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Formulation and Characterization of *Boswellia serrata* Resin Gel by Using Different Gelling Agents

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ABSTRACT

In the recent period, arthritis is common health problem having average about one in five people that create imbalance in their physical activities. Such problem required higher amount of drug concentration to achieve better therapeutic effect, hence topical application is suitable to reducing the inflammation of targeted tissue. The present research work is to formulate and evaluate topical gel containing *Boswellia serrata* act as anti-inflammatory therapeutic effect. Gel was formulated by the dissolving 1 percent of topical gel of *Boswellia serrata* in suitable solvents (propylene glycol, ethanol,) and to incorporate mixture into required quantity of gelling agents to form a homogenous dispersion and the pH was adjusted by triethanolamine, to prepared formulation was to undergone various preliminary evaluation like appearance, pH of gel, drug content, rheological study, spreadability, extrudability, drug releases, drug contents, and stability. All gel formulations shows suitable physical properties with references to color, homogeneity, consistency, spreadability, and pH value. Gel formulation was prepared with sodium alginate, HPMC K4M, and xanthan gum shows good homogeneity and stability. However, the HPMC K4M based gels proved to the method of selection because it shows the highest percentage of extrudability, good spreadability and rheological properties. Formulation (F4) shown best result as drug content (95.1±1.53 %) and % drug release (90.66 %) which containing 1% HPMC K4M as gelling agent.

INTRODUCTION

Topical gels formulation gives a proper drug delivery system at desired concentration of drug because these are less oily and can be simply remove from the skin. Gel formulations have good applications property and reliability in the comparison to cream, emulsion, semi-solid and ointments. Gel formulations are typically transparent or translucent, water based semisolid with good spreading properties and aesthetic characteristic containing a high ratio of solvent that shows no steady-state flow. The contact between polymer and the liquids dispersion medium form an interlaces three dimensional networks of particle of disperse phase. The increase thickness caused by interlaces and important inner resistance is responsible for the semisolid steady- state.

The topical gel formulation is the broad technology of growing interest for the dermatology field. In the present period topical drug delivery system is growing rapidly as well as another drug delivery system. Topical drug delivery system is most convenient method for the delivery of drug via mucus membrane or skin because it can easily reach to organ or targeted tissue of human body to achieve better therapeutic effect. It can conveniently passes to bottomless into skin and shows better absorption. Topical drug delivery system decreases the risk of G.I irritation, prevent the first pass metabolism and enhance the penetration of drug directly into the organ through skin during enhancing the bioavailability of the drug. Cream, lotion and ointment are other forms of topical drug delivery system.

In the recent period, arthritis is common health problems having average about one in five people that create imbalance in their physical activities. Such problem required higher amount of drug concentration to achieve better therapeutic effect, hence topical application is suitable to reducing the inflammation of targeted tissue. Inflammation is frequently caused by several infections, different types of immune reactions, burn and trauma [1, 2, 3].

Drug

Botanical names- *Boswellia serrata* Roxb, *Olibanum indicum.*

Family- *Burseraceae*

The *Boswellia serrate* (Salai Guggal) is the ancient plant used as an herbal medicine in ayurveda that is local to India, primarily the states of Punjab. In ayurveda, its extract is

known to reduce pain in the joints and is useful in case of swollen joints and anti-inflammatory join disorder. It rejuvenates the blood vessels damage by muscular contractions and also improves the blood supply to the joints. It has been evident in studied that it acts as an aid in attaining flexible joints and increased resistance against anti-inflammatory activity.

Figure 1: ***Boswellia serrata***

Chemical composition: Bark B- sitosterol, Glucosides

The resin consists of monoterpene, diterpene, triterpene, tetracyclic triterpenic acid and four major pentacyclic triterpenic acid i.e. β-boswellic acids, acetyl-β-boswellic acids, 11-keto-β-boswellic acids and acetyl-11-keto-β-boswellic acids [4, 5, 6].

MATERIALS AND METHODS

Boswellia serrata powder was received from Isha Agro Developers Pvt. Ltd., Pune. Sodium alginate, Xanthum Gum, HPMC K4M, PEG 4000 and Triethanolamine obtained from SD-Fine Chem. Ltd., Mumbai, India. Ethanol, Methanol, Chloroform and propylparaben obtained from Merk Ltd., Mumbai, India.

Preparation of Gel [7, 8]

Preparation of gel with sodium alginate: Accurately weighed sodium alginate was taken in a beaker also dispersed in 50 ml of distilled water. Kept the beaker aside to swell the sodium alginate are 30 min stirring should be done use mechanical stirred at 700 rpm for 30 minutes. Take 5 ml propylene glycol in another beaker and add weigh quantity of propylparaben, methylparaben to it and stirred properly. After all sodium alginate dispersed, 1 gm drug and preservatives solutions were added with continuous stirring. Finally makes up the volume up to 100 ml by adding residual distilled water and Tri-ethanolamine was added drops wise to the formulations for adjustment of require skin pH (5.5) and to obtained the gel at required reliability.

