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Research Article

FORMULATION, OPTIMIZATION AND EVALUATION OF ACECLOFENAC TRANSDERMAL GEL: A NOVEL APPROACH FOR PENETRATION ENHANCEMENT BY HERBAL EXTRACT

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ABSTRACT

The present research has been undertaken with the ambition to formulate, optimize and evaluate the gel containing *Eugenia caryophyllus oil*. The gel formulation was designed by using oil which obtained from the leaves of *Eugenia caryophyllus*. The gel was prepared by using aceclofenac (API) and optimum ratio of carbopol 941 P and HPMC K15M and other excipients are propylene glycol, triethanolamine, and methyl paraben. The *Eugenia caryophyllus oil* was used as a penetration enhancer. All prepared gel formulations were evaluated by pH, spredability, extrudability, viscosity, drug contents, *in- vitro* permeability studies and drug- polymer compatibility (FTIR studies). The absorption maxima of aceclofenac were found at 273 nm using pH 6.8 phosphate buffer solutions. The pH values of all formulation was in the range between 6.81 -7.13. Drug content of all formulation ranges from 82.00 – 88.89%. The result value of spreadability was range from 11.00 - 14.00(gm. cm / sec). Whereas the extrudability value of gel formulations from the collapsible tube varies range from 160.00 to 222.22 (gm.cm^2) and the viscosity of formulations ranges from 18554 cps to 20782 cps at 50 rpm. The % cumulative drug release range from 42.52 -63.02% in 6 hr.

Keywords: *Eugenia caryophyllus*, API, FTIR, *In- vitro* permeability studies, BCS class-II

INTRODUCTION

Aceclofenac is belonging from NSAIDs category; it is phenyl acetic acid derivative and having anti-inflammatory and analgesic activity. Aceclofenac is Non-steroidal Anti-inflammatory drug and chemically it is [(2,6Dichlorophenyl) amino] phenyl acetyloxyacetic acid. It widely used in the treatment of pain (headache, back pain, arthritis and joint pain) act by inhibiting prostaglandin synthesis, which is cause of inflammation. [1, 2] Aceclofenac belongs to BCS class-II, it possess solubility problem for drug delivery. Aceclofenac with oral therapy causes dyspepsia, abdominal pain, nausea and diarrhea other rare side-effects include dizziness, constipation, vomiting, ulcerative stomatitis, rash, dermatitis, headache, fatigue.[3,4] *Eugenia caryophyllus* commonly known as laung clove in India. It consists of dried flower buds of *Eugenia caryophyllus*, family-myrtaceae [5, 6].

Eugenia caryophyllus oil is most expensive and best quality product contains 80-90% eugenol. Other essential oil ingredients are Acetyl eugenol, Beta-caryophyllene and vanillin, methyl salicylate (pain killer), tannins- Gallotannic acid, triterpenes- oleanolic acid. [7, 8] *Eugenia caryophyllus* oil is used as anti-fungal- clove oil effective in reducing fungal infection (athlete's foot), anti-inflammatory- clove oil due to anti-inflammatory action having high content of flavonoids. It also used to cure the symptoms of rheumatism and arthritis, anti bacterial- (dental products), Respiratory Problems - This expectorant is useful in various respiratory disorders including coughs, colds, bronchitis, asthma, sinusitis, and tuberculosis. Muscular cramps are often relieved when the clove oil is applied as a poultice near the affected area. [9, 10]

MATERIALS AND METHODS

Chemicals- Aceclofenac [Tirupati Medicare Ltd, Paota Sahib (Himanchal Pradesh) India] carbopol 941 and HPMC K15M are propylene glycol, triethanolamine, and methyl paraben [Central Drug House (p) Ltd, New Delhi] Hifenac gel The Madras Pharmaceuticals, Chennai. Flowering buds of *Eugenia caryophyllus* collected from local market of Dehradun, Uttarakhand.

