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Preparation and characterization of vetiver oil encapsulated polymeric microcapsules for sedative and hypnotic activity

Syed Ansar Ali*[1], Amit Kumar Nayak[2], Kalyan Kumar Sen[3], Prabhakar T[1]

[1]Department of Pharmaceutics, Karnataka College of Pharmacy, Bengaluru, Karnataka, India
[2]Department of Pharmaceutics, Seemanta Institute of Pharmaceutical Sciences, Mayurbhanj, Odisha, India
[3]Department of Pharmaceutics, Gupta College of Technological Sciences, Asansol, West Bengal, India

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ABSTRACT

In the present work, in view of the medicinal properties of vetiver oil (extracted from the roots of *Vetiveria zizanioides* L.), we made an attempt to encapsulate vetiver oil in a biocompatible polymeric system made of sodium alginate with gellan gum or karaya gum. Sodium alginate and gellan gum or karaya gum were ionotropically cross-linked to encapsulate vetiver oil. Vetiver oil encapsulations in these microcapsules were 35.92 ± 3.18 % to 78.55 ± 3.35%. Vetiver oil encapsulated microcapsules were of spherically shaped with 656-769 μm mean diameter. This vetiver oil encapsulated microcapsules made of alginate-gellan gum blends were found capable of providing a long release of encapsulated oil, showing the potential for the sustained release application. These microcapsules were analyzed by FTIR, DSC, and SEM, etc. In addition, sedative and hypnotic activities of vetiver oil encapsulated polymeric microcapsules in the male Swiss albino mice were evaluated. The sedative-hypnotic activity of vetiver oil encapsulated polymeric microcapsules in rats was observing the number of crossing and motilities. The results proves that vetiver oil encapsulated polymeric microcapsules decreased motility when compared to the control group.

*Corresponding Author

Name: Syed Ansar Ali
Phone:
Email: pharmaalil2004@gmail.com

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INTRODUCTION

From the ancient era, there is a huge tendency for the use of various kinds of natural derived raw materials like oils (essential oils, fixed oils, and mineral oils), polymers (carbohydrate-based and protein-based), etc., for various medical, biomedical and pharmaceutical applications (Balasankar *et al.*, 2013; Arctander, 1960; Nayak *et al.*, 2018a,c; Nayak and Pal, 2016a). In recent years, a variety of essential oils are being extracted from natural resources, and also, these are being used as raw materials in different applications (Arctander, 1960; Nayak *et al.*, 2018a,c; Nayak and Pal, 2016a; Guenther, 1982). The vetiver oil is essential raw materials in perfumery, both as an adhesive and aroma ingredient. It used in toiletries and cosmetic industries. Vetiver root is moreover used in traditional remedies as a carminative, stimulant, and diaphoretic (Balasankar *et al.*, 2013; Chowdhury and Kumar, 2002; Weyerstahl *et al.*, 2000b).

Vetiver oil has a sedative properties (Kim *et al.*, 2005). The literature survey reveals that there is no established formulation method has been devel-

oped for the encapsulation of vetiver oil by the polymeric systems. Therefore, the present work was attempted to develop a new microencapsulation method using ionic cross-linking of sodium alginate with gellan gum or karaya gum to produce the sedative and hypnotic activities. Vetiver oil is an essential oil obtained by the steam distillation method. Source of oil is vetiver roots (Vetiveria zizanioides, syn.) The plant, *Vetiveria* are available in India and is commercially cultivated for its aromatic roots. Vetiver oil possesses various medicinal uses like anti-inflammatory, antiseptic, aphrodisiac, cicatrisant, nervine and sedative, tonic, and vulnerary. In view of its medicinal properties, we made an attempt to encapsulate vetiver oil in a biocompatible polymeric system (Hewawasam and Jayatilaka, 2015; Champagnat *et al.*, 2006; Weyerstahl *et al.*, 2000a). Vetiver root oil found around 150 constituents (Gangul, 1989). This is made of sodium alginate and gellan gum or karaya gum. The biocompatible polymeric system, sodium alginate, was cross-linked with gellan gum and karaya gum to encapsulate vetiver oil.

