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PHARMACEUTICAL ASSESSMENT AND PHARMACOLOGICAL EVALUATION OF CHIA SEED EXTRACT-*ALOE VERA* TRANSEMULGEL

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ABSTRACT

In the current investigation, polyherbal emulgels were prepared using *Aloe vera* and ethanol extract of Chia seed in varying proportions to (15mg/ml, 20mg/ml and 30mg/ml) and mixing the prepared gel in emulsion prepared using span 20 and buffers at a varying ratios (1:2, 1:1 and 2:1). The formulations were subjected to pharmaceutical evaluation for pH, viscosity, stability drug content and invitro drug release. Study showed that CEG1, CEG2 and CEG3 showed better results in all the evaluation tests but CEG3 as found to be stable in the accelerated stability tests. invivo anti-inflammatory and analgesic activity were performed on CEG3 using egg albumin induced paw edema and tail flick method. Results suggests that the prepared

formulation showed better activity compared to the induced group, *Aloe vera* gel and even better than standard diclofenac gel in some instances. Overall the prepared formulation was proven effective in controlling the inflammation and exhibited better analgesia in tail flick method. Further investigations are required in order to establish the pharmacokinetic profile of the emulgels and molecular isolation is also need to specifically determine the pharmacological mechanisms of extract.
Keywords: Chia seeds, Diclofenac gel, *Aloe vera* gel, egg albumin, paw edema

INTRODUCTION

Chia seeds (*Salvia hispanica*) belonging to family Lamiaceae is an annual native American plant has huge potential as antioxidant, antimicrobial and nourishing agent.[1,2,3] Chia have a high concentration of omega-3-α-linolenic acid, omega-6-linoleic acid (Vitamin F), fibers, antioxidants along side with essential minerals, fat soluble vitamins (A,D,E,K) and Vitamin B and proteins with various medical benefits.[4,5,6] Chia seeds were also known to support digestive, skeletal, cardiovascular systems with strengthening effect on bones, heart, stomach and also preventing diabetes.[5] This had caused a spike in the consumption of the seeds and had been in focus of scientific research.[7] Chia seeds will forms mucilage when macerated in water which is sticky and requires a specialized procedures for extraction from the seeds.[8] This is good source for fibers and have a high capacity to hold water with decent gelling and emulsifying properties. This is employed to improve texture and consistency of pharmaceutical preparations.[7,9] The mucilage has also identified for its biodegradable, biocompatible and nontoxic properties.[10,11]

Emulgels technology had recently been a promising mechanism for delivering hydrophilic and lipophilic drugs especially nutraceuticals like vitamins, polyunsaturated fatty acids and probiotics. As the oil droplets are not easily motile and their low degradation to the digestive juices in the stomach, they prevent the drug incorporated from degradation and enable the sustained release of the drug in the upper GI tract.[12] Emulgels are majorly used to address Low stability of drugs, poor solubility, and low absorption of drugs. They improve the bioavailability, sensory textures and release of the drug from the formulation.[13,14] They emerged themselves as reliable biomaterials that can be tailored to deliver neutraceuticals in a controlled manner to the site of action.[15] Thus to employ the aforementioned potential advantages of the emulgels, to incorporate Chia seeds extract to achieve controlled release and better antiinflammatory and analgesic activity in experimental rats. So the prepared emulgels were intended to exhibit better consistency and stability in evaluation tests.

MATERIALS AND METHODS

CHEMICALS AND REAGENTS

Fresh *Aloe vera* leaves, seeds of *Salvia hispanica* were collected from local supplier and authenticated duly by certified botanist and the herbarium sample is deposited in the institute library. Sodium alginate, span-20, liquid paraffin, parabens and chemical used in the invivo experiments were procured from SD Fine Chem Ltd, India and were of analytical grade.