Preparation of gel with HPMC K4 M: Accurately weighed 1 gm of drug was placed to a beaker and dissolve in 10 ml of propylene glycol into which preservative was added. HPMC K4 M was made to disperse in distilled water then heated up to 70-900^0 C with continuously stirred and it was allowed to cool. Then 1 % w/v drug loaded to propylene glycol solution were added to HPMC K4 M preparation and stirred strongly to mixed in cold condition and water was added to make up the volumes up to 100 ml and stirred in mechanical stirred well and got uniformed gels.

Preparation of gel with Xanthan gum: Correctly weighed Xanthan gums was placed in a beaker and disperse in 50 ml of distilled water and kept the beaker away to swell the Xanthan gum are 30 min stirring should be done use by mechanical stirrer at 1200 rpm for 30 min. Take 5 ml of propylene glycol and require quantity of drug. Take 5 ml propylene glycol in any more beakers and add weight quantity of propylparaben and methylparaben to it and stirred properly. After all Xanthan gum disperse, drug and preservatives solutions were added with continuous stirring.

Drug Polymer Interaction Study

The Drug-polymer compatibility studies were designed to ensure the stability to final formulation. The drug-polymer compatibility was further confirmed by taking the IR spectrum of the drug, the polymer and physical mixtures of drug-polymer in ratio 1:1. The IR spectrum of physical mixtures of drug and polymer was taking by placing them in stability chamber at a temperature of 40^{O}C and 75% RH for 21 days.

Table 1: Drug-Polymer Ratio

S. No.	Material	Quantity (mg)
1	*Boswellia serrata*	100mg
2	Drug + HPMC K100 M	100mg + 100mg
3	Drug + Sodium alginate	100mg + 100mg
4	Drug + Xanthan gum	100mg + 100mg

Table 2: Composition of various *Boswellia Serrata* Resin Gel Formulation

Ingredients	Sodium alginate			HPMC K4M			Xanthum gum		
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Boswellia serrata resin	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg
Sodium alginate	1 %	1.5 %	2 %	-	-	-	-	-	-
HPMC K4M	-	-	-	1 %	1.5 %	2 %	-	-	-
Xanthum gum	-	-	-	-	-	-	1 %	1.5 %	2 %
Propylene glycol	5ml	5ml	5ml	5ml	5ml	5ml	5ml	5ml	5ml
Triethanolamine	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Methyl paraben	0.05g	0.05g	0.05g	0.05g	0.05g	0.05g	0.05g	0.05g	0.05g
Ethanol	5ml	5ml	5ml	5ml	5ml	5ml	5ml	5ml	5ml
Purified Water Up to	100ml	100ml	100ml	100ml	100ml	100ml	100ml	100ml	100ml

Evaluation of Prepared Topical Gel [9, 10, 11]

Physical Evaluation

The prepared *Boswellia serrata* gels were inspect visually for their colors, spreadability, pH, homogeneity, viscosity, accelerated stability studies.

Measurement of pH

The pH of gel formulations are determined by digital pH meter. 1 gram of gel is dissolved in 100 ml of distilled water and then store for two hours. The quantity of the pH of each formulation is done in triplicate and then average values are calculated.

Drug content analysis

One gram of gel equal to 10 mg was taken and dissolved separately in 10 ml of methanol. The solutions were filtered then diluted and absorbance of solutions was determined at 254 nm by UV spectrophotometer. Then the actual drug content was calculated.

Determination of Viscosity

The viscosity of the prepared gel formulation is an important factor in determination were carried out by using Rotational viscometer (Fungi lab) in spindle number PF, PE, PD, PC, PB, PA, in angular viscosity range from 2-12 rpm. At a particular RPM is the maximum torque and its respected reading in centipoises and note down the readings and the average of reading was calculated to viscosity.

Spreadability

The spreadability of the gel formulation was determined by measuring diameter of 1 gm gel between horizontal plates (20×20 cm2) after 1 minute. The standardized weight on the upper plate was 1000 gm.

It is the calculated by using the following formula

$$(S) = M \times L / T$$

Where, S = spreadability (gcm/sec)

M = is the weight tied to upper slide,

L = length of glass slide

T = time taken to separate the slides.

Extrudability study

The formulations are filled in the collapsible tubes after the gel are set in a container. The formulation is determined in the terms of weight in gram required to extrude a 0.4 cm ribbon of gel in 10 seconds.

Zero Order Releases: Drug dissolution dosage forms that do not disaggregate and released the drugs slowly can be represented as-:

$$Q = Q0 + K0t$$

$$\log Q = \log Q0$$

Where Q is the amounts of drug released at time t, $K_{\circ}$ is the zero order released rate constants.

First Order Release: where Q is the percent of drug release at time t, K1 is the first order release rate constant into the following equation,

$$\text{Log } C = \text{Log } Co - k1t / 2.303$$

Where C is the amounts of drug release at time t, C0 is the initial amounts of drug in the solutions and K1 is the first order release constant.