Sodium alginate, gellan gum, and karaya gum are naturally derived biodegradable and non-toxic biopolysaccharides (Jana *et al.*, 2013; Nayak *et al.*, 2018d). Sodium alginate is a linear anionic polysaccharide extracted from marine brown algae. Sodium alginate is the sodium salt of alginic acid composed of α-l-guluronic acid residue, β-d-mannuronic acid residue, and regions of interspersed both the residues (Nayak *et al.*, 2018b; Hasnain *et al.*, 2018). It has been employed as a material for encapsulations of drugs and other biomolecules to accomplish sustained releasing of encapsulated materials over a prolonged period because of its gel-forming properties (Nayak *et al.*, 2018a,b; Hasnain *et al.*, 2018; Pal *et al.*, 2013; Nayak and Pal, 2013; Pal and Nayak, 2015; Martins *et al.*, 2017; Oliveira *et al.*, 2014). Gellan gum is also another water-soluble linear anionic biopolysaccharide extracted as a fermentation result by Pseudomonas elodea and contains saccharide units of glucose, glucuronic acid, and rhamnose in a ratio of 2:2:1 (Nayak *et al.*, 2014a). The gelation capability helps as gelling agent in foods and pharmaceuticals preparation (Nayak *et al.*, 2014b). Sodium alginate and gellan gum undergoes ionotropic gelation in the aqueous solutions in the presence of multivalent cations like Ca2+, Zn2+, Ba2+, Al3+, etc. (Nayak and Pal, 2013; Nayak *et al.*, 2014b). Karaya gum is also known as sterculia gum extracted from the plant, *Sterculia urens* Roxb., and other species of Sterculia, which are belonging to the family, Sterculiaceae (Nayak and Pal, 2016b). For many years, karaya gum has been used as an emulsifier, stabilizer, and thickening agent in various food, cosmetic, and pharmaceutical preparations (Bera *et al.*, 2015; Anderson, 1989; Anderson and Wang, 1994). It is a strongly acidic natured plant-derived branched and partially acetylated polysaccharide showing good stability in the acidic milieu (Nayak and Pal, 2016b; Cerf *et al.*, 1990). The main objectives of the current research were to prepare and characterize the vetiver oil encapsulated polymeric system made of sodium alginate with gellan gum or karaya gum. In addition, the sedative and hypnotic activities of vetiver oil in the male Swiss albino mice were evaluated in the current work.

MATERIALS AND METHODS

Materials

Vetiver oil was purchased from Falcon (exporters of essential oil), India. Gellan gum and karaya gum were purchased from Yarrow Chem Products, India. Sodium alginate purchased from Karnataka Fine Chemicals, India. Sodium citrate tribasic dihydrogen (Sisco Research Laboratories Pvt. Ltd, India) and n-hexane (Merck Specialities Private Limited, India) were used. All other reagents used in the experiment were of analytical grade and was used without any pre-treatment. The water of double-distilled grade was used.

Preparation of alginate-gellan gum solutions

Sodium alginate (1-4 g/L) and gellan gum (0.1-0.2 g/L) powders were mixed and dispersed in double distilled water to produce alginate-gellan gum solution of the desired concentration. The solution was left standing for 24 h. to disengage bubble before use. A calcium chloride solution (1-6 g/L) was prepared by dissolving the same in distilled water.

Preparation of alginate-karaya gum solutions

Sodium alginate (1-4 g/L) and karaya gum (0.1-0.2 g/L) powders were mixed and dispersed in double distilled water to produce alginate-gellan gum solution of the desired concentration. The solution was left standing for 24 h. to disengage bubble before use. A calcium chloride solution (1-6 g/L) was prepared by dissolving the same in distilled water.