Constitution of *Aloe vera* based gel

Aloe vera leaves were washed and slits were made along the blade and inverted to drain the yellow sap. They were washed properly and central gelly parenchymatous pulp was scooped out.[16] This was subjected to vacuum filtration to obtain a clear liquid. to this 1%w/w of sodium alginate and 0.5%w/w (1:1) methyl and propyl parabens were added under continuous stirring using a magnetic stirrer. In order to assist the gelling property of alginate and to regulate the acidic pH of *Aloe vera* gel, 0.1N NaOH was added drop-wise until a thick gel is formed. This gel (*Aloe vera* gel) is stored in air tight container till further use.

Extraction

Dried Chia seeds were extracted by modifying the basic methodologies.[17,18] Seeds were soaked in distilled water (1:30w/v) using a magnetic stirrer for 3hr at 25^{o}C. The seeds were separated

from the mucilage using vacuum filtration with a muslin cloth. The seeds were washed with distilled water and shade dried for 5days. They were ground into fine powder and passed through #40 mesh. 50g of powder was packed in whatman filter paper and extracted with ethanol using soxhlet apparatus. The clear extract was collected and evaporated to dryness in a rotary evaporator. The thick extract (24.38%w/w) was dissolved in the previously prepared *Aloe vera* gel to achieve various concentrations (15, 20 and 30mg/ml) named as gel-15, gel-20 and gel-30 respectively and stored in air tight container till further use.[19]

Preparation of emulgels

The emulgels were prepared using emulsion incorporated with gel. Oil phase was prepared by mixing span-20 (0.5ml) in liquid paraffin (4.5ml). Tween-20 (0.5%) in distilled water comprises the aqueous phase. Oil and aqueous phases were heated to 70^0C in separate beakers before mixing them. Oil phase was added drop wise into aqueous phase under continuous stirring till the solutions were cooled and formation of emulsion was confirmed.[20] To this emulsion previously prepared gels (gel-30, gel-20 and gel-15) were added slowly at ratios of 2:1, 1:1 and 1:2 and named as CEG1, CEG2 and CEG3 respectively.

Evaluation of the polyherbal gels

Visual appearance:

The physical appearance of the prepared emulgels was carefully examined for the colour, consistency and texture.

Physical Characterization:

pH and viscosity of the emulgels were determined using digital pH meter (Elico LI I20) and Brookfield viscometer at 50rpm and 25^0C. All the values were taken as triplicate measurements.[21] Prepared emulgels were characterized by using FTIR spectrometer (Bruker, Germany).

Determination of Drug content:

Chia seed extract was serially diluted using ethanol to make concentration of 0.5-2.5mg/ml. The respective absorbance values were measured using UV spectrophometer at 320nm and the calibration curve was generated. 1g (~200ml) of the prepared emulgel was diluted with ethanol to make a concentration of 5mg/ml and the absorbance was measured using UV at 320nm in triplicate readings.[19] The drug content was calculated using the equation of the calibration curve and expressed as % drug content.

Determination of Invitro Drug Release:

The invitro diffusion studies were carried out using egg membrane barrier layer in a Franz diffusion cell using phosphate buffer pH 7.4 as medium. 25mg of prepared emulgel was placed on the membrane while the solution was maintained at 37^0C with gentle stirring. Aliquots of sample were withdrawn at regular intervals of 30, 60, 120, 150 and 180min replacing with fresh buffer solution to maintain sink. The samples were analyzed using UV at 320nm and the percentage drug release was measured and expressed in triplicate readings.[22]

Stability testing:

The stability testing of the prepared emulgels was performed by storing them at ambient temperature and conditions with varying temperature and humidity 25°C and 60% RH, 40°C and 60% RH and 55°C and 75% RH for 45 days.[20] Formulations were carefully observed for any physical changes and Drug content was determined to identify chemical changes as a result of variable temperatures.