Extraction of *Eugenia caryophyllus* oil - 200 gm of flowering buds of *eugenia caryophyllus* was coarsely powdered and placed in 1000 ml round bottom flask and extracted in Clevenger apparatus using water for 5- 8 hr. the oil was collected which was colourless with aromatic odour [11, 12].

Phytochemical test of *Eugenia caryophyllus* [13]

Test for alkaloids-Hager's test- To a few drop of test solution and add 2 ml of Hager's reagent. A yellow precipitate indicates presence of alkaloids.

Test for Carbohydrate - Molish test- 1ml of test solution with few drops of α-napthol. Add 0.2 ml of concentrated sulphuric acid slowly from the side of tube, purple to violet colour ring appears at the junction.

Test for Protein- Ninhydrin test- 1ml of plant extract and add 2 ml of ninhydrin solution a purple colour produce that indicate presence of amino acids.

Test for phenolic compounds- ferric chloride test- Take 0.5ml of extract mixed with 5 ml of distilled water and add few drops of 5% ferric chloride. A dark green colour produced that indicate presence of phenolic compound.

Test for Terpenoids - libermann-burchard test- Take 0.5 ml of plant extract heat and add few drops of acetic anhydride in a test tube and boil and cool, add few drops of concentrated sulphuric acid with drop wise, a red colour was produced due to presence of terpenes.

Test of fixed oils and fats- spot test- a small quantity of plant extract was pressed in between the two filter paper. Oil stain on the filter paper indicates the presence of oils and fats.

Gel preparation Dispersion method- Disperse the carbopol 941 P and HPMC K15 M in distilled water and soaking for 8 hr. Dissolve the drug in propylene glycol, and slowly mixed into the polymer solution with continuous stirring and addition of penetration enhancer, methyl paraben then pH adjustifier (TEA) incorporated to modify the buffering capacity of the gel. [14]

Evaluation parameter of gel

Measurement of pH-The pH of various gel formulations was determined by using digital pH meter. 1gm of gel was dissolved in 100 ml distilled water and stored for 2 hr. The readings were taken for average of 3 times [15].

Spreadibility -0.5g gel was placed within a circle of 1 cm diameter pre marked on a glass plate over which a second glass plate was placed. A weight of 500 g was allowed to rest on the upper glass plate for 5min. The increase in the diameter due to spreading of the gels was noted [16].

Extrudability- a good gel extrudes from the tube with slight pressure applied. The extrudability of formulations from aluminium collapsible tubes was determined using universal tube filling machine. Aluminium collapsible tubes filled with 20g gels and tube was compressed and extrudability of the formulation was determined in terms of weight in grams required to extrude a 0.5 cm. ribbon of gel in 10 seconds [17].

Drug content- A 100 mg of developed gel dissolved in 100 ml of phosphate buffer with pH 6.8. The volumetric flask containing gel solution was shaken for 2 hr on mechanical shaker in order to get complete solubility of drug. This solution was filtered and estimated spectrophotometrically at 273 nm using phosphate buffer (pH 6.8) as blank [18].

Viscosity-The measurement of viscosity of the prepared gel was done with a Brookfield Viscometer. The gels were rotated at 50 rotations per minute. 50 gm of preparation was kept in 50 ml beaker which was set till spindle groove was dipped and rpm was set and dial reading was measured after three minutes. From the reading obtained, viscosity was calculated by using factor. The readings were taken for average of 3 times [19, 20].