Preparation of oil in water (o/w) emulsions

Vetiver oil (2 mL) and 10 mL of alginate-gellan gum aqueous solutions or alginate-karaya gum aqueous solutions were mixed together in a beaker and subjected for homogenization in a digital high shear homogenizer (Ultra-Turax, Model T-25, IKA, India) using of 6000 rpm speed for 30 min to make oil in water (o/w) type emulsions. The oil was mixed

Table 1: Formulation chart of various vetiver oil encapsulated polymeric microcapsules with oil encapsulation (%) results

Formulation	Sodium alginate (g)	Karaya gum (g)	Gellan gum (g)	Calcium chloride solution (%)	Vetiver oil (%)	Oil encapsulation (%)*
F1	2.40	0.60	-	4	20	35.92 ± 3.18 %
F2	2.10	0.90	-	4	20	36.88 ± 3.54 %
F3	2.40	-	0.60	4	20	67.23 ± 3.03 %
F4	2.10	-	0.90	4	20	71.08 ± 3.37 %
F5	3.00	-	0.20	4	20	78.03 ± 3.31 %
F6	3.00	-	0.20 with 2 % Tween 80	4	20	78.55 ± 3.35 %
F7	3.00	-	-	4	20	58.22 ± 3.03 %

*Mean ± S.D., n = 3

Table 2: Comparative sedative-hypnotic effect of vetiver oil encapsulated polymeric microcapsules and essential oil of Vetiveria zizanioides (vetiver oil) with standard drug (diazepam)

Group	Dose/kg body wt	Onset of sleep (min)*	Sleep duration (min)*
Control	Vehicle	13.3 ± 1.2	21.4 ±3.6
Diazepam	3 mg	7.7 ± 0.8	43.8 ± 4.1
Vetiver oil encapsulated polymeric microcapsules (low dose)	63 mg	9.4 ± 1.0	27.2 ± 2.0
Vetiver oil encapsulated polymeric microcapsules (high dose)	82 mg	8.2 ± 0.4	31.3 ± 3.3
Vetiver oil	2 ml (68.53 mg)	7.9 ± 0.5	39.5 ± 4.5

*Mean ± SD

slowly to the gum solutions till the total oil is added.

Determination of emulsion stability

Emulsions (50 mL) were left standing for 1 h to determine the extent of any phase separation. Emulsion stability was determined depending on the phase separation interface position, which was measured based on the volume of remaining emulsion and on the volume of the initial emulsion.

Encapsulation of oil

The alginate-based o/w type emulsions were passed through a 0.55 mm needle and were dripped into calcium chloride (ionotropic cross-linker) solution to form oil-loaded calcium alginate-based beads. The tip of the needle was fixed at 15 cm above the surface of the solution. The cross-linker solution was gently stirred by a magnetic stirrer (Remi Motors, India), which prevents the prepared beads from sticking together. The prepared particles were hardened for 30 min in the cross-linker solution. Then, these beads were kept for drying overnight at room temperature. The formulation chart is presented in Table 1.

In vitro dissolution study

In vitro drug release performed by paddle-type dissolution apparatus (TDT-08L, Electro Lab, India) consisting of six baskets. Dissolution studies were carried out at a temperature of 37°C (± 0.5°C), 7.4 pH, and rotor speed was maintained below 75 rpm. Sample aliquots were withdrawn at regular intervals of time and analyzed in triplicates by using a double beam UV-vis spectrophotometer (UV-1800, Shimadzu, Japan) by selecting 235 nm as detection wavelength. The cumulative percentage of vetiver oil released was plotted as a function of time.

Physico-chemical characterization

Fourier transform infrared (FTIR) spectroscopy

In vitro drug release performed by paddle-type dissolution apparatus (TDT-08L, Electro Lab, India)

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Differential scanning calorimetry (DSC)

DSC thermograms of samples were measured with Perkin-Elmer (Pyris-Diamond TG/DTA, Japan). Sample weighing 5 mg was placed in a hermetically sealed aluminum pan. It was heated in the temperature range of 25-3500C at a speed of 100C under a nitrogen atmosphere.

Scanning electron microscopy (SEM)

Vetiver oil-loaded microencapsules shape and surface characters were evaluated by SEM (JSM-6390, Japan) with required magnification using the secondary electron image as a detector and an increasing voltage of 5 KV.