Skin irritation test:

The skin irritation test was performed on healthy albino wistar rats. The dorsal hair of the rats was shaved (1cm^2 patch) before 5hr. Emulgel was applied on the shaven surface and observed for changes of the site of application for 24hr.[23]

Anti-inflammatory activity using Paw Edema Model

The experimental animals were divided randomly into 4 groups consisting of 6 animals each with drug treatment as follows

Group 1 (Control): induced group treated with 0.1ml egg albumin in 1% normal saline

Group 2 (*Aloe vera* gel): *Aloe vera* gel applied topically

Group 3 (Diclofenac gel): 1% diclofenac gel (Volteran gel, GlaxoSmithKline) applied topically

Group 4 (CEG3): Prepared emulgel CEG1 applied topically

All the groups were administered with egg albumin in the subplantar tissue of the left hind paw of the rats. 30min after induction of inflammation the gels were topically applied and the circumference of the paw was measured using plethysmometer at 0, 30, 60, 120, 180 and 240min.[24,25] The percentage inhibition was determined using the formula,

$$\%\text{inhibition} = \frac{\text{Vc} - \text{Vt}}{\text{Vc}}$$

Analgesic activity using Tail Flick method

Animals were divided into 4 groups with 6 animals per group and the treatment is as follows

Group 1 (Control): No drug treatment

Group 2 (*Aloe vera* gel): *Aloe vera* gel applied topically

Group 3 (Diclofenac gel): 1% diclofenac gel (Volteran gel, GlaxoSmithKline) applied topically

Group 4 (CEG3): Prepared emulgel CEG1 applied topically

The tail flick test was performed by subjecting heat to the dorsal surface of the tail. The response time of the rats to the heat stimulus was measured using analgesiometer. The maximum latency was imposed at 30min to prevent tissue damage. Rats were tested for latency at 0, 30, 60, 90, 120, 150 and 180min after application of the gels topically.[26]

Statistical Analysis

The measurements were made in triplicate readings for invitro studies and 6 animals were employed for invivo studies. The values were expressed as mean and their relative standard errors of the mean and were evaluated for difference in comparison to normal group and diclofenac gel using ANOVA followed by dunnet's test. A confidence level of $p<0.05$, 0.01 and 0.001 were considered significant which ever was suitable.

RESULTS

Physical evaluation

The prepared emulgels were clear and off white-creamy colour, translucent with homogeneous, glossy appearance which is appealing for a topical formulation.

pH

As the emulgels were comprised of *Aloe vera* gel, naturally they are expected to be slightly acidic. It was neutralized using 0.1N NaOH and the gels were slightly turned basic to facilitate the formation of sodium alginate gels. Further after formation of emulgel, the pH of the final formulation remained near to neutral leaning towards basic pH ranging from 7.2-7.5 which was consistent across all the formulations.

Viscosity

The spreadability and flow of the gel depends directly on the viscosity of the formulation. Viscosity results from table 1 indicate that gels (CEG1) made of low concentration of *Aloe vera* gel were less viscous compared to the gels (CEG3 & *Aloe vera* gel) had higher concentrations of *Aloe vera*. Thus it can be concluded that concentration of *Aloe vera* gel had a direct influence on the flow property of the prepared emulgel final formulation.

Table 1: Results of Physical Evaluation of the prepared gels

S.No.	Formulation	Appearance	pH	Viscosity (CPs)
1	CEG1	homogenous, flowing	7.23±0.18	113.2±3.28
2	CEG2	homogenous, flowing	7.19±0.12	132.5±2.94
3	CEG3	homogenous, thick	7.21±0.15	172.9±3.87
4	*Aloe vera* gel	homogenous, thick	5.29±0.28	183.4±2.55

FTIR

It is a characteristic of chia seed extract to display a broad peak at 3441cm^{-1}. This corresponds to the -OH group similar to water molecule/ethanol.[11] Stretches of aliphatic -CH corresponding to CH_2, CH_3 were also noted at 2900cm^{-1}.[27] The spectrum showed a carbonyl (-C=O) stretching at 1600-1640cm^{-1} and another peak at 1650-1690cm$^{-1,}$ a carboxyl (-COO-) stretching at 1400cm^{-1} are characteristic for chia seeds. A stretching peak of -C-O-C- was noted at 1000-1100cm^{-1} an indicative of polysaccharides of anionic type.[17] Characteristic peaks corresponding to aromatic CH_3,OH and phenyl groups were noted at 750, 1050 and 1450cm^{-1}. All the peaks were observed in the spectra of Chia seed extract and admixtures of formulation ingredients. Thus, it can be suggested that there are no chemical interactions between then constituents of the formulations that can possibly cause chemical changes which can be observed from FTIR spectra.