Higuchi Model: where Q is the % of drug released at time t, K2 is the Higuchi square root of time released constant.

$$Q = K2 \sqrt{t}$$

Accelerated stability studies

Stability studies are define as the extent, which a product retain within a specified limits and throughout its periods of storage and use i.e. shelf life, stability studies, were carried out in optimization formulation according to international conference on harmonization guidelines. The stability study was carried out for the most satisfactory formulation. A sufficient amount of formulation is previously sterilized was stored in desiccators, which gives a relative humidity of 75±5%. The desiccators were placed in a humidity chamber was maintained at a temperature 40±50C and at a room temperature. These samples were withdrawn at 0 day, 15 days, 30 days, 45 days, 60 days, 75 days, 90 days interval. The perfect drug remaining was calculated and plotted against time in day.

RESULTS AND DISCUSSION

Preparation of calibration curve of *Boswellia serrata* resin in phosphate buffer pH 5.5: 50 mg of *Boswellia serrata* resin was weighed accurately and dissolved in 50 ml phosphate buffer pH 5.5, the solution marked as stock solution-1 from this solution 10 ml of solution was withdrawn in 100 ml volumetric flask and make the volume up to 100 ml by distilled water. Then solution was sonicated for 10 min. This solution marked as stock solution-2.

- From stock – 2, dilution having concentration 2 µg/ml, 4 µg/ml, 6 µg/ml, 8 µg/ml, and 10 µg/ml was prepared by distilled water.

Above prepared solution were observed in double beam UV- spectrophotometer to measure the absorbance in increasing order of concentration.

Table 3: Calibration curve of *Boswellia serrata* resin in phosphate buffer

S. No	Concentration (µg/ml)	Absorbance (λmax=254nm)
1	2	0.1698
2	4	0.2669
3	6	0.3543
4	8	0.486
5	10	0.5501

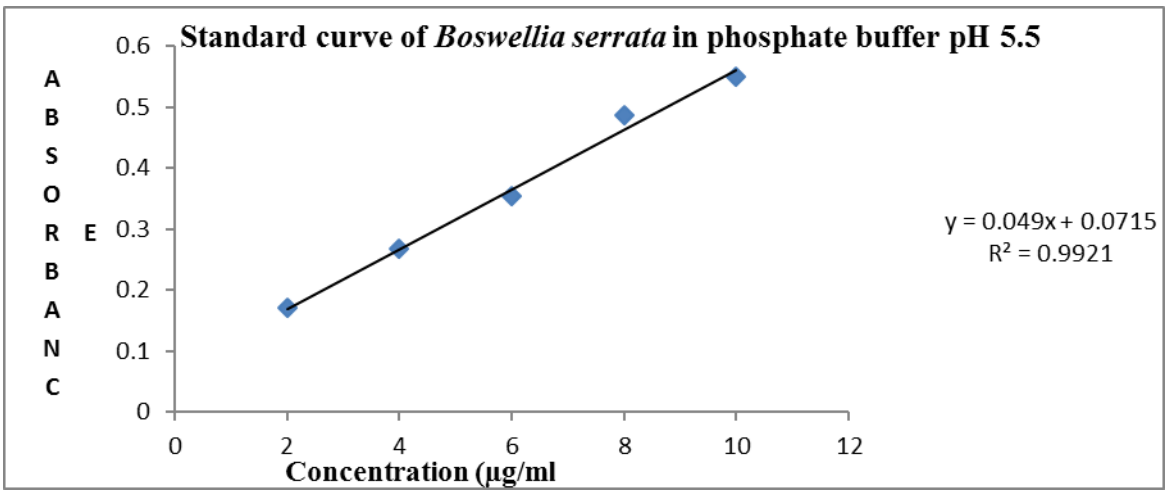

Figure 2: Calibration curve of *Boswellia serrata* resin in phosphate buffer

Drug Excipients Compatibility Study

The drug and excipient were taken in 1:1 ratio and mixed properly using a poly bag. Now the mixtures were transferred into the glass vials and samples were placed in stability chamber at 40^0C for 21 days. Glass vials filled with plane drug and polymers were also placed in the same way.

Through Fourier Transform Infrared Spectroscopy: Drug excipients compatibility study was confirmed by FTIR analysis.