Particle size analysis

Phase-contrast microscopic examination was done by using a Phase contrast microscope (Ernst Leitz GMBH, Wetzlar, Germany) to achieve morphology and particle size of the microencapsulated formulations. Sample was placed on a slide and observed.

Flow properties

Flow properties of the microencapsulated formulations were evaluated by measuring Carr's index and Hausner ratio. The bulk and tap densities of the microencapsulated formulations were also measured in a 100 mL graduated measuring cylinder.

Carr's index was determined by the following formula:

Carr's index (C) = (tapped density - bulk density) / tapped density ×100.

Carr's compressibility index ranges for good flow property in the range of 15-25%. The Hausner ratio measure the flow of a granular material. The formula is as below.

Hausner ratio (H) = 100/ (100 – C)

The poor flow will occur when the value of the Hausner ratio is more fixed height funnel method was used to determine the angle of repose. A funnel is taken in a stand. The stand height is fixed based on powder heap height so that it touches the funnel tip. The powder was made to fall liberally through the funnel onto the surface. The angle of repose was calculated by measuring the height and diameter of the sample cone.

In vivo animal study

Male Swiss albino mice (Thirty) were purchased from an authorized supplier (Bangalore, India). The rats were randomly divided into five groups (n=6). All animals were maintained in a specific pathogen-free (SPF)-conditioned standard laboratory room. Food (standard pellet) and tap water were provided ad libitum to all animals. All procedures involving rats were carried out according to the guidelines of the Ethical Research Committee (Protocol No.Sl. no.KCP/IAEC/2/17-18/13/15-04-17; dated: 20.04.2017) and Supervision of Experiments on Animals (CPCSEA).

Animal groupings

Mice randomly divided into five groups (n=3): Group I: control rats received distilled water orally, Group II: rats receiving standard vetiver oil and the Group III: treated with formulated vetiver oil encapsulated microspheres for 12 h.

Rota-rod assembly apparatus

This was performed to determine the effect of the drug. The grip of mice on a rotating rod is due to the muscle grip strength. The grip strength was reduced by using of a sedative-hypnotic drug, and mice were fall from the rotating rod for the sedative and hypnotic agents. Loss of grip strength is directly correlation with muscle relaxant agents, and the effect is considered as motor coordination. Animals were transferred on rotating rod (13-15 rpm) for 1 min followed by 1 hr of drug dosing. The fell down the rate of animals in 1 min was calculated as the loss of grip strength. To determine motor co-ordination (muscle relaxant activity) of the drugs, 3 repeated cycles was compared between groups (Vogel, 2008; Bhadoriya *et al.*, 2009).

Locomotor activity test

The spontaneous locomotor movement of mice was considered as degree of a sedative effect. ZZ-6 locomotor activity tester (Taimeng Software Co. Ltd., China) was used to measure locomotor activity, which was connected with a microcomputer control system and 6 separable reaction tanks that possessed 36 points of the infra-red array probes. A period of 30 min after the oral administration of formulation and standard, mice were transferred to in the locomotor activity tester individually. The locomotor activity was recorded, followed by 5 mins acclimatization.

Statistical analysis

The duration of sleep and its onset were evaluated by ANOVA analysis for the independent batches.

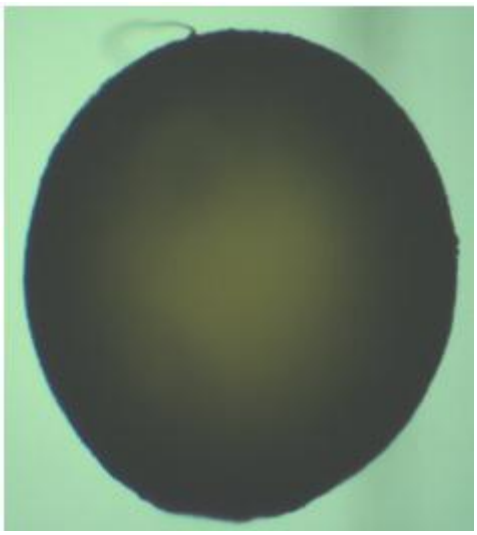

Figure 1: Light microscopy image of polymer microcapsules blends of vetiver oil

Two way ANOVA analysis and then the post-hoc Duncan test was done for spontaneous locomotor activities. For all studies, statistical significance was fixed at 5% level, and values were written as average ± SD. (standard deviation).