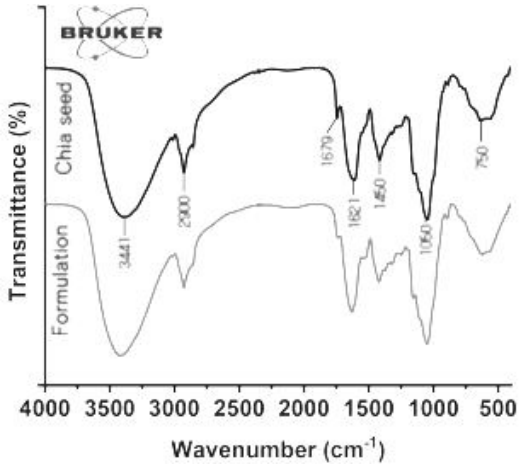

Figure 1: FTIR analysis of Emulgels containing Chia seed extract

DRUG CONTENT

Drug content was determined using the calibration curve of Chia seed extract and %drug content remained at par with the theoretical content. The result in the table 3 shows that over 99% of drug was loaded in CEG1, CEG2 and CEG3 which is highly desirable.

Invitro Drug Release Studies

The invitro drug diffusion studies indicated that drug release from the formulations followed a linear fashion. Results in table 2 indicates that the drug release from formulation CEG1 and CEG2 followed similar pattern with initial burst release of over 50% in the initial 30mins and later slowed the release. Almost 90% of the drug was released in 1.5hr from CEG1 and 2.5hr from CEG2. Contrarily, CEG3 showed a controlled and extended the drug release up to 3hr with 96% release. Though the drug release from CEG2 was 90% in 2.5hr, only 92% was released from the formulation in overall study. Thus, it can be concluded that CEG1 and CEG3 showed better overall release with different patterns where CEG1 showed an initial burst release and maxed at 1.5hrs of administration and CEG3 showed a linear and controlled release of the drug over 3hr duration as shown in figure 2.

Table 2: In vitro Drug release studies of prepared emulgels

Time	% Drug Release		
	CEG1	CEG2	CEG3
30	62.14±1.32	50.84±1.56	29.49±1.52
60	81.23±1.85	67.15±1.98	47.31±1.63
90	90.19±2.51	77.64±2.1	60.98±1.96
120	95.62±2.74	83.63±2.39	72.55±2.52
150	97.58±2.89	89.37±2.85	83.64±2.68
180	98.25±2.95	92.31±2.91	96.37±2.81

The values were expressed as mean±SEM (n=3)