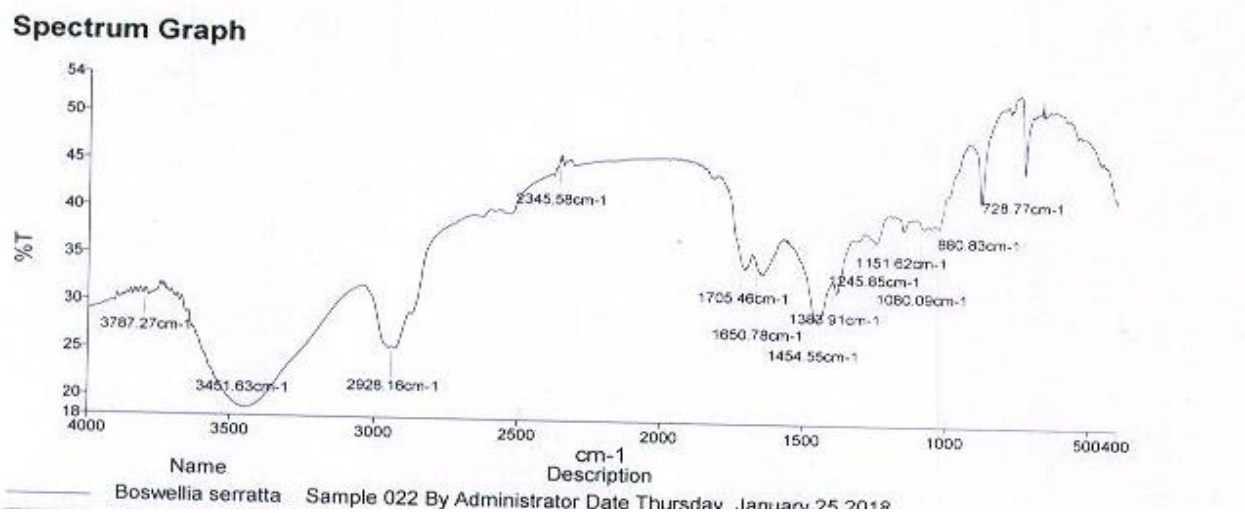

Figure 3: FTIR of *Boswellia serrata*

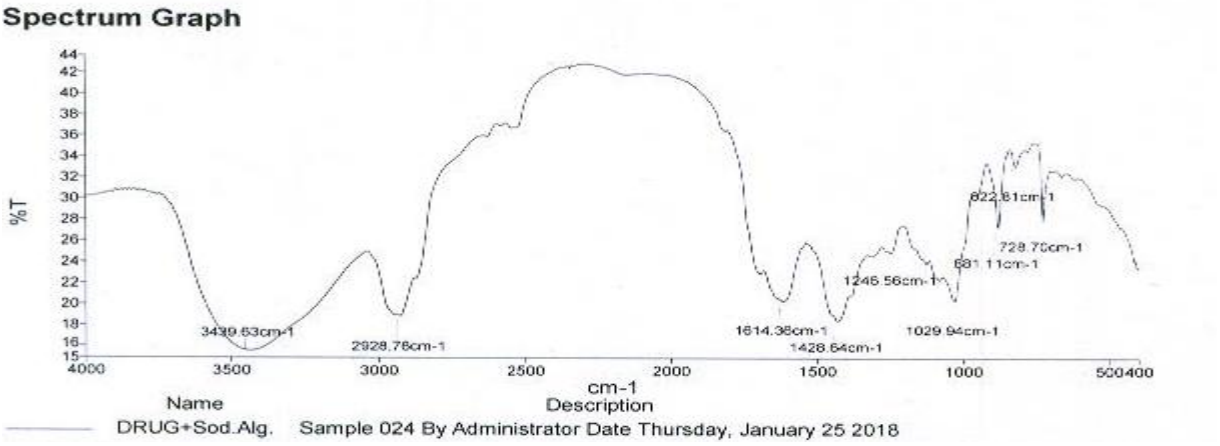

Figure 4: FTIR of drug (*Boswellia serrata*) + Sodium alginate.

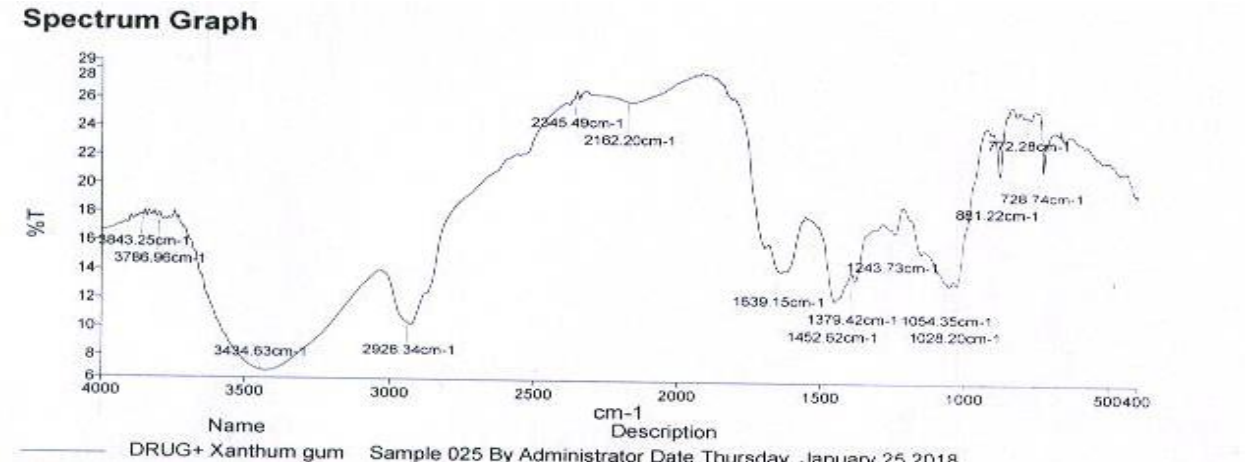

Figure 5: FTIR of drug (*Boswellia serrata*) + Xanthum gum.