***In-vitro* diffusion studies-** The *in- vitro* diffusion studies of formulated gel were carried out in Franz diffusion cell using an egg membrane, 10 ml of phosphate buffer solution (pH 6.8) was used as receptor compartment, and then 100 mg of gel was placed on the membrane. The donor phase was kept in contact with a receptor phase and the temperature at range from 36 to 37°C and solutions stirred by using externally driven magnetic bars, and take 3ml of solution from the receptor compartment and replaced the same concentration fresh phosphate buffer solution. This test will be repeated for 6 times with 1 hr. interval. Then the samples were analyzed by UV-visible spectrophotometrically at 273 nm using phosphate buffer solution (pH 6.8) as blank for drug release [21, 22]

Stability studies-The stability studies were carried out for all the gel formulation by, by subjecting the product to a temperature at 25°C, 40°C for 45 days, The formulation was analyzed for the change in appearance, pH or drug content [23, 24]**.**

RESULTS

EXTRACTION OF *EUGENIA CARYOPHYLLUS* OIL-

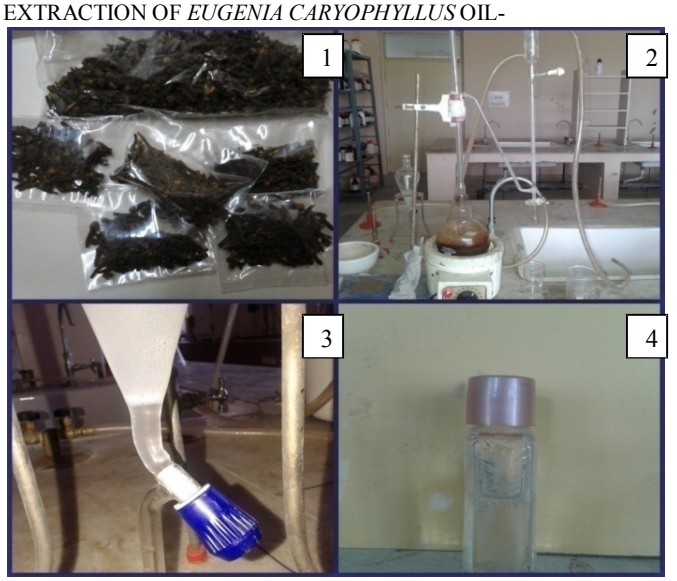

Figure 1. Extraction processes of *Eugenia caryophyllus* (1. Collected sample, 2. Extraction of flowering buds 3.separation of oily portion, 4. Collected oil)

PHYTOCHEMICAL TESTS OF *EUGENIA CARYOPHYLLUS*

Table 1: Phytochemical tests of *Eugenia caryophyllus*

S. No.	Constituents	Tests performed	Results
1.	Carbohydrate	Molisch's test	+
2.	Alkaloid test	Hager's test	+
3.	Proteins & amino acid	Ninhydrin test	+
4.	Fixed oils and fats	spot test	+
5.	Phenolic compounds	Ferric chloride test	+
6.	Triterpenoids	Libermann burchard test	+

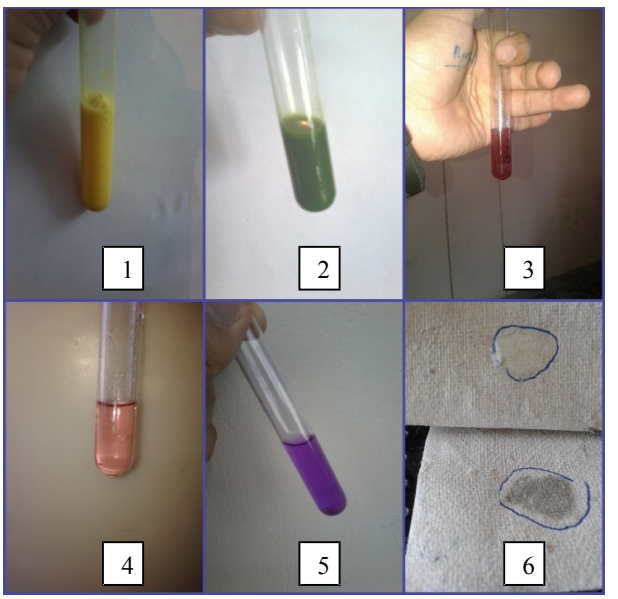

Figure 2: Phytochemical tests of *Eugenia caryophyllus* (1.Hager test 2.Ferric chloride test 3.Liberman-burchard test 4.Molish test 5.Ninhydrin test 6.Spot test)