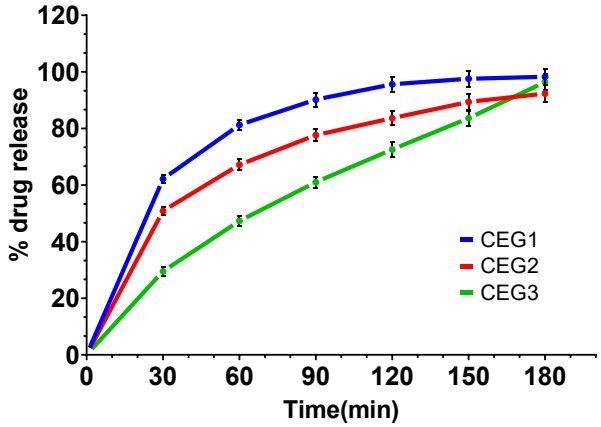

Figure 2: Invitro Drug release from the prepared emulgel

Stability testing

Stability studies were conducted for 3 formulations over three conditions, 25°C, 40°C and 55°C and the % drug content was estimated in order to determine if there is any degradation. All the formulations were stable at 25°C and 40°C where the % drug content was not significantly different from those stored in normal conditions (34±1°C with 70% RH). Although the % drug content did not show much decline numerically, statistical analysis suggests that CEG1 and CEG2 showed a significantly lower drug content compared with drug content of those stored in normal conditions. However, there were no visible signs of instability such as creaming, cracking or phase separation in all the prepared emulgels. CEG3 showed a better stability with no significant changes in the % drug content at all the storage conditions. Thus, CEG3 was selected for evaluating the anti-inflammatory and analgesic activity in albino wistar rats.

Table 3: Results of Stability Studies of the prepared emulgels

Storage condition	% Drug Content		
	CEG1	CEG2	CEG3
Normal	99.37±0.51	99.52±0.54	99.41±0.59
25°C 60%RH	99.11±0.72	98.89±0.66	99.04±0.51
40°C 60%RH	97.36±0.75	98.35±0.73	97.89±0.89
55°C 75%RH	96.22±0.62*	96.17±0.68**	97.78±0.62

The values were expressed as mean±SEM (n=3), ***p<0.001, **p<0.01, *p<0.05 indicates significance compared to the normal group

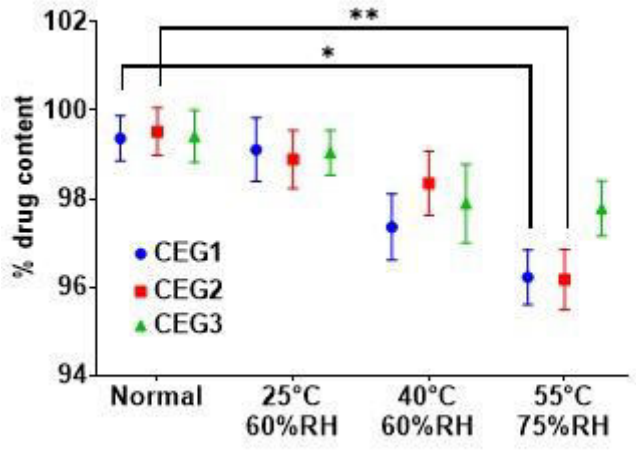

Figure 3: Stability studies of the prepared emulgels

Skin irritation test

The skin irritation test was performed using CEG3 on the wistar rats and it was clearly noted that there were no changes in the skin colour or texture. There is no sign of redness or edema or rash at the end of 24hr. This suggests that the prepared emulgel CEG3 showed no irritation on the skin.

Anti-inflammatory activity of prepared emulgel

The anti-inflammatory activity of the prepared emulgel was investigated against paw edema induced by fresh egg albumin in wistar rats and compared with standard, Diclofenac gel formulation. The paw volume was noted in regular intervals of 0, 30, 60, 120, 180 and 240min and the values were tabulated in table.

The induced group had a increase in paw volume in the initial 2hr of induction of inflammation and a slight reduction was noticed as the rat counteracted the inflammation as a natural mechanism. On the other hand *Aloe vera* gel showed increase in the paw volume in first 30min which reduced in later part of study duration. *Aloe vera* gel after 2hrs showed significant activity compared with the induced group. Diclofenac gel and CEG3 showed significant activity showed significant activity compared with the induced group within 30min of the start of the study. There was no significant increase in the paw volume in CEG3 and standard group indicating a better anti-inflammatory activity similar to the standard, Diclofenac. Values of % inhibition of the inflammation was calculated using paw volumes and the results displayed in table 4, suggested significant activity of CEG3 compared to the *Aloe vera* gel. In contrary there was no significant inhibition of paw volume by diclofenac gel compared to *Aloe vera* gel indicating that the prepared emulgel CEG3 showed a better activity than the standard group.