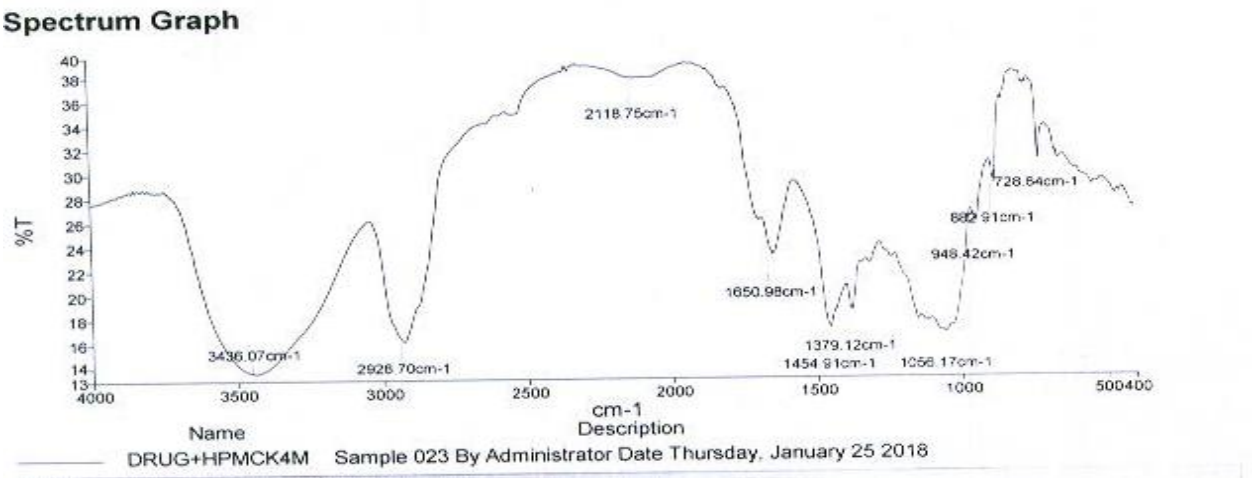

Figure 6: FTIR of drug (*Boswellia serrata*) + HPMC K4M.

Evaluation Studies

Physical appearance: The formulations are evaluated for color, homogeneity and consistency.

Table 4: Physical appearance of prepared gel formulations

Formulation code	Color	Homogeneity	Consistency	Phase separation
F1	Transparent	Amorphous	Smooth	-
F2	Transparent	Amorphous	Smooth	-
F3	Transparent	Amorphous	Smooth	-
F4	Transparent	Amorphous	Smooth	-
F5	Transparent	Amorphous	Smooth	-
F6	Transparent	Amorphous	Smooth	-
F7	Transparent	Amorphous	Smooth	-
F8	Transparent	Amorphous	Smooth	-
F9	Transparent	Amorphous	Smooth	-

The physical appearance of all the formulation F1 to F9 result is found to be, transparent, homogenous and consistent.

Measurement of pH: The pH values of all gel formulation F1to F9 range 5.7- 6.9. All formulations are measured suitable to the avoid the risk of irritation after skin application.

Table 5: pH of the prepared gel formulations.

pH	Formulation Code (F)								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
	5.7	5.9	6.2	7.3	6.4	6.1	6.9	6.1	6.6

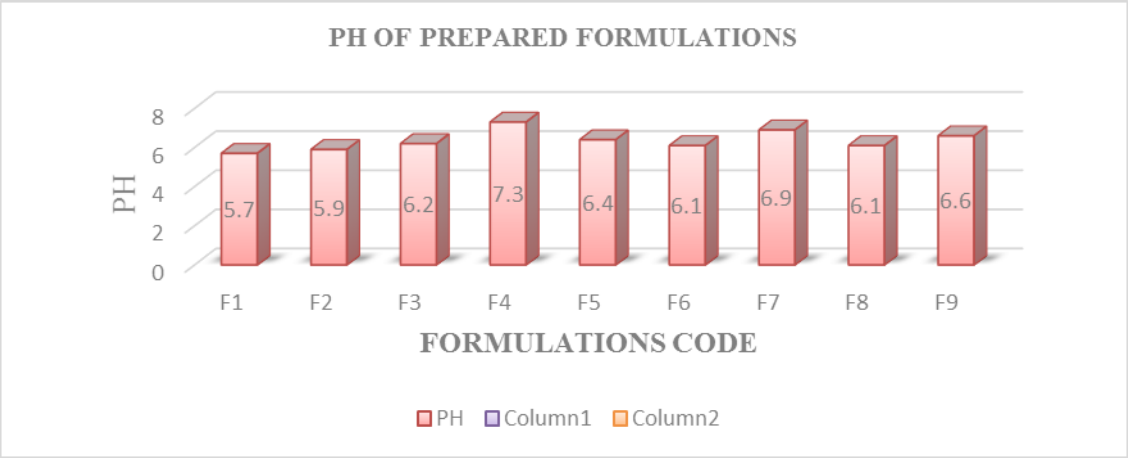

Figure 7: pH of the prepared gel formulations

Spreadability

The spreadability of *Boswellia serrata* gel formulation is depicted in table no.15 from the combined graph of all formulation it was concluded that all the developed formulations showed acceptable spreadability. Xanthan based formulation showed better spreadability than the sodium alginate and HPMC K 4 M formulations. All formulation shows good spreadability after compare.