DRUG IDENTIFICATION STUDIES

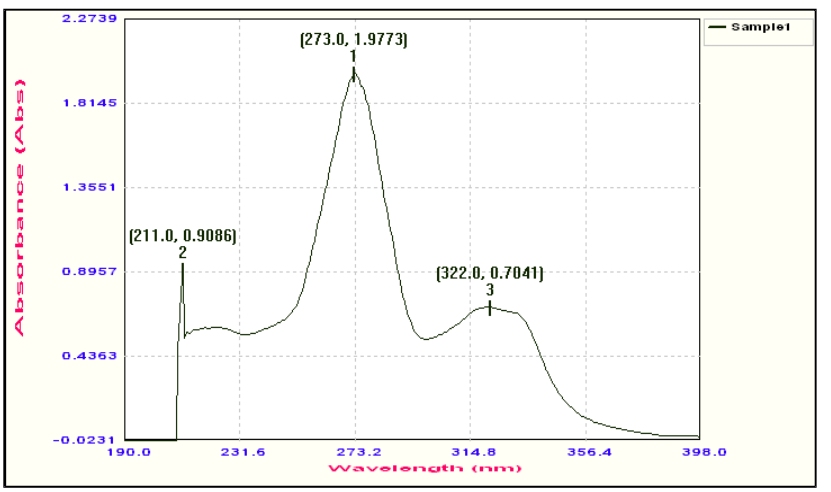

Figure 3: Absorption maxima (λmax) of aceclofenac in phosphate buffer pH 6.8

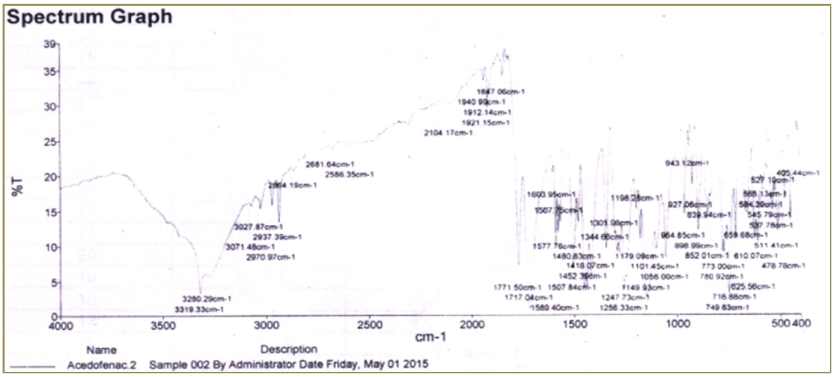

Figure 4: FTIR spectroscopy of aceclofenac sample

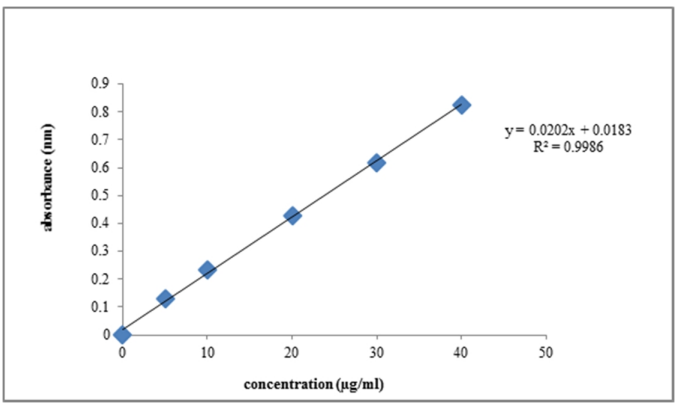

Figure 5: Calibration curve of aceclofenac in phosphate buffer solution pH 6.8

COMPATIBILITY STUDY OF GEL BY FTIR (NUJOL METHOD)