Table 4: Results of anti-inflammatory activity of prepared emulgels

Time (min)	Induced	*Aloe vera* Gel	Diclofenac Gel	CEG3
0	0.42±0.024	0.4±0.021	0.32±0.022	0.29±0.026
30	0.47±0.027	0.41±0.036	0.38±0.038	0.32±0.029*
60	0.52±0.052	0.39±0.038	0.32±0.041**	0.24±0.032***
120	0.56±0.048	0.36±0.042*	0.31±0.046***	0.22±0.035***
180	0.51±0.041	0.32±0.049**	0.27±0.049**	0.2±0.042***
240	0.46±0.05	0.29±0.051**	0.24±0.051***	0.18±0.051***

The values were expressed as mean±SEM (n=3), ***p<0.001, **p<0.01, *p<0.05 indicates significance compared to the normal group

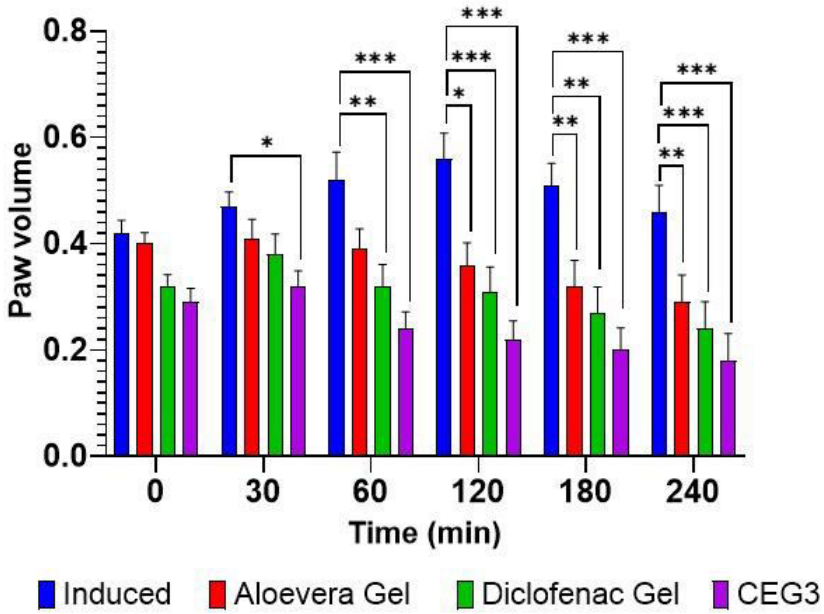

Figure 4: Anti-inflammatory activity of prepared emulgels

Table 5: Inhibition of paw edema by prepared emulgels

Time (min)	*Aloe vera* Gel	Diclofenac Gel	CEG3
0	4.76±0.52	2.8±1.25	30.9±1.23***
30	12.72±0.71	19.1±1.52	31.9±1.25***
60	25.01±1.75	38.461±1.69	53.8±1.65***
120	35.71±1.74	44.64±1.74	60.7±1.75***
180	37.24±2.12	47.05±1.98	56.8±1.84**
240	36.92±2.35	47.8±2.01	56.5±1.98**

The values were expressed as mean±SEM (n=3), ***p<0.001, **p<0.01, *p<0.05 indicates significance compared to the normal group