RESULTS AND DISCUSSION

Characterization of emulsion

In this work, natural polymer microcapsules blends of vetiver oil were developed by o/w emulsion technology. The formation structure of emulsion by this technique was confirmed by light microscopy (Figure 1). Prepared o/w emulsion was found stable and indicated good stability after standing overnight. This may be due to the improved viscosity imparting by the prepared aqueous gum solution covering the oil phase via restricting their movements and fusing the droplets with each other.

Preparation of vetiver oil encapsulated polymeric microcapsules and oil encapsulation

Vetiver oil encapsulated polymeric microcapsules made of sodium alginate with gellan gum, or karaya gum was prepared using calcium chloride (ionotropic cross-linker) solution. For the preparation of vetiver oil encapsulated polymeric microcapsules, sodium alginate-based o/w type emulsions were extruded through a needle (0.55 mm) and were dripped into the ionotropic cross-linker (calcium chloride) solution to form vetiver oil encapsulated calcium alginate-based microcapsules.

The microencapsulation of vetiver oil efficiency based on the values obtained for the total amount of encapsulated oil, and this is one of the quality parameters used to determine the amount of oil successfully encapsulated via an ionotropic crosslinking method. The value of oil encapsulations within these polymeric microcapsules was calculated with the range, 35.92 ± 3.18 %, and 78.55 ± 3.35% (Table 1). It was also seen that the vetiver oil encapsulation within the polymeric microcapsules made of alginate and karaya gum was comparatively lower than that of the microcapsules made of alginate and gellan gum (Table 1).

In vitro oil release study

In-vitro release study of oil was performed, and the percentage cumulative release vs. time data Figure 2. All the formulations of vetiver oil encapsulated microcapsules were rover a period of 8 hrs. The vetiver oil encapsulated microcapsules formulation F7 (made of alginate) showed a higher release rate than others, and similarly, the vetiver oil encapsulated microcapsules formulation F3 (made of alginate and gellan gum) showed the lowest release rate than other microcapsules. The vetiver oil encapsulated microcapsules formulation F6 (made of alginate and gellan gum with 2 % Tween 80) also exhibited a higher release rate almost comparable to microcapsules formulation F7 (made of alginate). Hence, microcapsule formulation F5 was selected for further investigation in this work due to its higher oil encapsulation (78.03 ± 3.31 %, which was almost nearer to that of F6) and slower release of encapsulated oil.

FTIR analysis

The compatibility of the entrapped vetiver oil with the gum was evaluated qualitatively through FTIR analysis. FTIR spectra of sodium alginate, gellan gum, vetiver oil, and vetiver oil encapsulated microcapsules (Formulation F5) is presented (Figure 3). Sodium alginate FTIR spectra showed the distinguishing peaks at 3218 cm−1 owing to -OH stretch-