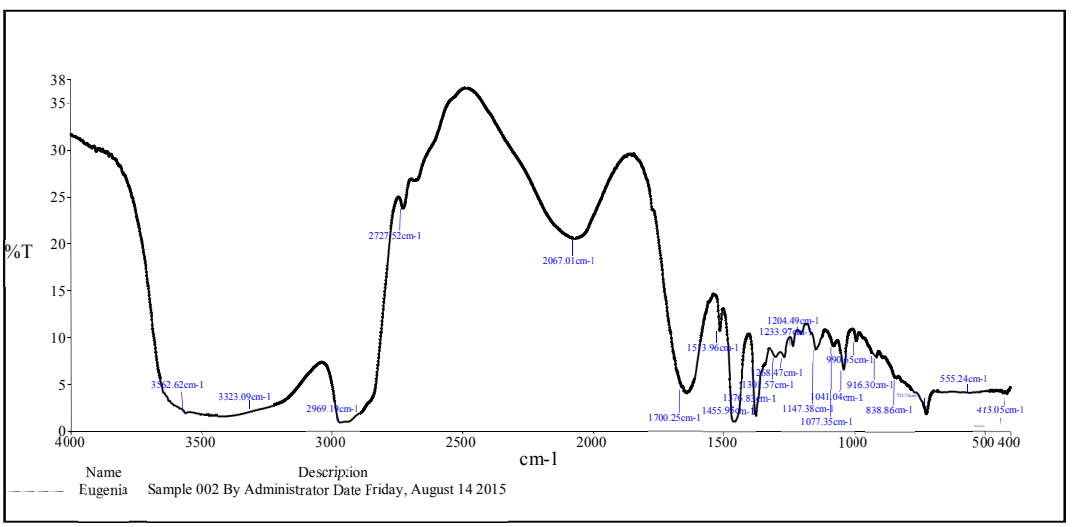

Figure 6: FTIR of aceclofenac gel contain *eugenia caryophyllus*

PREPARATION AND EVALUATION OF GEL

Table 2: Preparation of gel contain *Eugenia caryophyllus*

S.NO.	INGREDIENTS	F1	F2	F3	F4	F5
1.	Aceclofenac(gm)	1	1	1	1	1
2.	Carbopol 941 P(gm)	1	1	1	1	1
3.	HPMC K15(gm)	1.5	1.5	1.5	1.5	1.5
4.	Methyl paraben (gm)	0.2	0.2	0.2	0.2	0.2
5.	Propylene glycol(ml)	10	10	10	10	10
6.	Triethanolamine(ml)	1	1	1	1	1
7.	*Eugenia caryophyllus* oil(ml)	1	1.5	2	2.5	3

Table 3: Evaluation data of gels formulation containing *Eugenia caryophyllus*

Formulation code	pH	Spreadability (gm.cm/sec)	Extrudability (gm.cm^2)	Drug content %	Viscosity (cp)
EF1	6.75	11.00	160.00	84.18%	18554
EF2	7.09	13.33	166.66	88.89%	18790
EF3	6.81	11.33	222.22	85.92%	19822
EF4	7.13	14.00	235.29	82.00%	19482
EF5	6.82	11.66	160.00	88.62%	20782
Plain gel	7.02	10.33	400.00	81.39%	23260
Hifenac gel	6.69	11.66	250.00	90.57%	22150