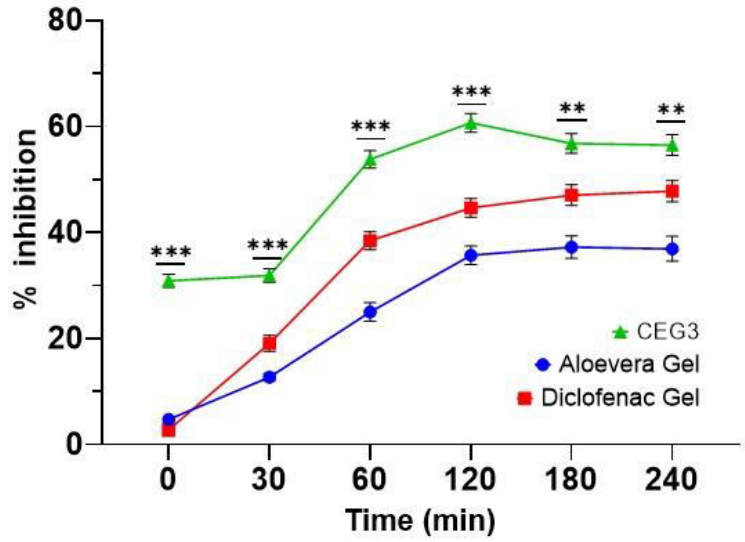

Figure 5: Percentage inhibition of paw edema by prepared emulgels

Analgesic activity of prepared emulgel

The analgesic activity of the prepared emulgel was investigated in tail flick method by observing the latency of reaction of the rat to the heat stimulus given to the dorsal surface of the tail. The normal group of rats showed a longer latency initially and it lowered and immediately showed a reflex due to the fact that the rat had accustomed to the stimulus and memorized the stimulus upon induction of heat. Values in the table suggest that *Aloe vera* gel showed a significant activity compared to the normal group at 2-3hr of study. On the other hand, standard group showed significant activity compared to the normal group within 1.5hr of the study. CEG3 also showed similar activity as that of the standard however, it showed significantly better activity compared to the standard drug at 2.5-3hr. Overall it can be advocated that the prepared emulgel had a better activity compared to the standard formulation.

Table 6: Analgesic activity of prepared emulgels

Time (min)	Normal	*Aloe vera* Gel	Diclofenac Gel	CEG3
Initial	4.45±0.14	4.34±0.24	4.19±0.27	4.36±0.16
30	4.39±0.1	4.21±0.11	5.39±0.1	5.25±0.11***
60	4.28±0.11	4.82±0.14	6.27±0.11	6.57±0.14***
90	4.15±0.14	5.12±0.13*	7.12±0.13***	7.56±0.15***
120	3.74±0.18	5.13±0.16**	6.81±0.15***	8.04±0.17***
150	3.79±0.19	5.45±0.18**	6.38±0.17**	8.11±0.19***[a]**
180	3.81±0.2	5.88±0.21**	5.93±0.19**	7.68±0.21*** [a]**

The values were expressed as mean±SEM (n=3), ***p<0.001, **p<0.01, *p<0.05 indicates significance compared to the normal group, [a]compared to Diclofenac gel