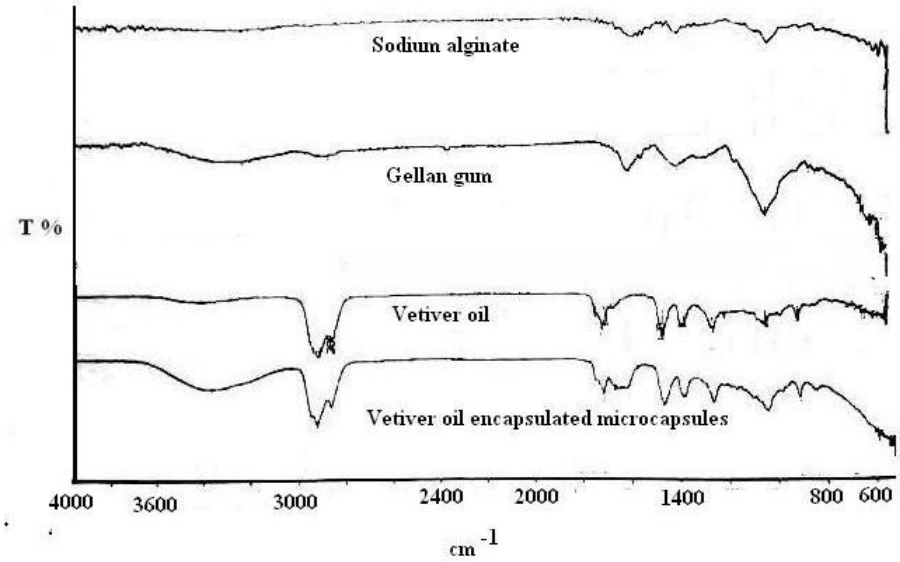

Figure 2: In vitro oil release study of encapsulated microcapsules

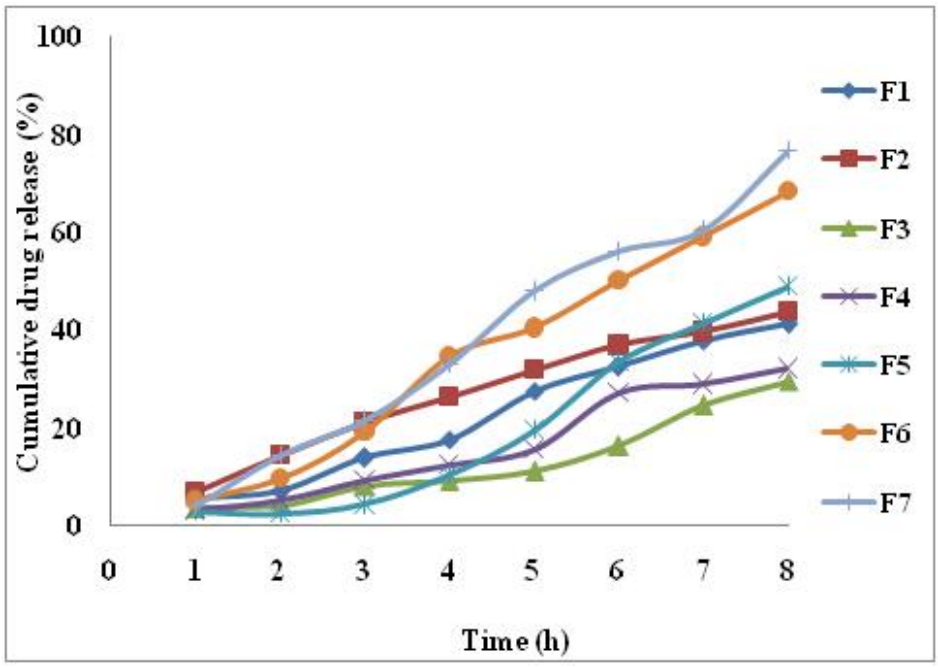

Figure 3: FTIR spectra of sodium alginate, gellan gum, vetiver oil and vetiver oil encapsulated microcapsules