Table 4: Evaluation data of gels formulation containing *Eugenia caryophyllus*

Time (hr)	% cumulative release						
	Eugenia caryophyllus					Formula	Marketed
	EF1	EF2	EF3	EF4	EF5	Plain gel	Hifenac
0	0	0	0	0	0	0	0
1	1.37	1.18	2.11	2.51	2.08	1.39	2.55
2	5.12	5.05	6.73	8.87	5.93	3.74	7.21
3	10.92	10.41	15.33	18.46	13.24	6.95	16.35
4	19.30	18.48	27.40	29.79	25.43	11.13	29.52
5	29.80	30.40	42.35	44.36	42.21	15.82	47.91
6	42.52	45.04	58.78	61.57	63.02	21.00	69.69

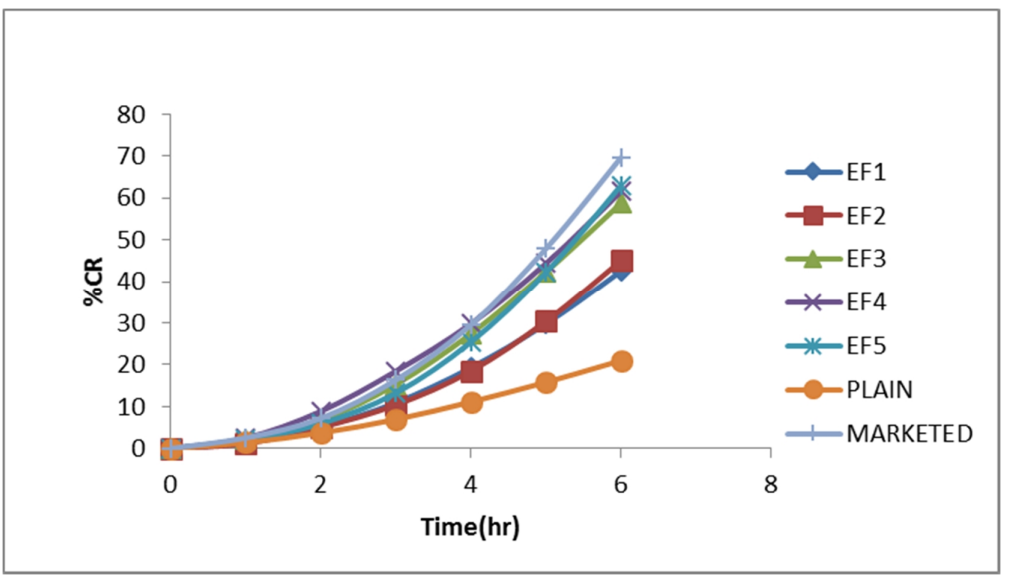

Figure 7: *In-vitro* %cumulative drug release data

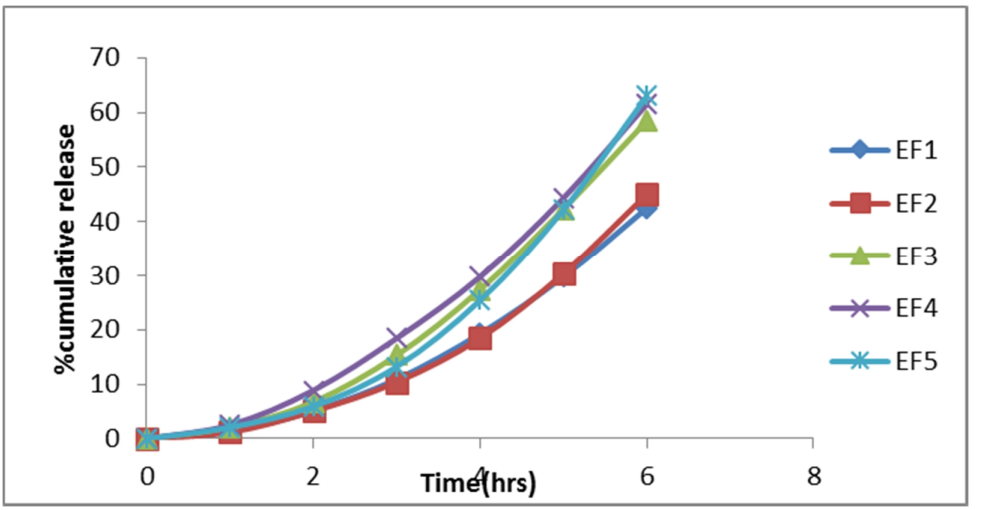

Figure 8: Zero order release profile of aceclofenac gel containing *Eugenia caryophyllus*