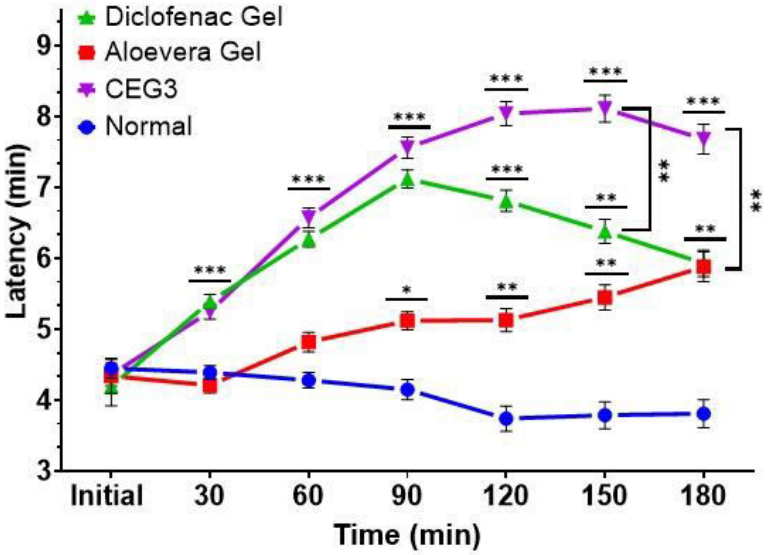

Figure 5: Latency time of the rats treated with prepared emulgel

DISCUSSION

Considering the therapeutic potential of chia seeds and advantages of emulgels to deliver the drugs and control the release of drug, the extracts of the seeds were incorporated into emulgels formulation. Three formulations were prepared by altering the ratios of *Aloe vera* gel and chia seed extract. In the physical evaluation of the formulations much variations were not observed in pH of the formulations because the pH of the formulations was manually adjusted by adding 0.1N NaOH. Interesting results were shown in the values of viscosity as CEG1 showed lesser values in comparison to CEG3. The obvious reason to this can be drawn from the design of formulation which had varying concentrations of *Aloe vera* gel, where increase in *Aloe vera* gel

had imparted more viscosity to the prepared formulation which was also supported by previous studies.[20]

As the FTIR showed similar peaks that are characteristic of the chia seeds extract both isolated and in the formulation without new peaks that are suggestive of any chemical degradation. As all the formulations showed drug content above 99% it is evident that all the formulations exhibited a better drug loading. As a part of stability studies, upon storage under variable conditions, physical changes suggestive of degradation or breaking of emulsion like creaming or cracking were not observed. However, CEG1 and CEG2 showed significant changes in the drug content when stored at 55°C compared to normal conditions indicative of drug degradation or some changes in the formulations. On the other hand, results of drug content of CEG3 in the stability studies showed no variations suggesting the stability of the formulation which can be attributed to the *Aloe vera* gel that is present in the formulation which might have prevented drug degradation.

CEG3 was selected for invivo studies and was tested for skin irritation in albino wistar rats. Results indicated that there was no irritation or any inflammatory changes on the skin of rats. Anti-inflammatory activity of the prepared emulgel CEG3 was investigated in fresh egg albumin induced paw edema and compared with standard, diclofenac gel and *Aloe vera* gel as shown in figure 4. Results suggested that CEG3 showed significantly activity compared to the induced and similar to the standard formulation. The prepared emulgel showed activity within 30min of the application which can be explained by observing the invitro diffusion study results. The drug release from the formulation was controlled and sustained till 3hr duration as shown in the figure 2. Diclofenac gel showed significant activity from 30min and the activity lasted similar to CEG3. In the investigation of analgesic activity, CEG3 showed significantly better activity compared to normal group and *Aloe vera* gel during the course of study. It even showed better activity compared to diclofenac gel during prolonged study more than 2.5hr which can be attributed to the controlled and sustained release of the extract from the formulation. This has contributed for the extended activity of the prepared emulgel, CEG3 compared to the standard formulation.

Previous studies stated that phenols and other constituents like lipids and proteins, present in chia seeds showed antioxidant activity and potential against degenerative diseases which might have contributed for the anti-inflammatory and analgesic activity of the formulations.[28,29,3] The phyto-constituents present in Chia seed extract was responsible for the activity which is better than *Aloe vera* gel. The presence of *Aloe vera* gel has assisted for the significant activity better than the synthetic drug, diclofenac. As the stability studies of CEG3 had proven its stability, invitro diffusion studies proved its better drug release and loading capacity. Considering the significant invivo activity, CEG3 can be advocated as a best formulation and further investigations have to be performed in order to establish the pharmacokinetic profile of the formulation and sophisticated and reliable analytical method development enables the easy and precise estimation of drug contents and to correlate the pharmacological activity.

CONCLUSION

The present study proved the anti-inflammatory and analgesic activity of chia seed extract in rats and pharmacokinetic evaluation showed controlled drug release and better stability of the prepared emulgels. The technology of emulgels was effectively employed in this research and this work opens up arena for incorporating the herbal extracts into novel technologies of drug delivery. As the prepared gels were smooth and even textured, the composition can be used to manipulate the patient compliance for similar kind of topical delivery systems. Also the prepared emulgels showed synergistic activity which also opens up scopes for future research to probe into explaining and establishing the synergistic potential of the herbs and to employ them to prepare better formulations resulting in efficient therapy of diseases.

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Conflicts of Interest: The authors declare no conflicts of interest.

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