Table 6: Spreadability of gel formulations (mean ±S.D)

Spreadibility (gm.sm/sec)	Formulation Code (F)								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
	12.2	12.4	12.6	13.7	12	11.7	12.7	13.7	13

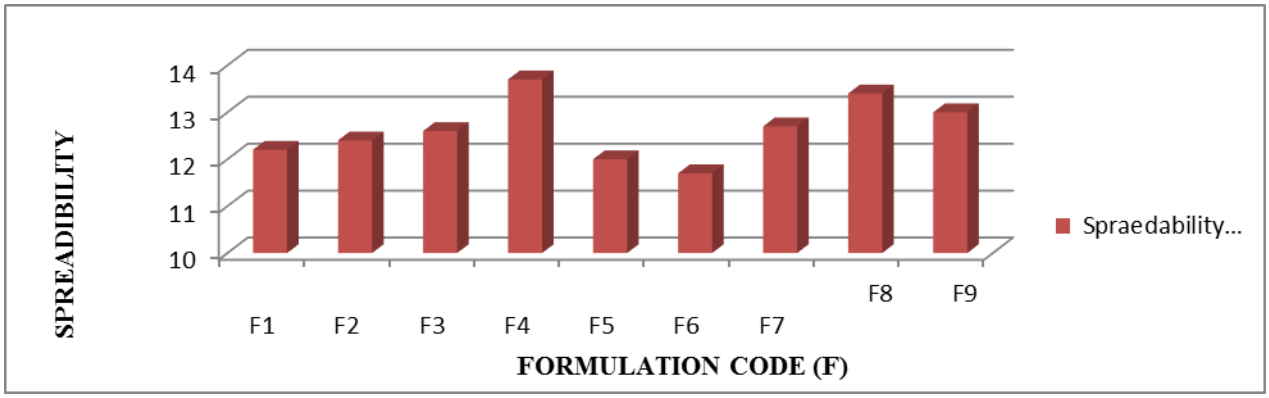

Figure 8: Spreadability of prepared gel formulations

Viscosity Studies

The viscosity of gel formulations (F1 to F9) and the measurement of viscosity of the prepared gel was done with Brookfield viscometer. In all these formulations the highest viscosity was found in formulation of sodium alginate, 1%, 1.5% and 2% is best.

Table 7: Viscosity study of prepared gel formulations.

Shear rate (RPM)/ST	Viscosity of the formulation in centipoises								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
12	6722.1	24853	32784	55785	61324	17869	18968	25681	32841
10	7251.1	74876	42697	62776	72415	24634	14692	34634	32432
08	8136.8	108692	61976	78528	89120	34952	35681	78356	96324
06	6341.2	129481	77823	96423	96419	88676	89451	95621	34659
04	7517.1	157641	102547	13847	137239	193541	18542	10648	45089
02	9869.6	194151	149572	238757	132982	265753	25769	67843	76081

Extrudability Study

Extrudability of all formulations F1 to F9 shown in table 8. The Extrusions of the gel from the tube is an important during its application and in patient acceptance. Gels with elevated consistency may not extrude from tube whereas, low viscous gels may flow quickly and hence suitable consistency is required in order to extrude the gel from the tube. An Extrudability of HPMC K4 M gel formulation was found to be good. Whereas, Extrudability of xanthan gum, sodium alginate and gels were acceptable.

Extrudability = weight applied to extrude gel from tube (g)/Area (cm2)

Table 8: Extrudability study of gel formulations.

Extrudability (g/cm^2)	Formulation code (F)								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
	15.06	15.51	17.30	17.90	15.80	15.86	16.06	17.50	17.56

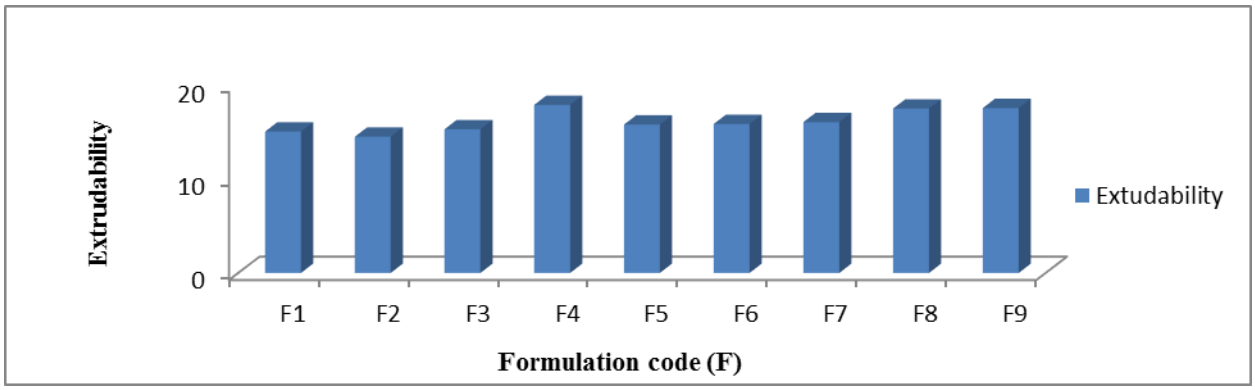

Figure 9: Extrudability study of gel formulations.