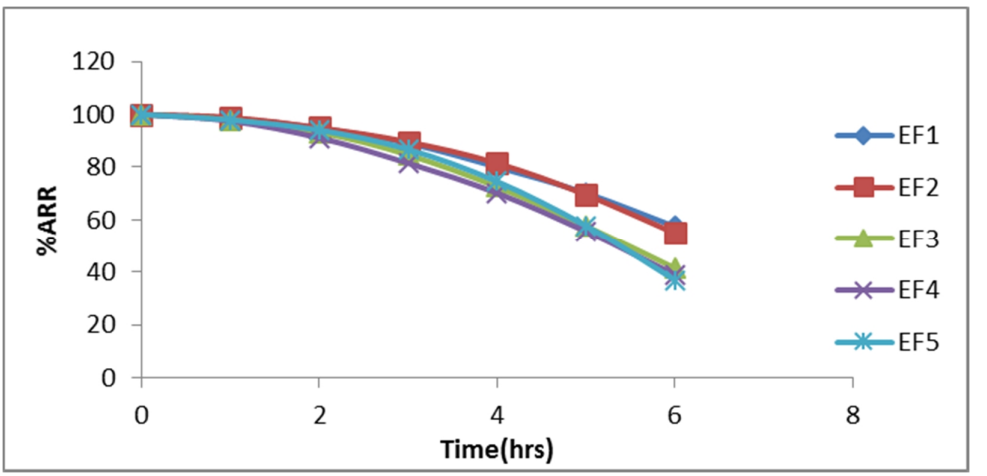

Figure 9: First order release profile of aceclofenac gel containing *Eugenia caryophyllus*

