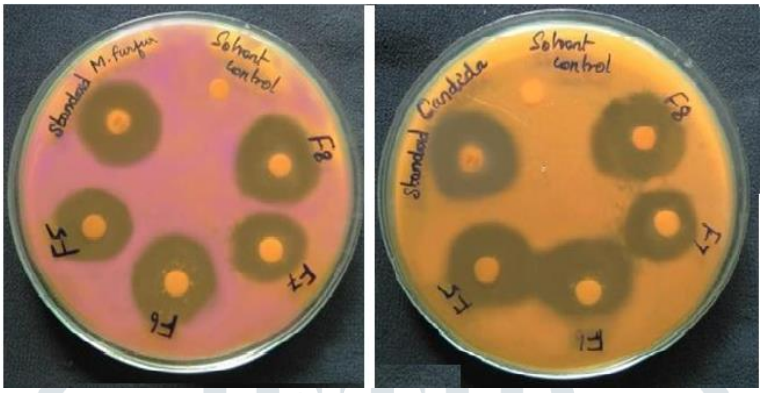

Figure 6: Antifungal activity using (A) *Malassezia furfur* (B) *Candida albicans*

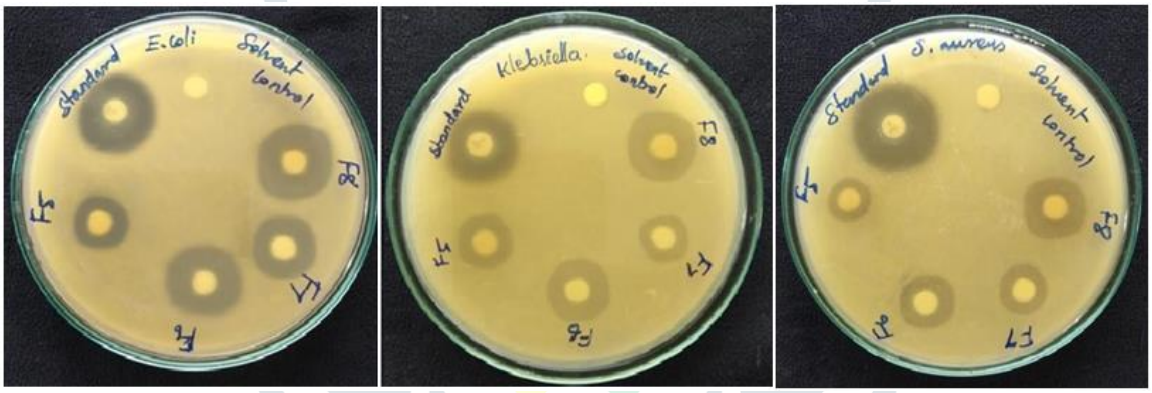

Figure 7: Antibacterial activity using (A) *Escherichia coli* (B) *Klebsiella aerogenes* (C) *Staphylococcus aureus*

F_5- Herbal Antidandruff Gel containing aqueous extract of *Emblica officinalis*

F_6- Herbal Antidandruff Gel containing aqueous extract of *Citrus limonum*

F_7- Herbal Antidandruff Gel containing aqueous extract of Adjuvants such as *Allivum sativum, Zingiberofficinale, Aloe barbadensis.*

F_8- Herbal Antidandruff Gel containing Aqueous extract of *Emblica officinalis*, *Citrus limonum* and adjuvants

Ciprofloxacin: 5µg /disc for bacteria,

Nystatin: 100 units /disc for *Candida albicans*

Ketoconazole: 100 units/disc for *Malassezia furfur*

Solvent: DMSO

When compared to F_5, F_6, F_7 the formulation F_8 showed greater inhibition against *Malassezia furfur, Candida albicans, Staphylococcus aureus, Escherichia coli, Klebsiella aerogenes.* So formulation F_8 has been selected for skin irritation, *ex-vivo* and stability studies.

Table No. 6: Screening of Antimicrobial activity

Name of theOrganism	Zone of Inhibition in mm					
	Sample				Solvent Control	Standard
	F_5	F_6	F_7	F_8		
Malassezia furfur	27	28	23	33	Nil	35
Candida albicans	25	27	20	29	Nil	32
Staphylococcus aureus	12	16	15	20	Nil	35
Escherichia coli	18	22	20	24	Nil	38
Klebsiella aerogenes	17	20	15	22	Nil	30

Stability study of Herbal Antidandruff Gel F_8

Table No. 7: Stability study of F_8

Parameter	Observation						
	Initial	At the end of 1st month		At the end of 2nd month		At the end of 3rd month	
		RT	40±2°C & RH 70±5%	RT	40±2°C & RH 70±5%	RT	40±2° & RH 70±5%
Appearance	Smooth	Smooth	Smooth	Smooth	Smooth	Smooth	Smooth
pH	7.2	7.0	7.2	7.2	7.2	7.2	7.1
Spreadibility	18.07	18.06	18.07	18.07	18.07	18.07	18.07
Extrudability	Excellent	Excellent	Excellent	Excellent	Excellent	Excellent	Excellent
% drug content	85.46	85.46	85.44	85.46	85.46	85.46	85.46

The stability studies of Herbal Antidandruff Gel of formulation F_8 was carried out for three months. During this period, the formulations were stable and showed no significant changes in visual appearance, pH, Spreadability, Extrudability, % drug content.

CONCLUSION

Eight batches of Herbal Antidandruff gel were formulated. All the formulated gels were subjected to Physiochemical evaluations such as Clearance, pH, Homogeneity, Spreadability, Extrudability, Viscosity, Drug content was evaluated. Based on the physicochemical evaluations formulation F_5, F_6, F_7 and F_8 were selected as

the optimized gel formulation. Based on the phytochemical screening on aqueous extract of *Emblica officinalis* and *Citrus limonum* are rich in bioactive compounds. However, further studies are needed in order to isolate, identify, characterize and elucidate the structure of the bioactive compounds responsible for antidandruff activity. For the above selected formulations, i*n-vitro* release profiles were performed. The data obtained from *in vitro* release profile after 5 hours was fitted with various kinetic equations to determine the mechanism of active constituents release and release rate as indicated by higher correlation coefficients (r^2). The active constituents release from gel formulation follows zero order and non-fickian diffusion. Base on the i*n-vitro* release profile it was found that release of active constituents from prepared gels followed first order kinetics. To confirm the release mechanism, the data of F_5, F_6, F_7, F_8 release were applied to Korsmeyer- peppas equation to find out the release exponent 'n', which indicates the mechanism of drug diffusion from the gel formulation. Then they were subjected to Screening of antimicrobial activity.

The Antimicrobial screening result showed that the formulation F_8 was highly inhibited the fungi and bacterial growth around the patch. So F_8 was selected for further evaluations such as Skin irritation, *Ex- vivo* and stability studies. The stability studies were performed for the selected formulation (F_8) by both the technique as per the ICH guidelines. The gel was subjected to stability study at 40°C±2°C and 75±5% RH, samples were withdrawn on 1 month, 2 month, 3 month and analyzed. The result shows that the product was stable for 3 months without change in physical changes. Since the antimicrobial studies has given encouraging results in enhancing the antidandruff activity of F_8 formulation , it is concluded that the F_8 Herbal antidandruff gel may be subjected to further *in-vivo* and clinical trials.

CONFLICT OF INTERESTS

There are no conflicts of interests.

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