Drug Content

Table 9: Drug Content of prepared gel formulations

Drug Content (%)	Formulation Code (F)								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
	85.7 ±1.26	89.2 ±1.57	82.8 ±1.64	95.1 ±1.53	86.4 ±1.62	92.9 ±1.35	87.8 ±1.22	91.7 ±1.24	93.2 ±1.34

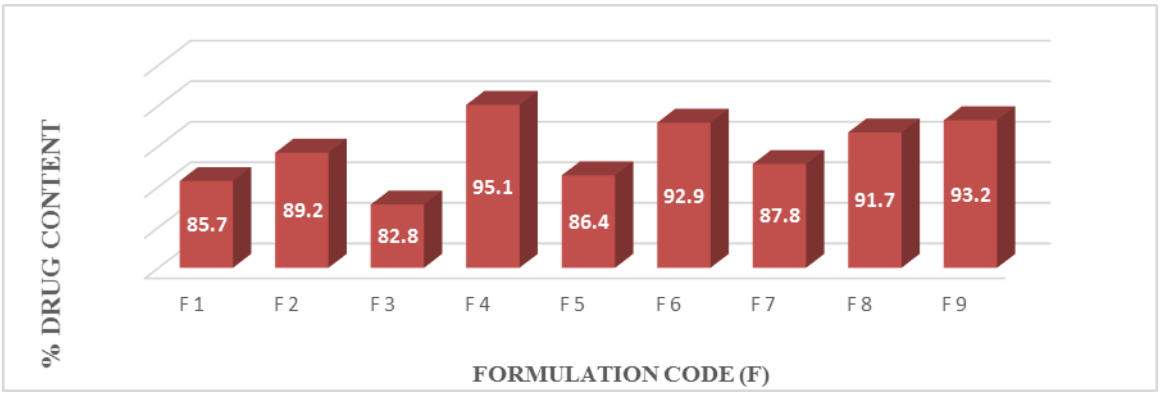

Figure 10: % Drug Content of prepared gel formulation

***In Vitro* Relase Studies**

The topical gel prepared by these methods showed improved dissolution rate and the solid dispersion was prepared by the ratio 1:1, and it should greater the solubility and then the other ratio was selected as ideal batches of formulation for incorporation into gels. The *in-vitro* release study of *Boswellia serrata* resin drug from the prepared the formulation was adopted through the dialysis membrane using diffusion cell. The release studies of prepared gelling system were carried upto in 3 hrs.

Table 10: % cumulative release of different formulation in phosphate buffer (pH 5.5)

Time	(%) Percentage drug relase of different formulation								
(in min)	F1	F2	F3	F4	F5	F6	F8	F8	F9
0	0	0	0	0	0	0	0	0	0
30	14.33	16.58	17.51	19.12	10.61	10.91	12.11	13.11	13.64
60	15.13	16.16	31.85	39.76	28.76	30.41	33.64	38.12	36.23
90	23.88	25.71	44.45	49.89	38.39	41.76	48.12	40.16	40.88
120	44.34	50.76	5872	65.78	47.49	47.54	49.87	50.90	55.65
150	49.36	55.67	63.65	76.98	58.27	50.87	55.11	67.45	72.23
180	53.42	66.32	74.52	90.66	69.68	76.67	63.56	69.89	89.74