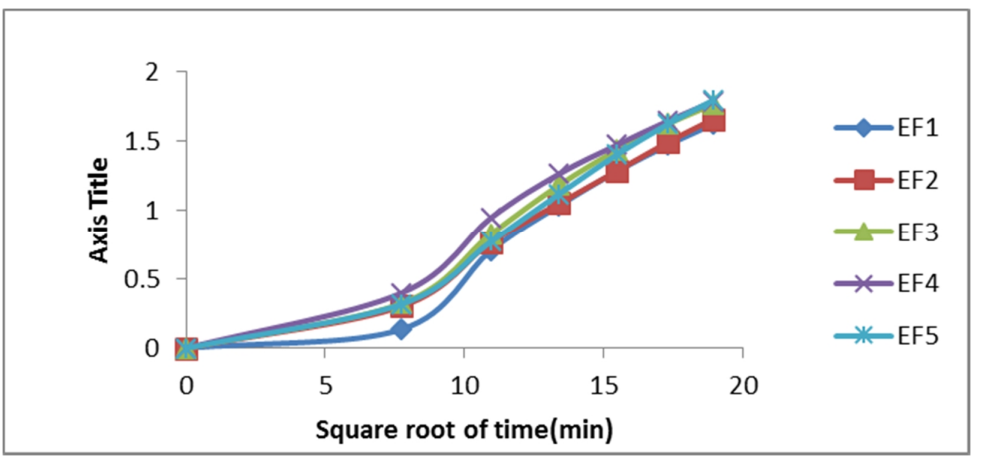

Figure 10: Higuchi curve of aceclofenac gel containing *Eugenia caryophyllus*

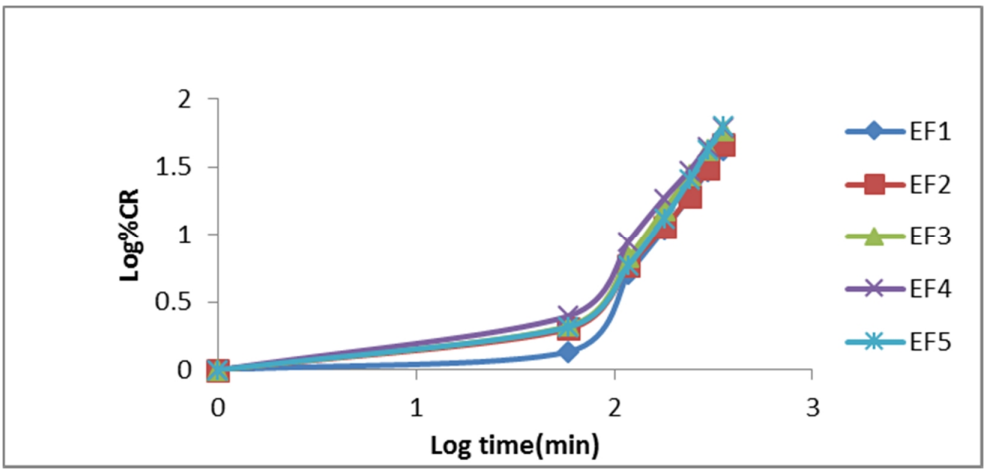

Figure 11: Korsmeyer-peppas curve of aceclofenac gel containing *Eugenia caryophyllus*

Table 5: Mathematical modelling and drug release kinetics of aceclofenac gel

Formulation code	*Eugenia caryophyllus*			
	Regression coefficient(R^2)			Slope (n) value
	Zero order	First order	Higuchi's	Korsmeyer-peppas
EF1	0.928	0.928	0.915	0.619
EF2	0.909	0.916	0.899	0.629
EF3	0.931	0.932	0.953	0.667
EF4	0.947	0.948	0.967	0.677
EF5	0.897	0.897	0.947	0.661
Marketed	0.912	0.912	0.963	0.680
Plain gel	0.965	0.965	0.924	0.832

DISCUSSION

Formulated gel containing *Eugenia caryophyllus*- The pH value of all formulated gels lies in between 6.81 - 7.13. Drug content of all formulation ranges from 82.00 to 88.89%. The result of spreadability range from 11.00 to 14.00 (gm. cm/sec). Whereas the extrudability of gel formulations from the collapsible tube varies from 160.00 – 222.22 gm.cm^2 and the viscosity of formulations ranges from 18554 cps to 20782 cps at 50 rpm. The % cumulative drug release range from 42.52 -63.02% in 6 hr.

CONCLUSION

In- vitro drug release study results show the formulations containing *Eugenia caryophyllus* the drug releasement are faster as compared to plain formulation of gel which does not contain *Eugenia caryophyllus*. It may be concluded from the results that as the concentration of *Eugenia caryophyllus* 1 to 5 ml (42.52-63.02 %CR) increases in the formulations the rate of drug release also increases. Percent drug release data also show the formulation of gel that contains *Eugenia caryophyllus* oil (F5-5ml) a best formulation that is similar to marketed formulation (Hifenac gel), In which the drug release 42.02% more after addition of penetration enhancer compare to plain gel in which only 21.00% drug was release. The mathematical kinetic studies is showed the value of correlation coefficient (r^2) 0.947 in case of higuchi diffusion model and this value was supported by n value i.e. 0.661 korsmeyer peppas (in the literature 0.5 n value was perfect fickian diffusion but after in various literature 0.5 to 0.6 believe to be fickian types of diffusion). So we can state that the selected formula of gel release entrapped amount of drug by diffusion way which was more or less ficknian types. It is clear that *Eugenia caryophyllus* can significantly enhance the penetration of aceclofenac from gel formulation across the skin. The usage of herbal oil was found to be efficient in releasing of the drug

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