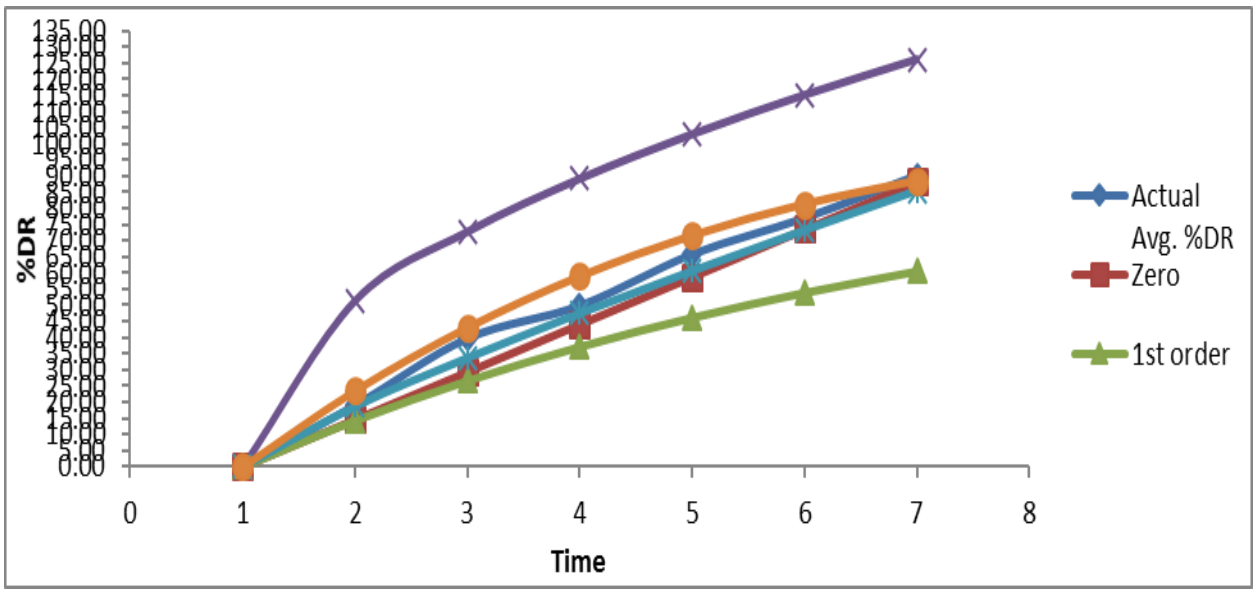

Figure 11: % cumulative release of different formulation in phosphate buffer (pH 5.5)

Accelerated Stability Studies: According to ICH guideline, the accelerated stability studies were carried for prepared gelling system. All these formulations were too analyzed for visual appearance, clarity, pH and drug content remaining. Six weeks of stability study reveal that there was no change in visual appearance and clarity. All these formulations showed slight change pH but it was in acceptable limits.

Table 11: Stability Studies of Formulation at room temp (PBS pH-5.5)

S. No.	Number of day	% Drug Remaining								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	0	58.27	68.17	97.56	98.40	95.78	94.97	78.12	93.12	91.82
2	15	57.26	67.95	97.42	98.68	98.65	94.75	78.34	93.37	91.80
3	30	57.40	67.65	97.11	98.81	98.62	94.60	78.23	93.76	91.75
4	45	57.17	67.37	96.67	98.58	98.52	94.55	78.94	93.90	95.89
5	60	56.94	67.17	96.37	98.53	98.53	94.52	87.45	94.12	95.65
6	75	56.76	66.94	96.18	98.47	98.45	94.50	87.67	94.27	95.60
7	90	56.44	66.87	96.6	98.40	98.41	94.45	80.88	94.89	95.55

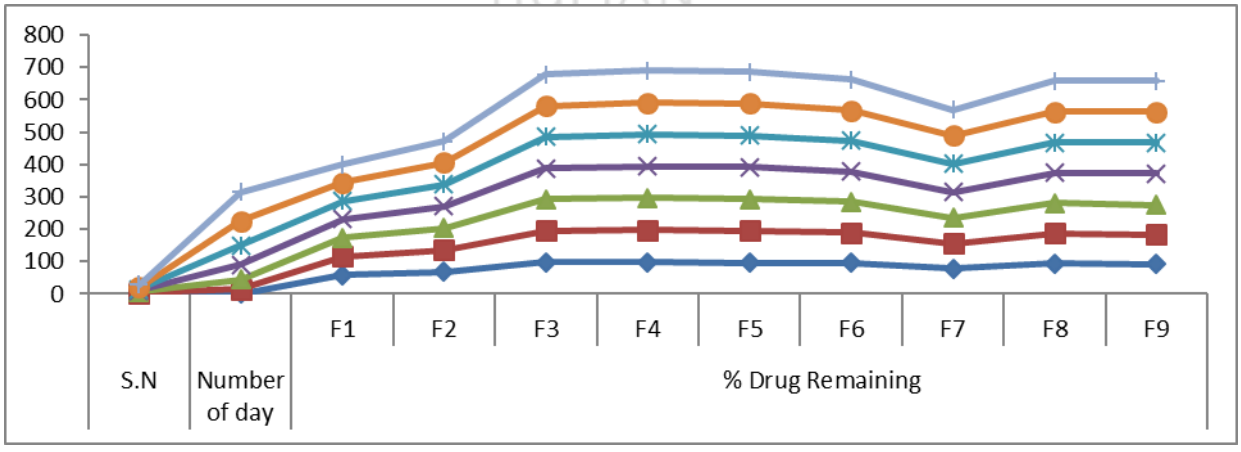

Figure 12: Stability Studies of Formulation at room temp (PBS pH-5.5)

CONCLUSION

This research work was carried out to develop out a new topical gel formulation for topical application. The pH of every one formulation was reported in the ranges compatibles with normal pH ranges of skin. The result indicated that viscosity of gel formulations was

consistent neither thick nor thin. These formulations prepared with sodium alginate, HPMC K4M, Xanthan gum shown good homogeneity act as anti-inflammatory activity. However, the HPMC K4M based gel proved to the formula of choice, since it shown the high percentage of extrudability, good spreadability and rheological properties. Formulation (F4) 1% by gelling agents (HPMCK4 M) shown the best formulation with higher drug content (95.1 %) and drug release (90.66 %). Based on the above parameter, the formulation (F4) was concluded as most promising formulation.

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