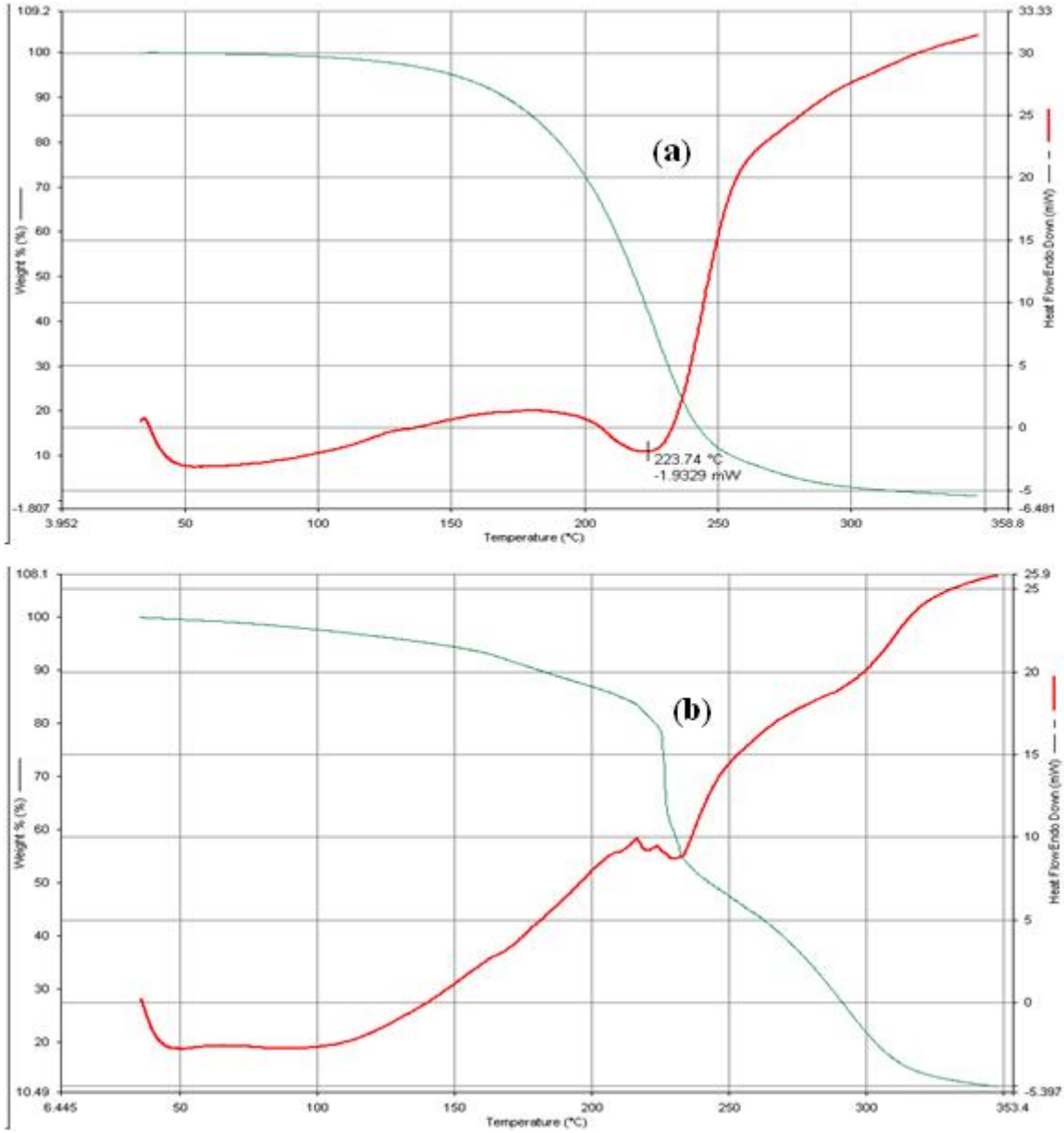

Figure 4: (a) DSC thermogram of pure vetiver oil (b) DSC thermogram of vetiver oil encapsulated microcapsules

ing, 1649, and 1456 cm−1 due to COO- asymmetric and symmetric stretching, and 1032 cm−1 because of C-O-C stretching, respectively. The gellan gum FTIR spectrum showed peaks at 3729 cm−1 due to stretching of -OH, 1399 cm−1 due to C-H bending of methyl, and 1017 cm−1 for –C-O stretching of alkyl ether. Pure vetiver oil FTIR spectrum exhibited some distinctive peaks at 1670–1736 cm–1 due to the carbonyl stretching. Some strong vibration peaks were observed at 1456 cm–1, 1363 cm–1, 1247 cm–1, 1196 cm–1, and 1023 cm–1 due to CH2 asymmetric and symmetric bending vibrations, C–N, C–C and C–O stretching vibrations. Similar vibration peaks of this entrapped oil were detected in the spectrum of vetiver oil encapsulated microcapsules made of sodium alginate and gellan gum (Formulation F5) with very minor or without differences in frequencies. Therefore, the FTIR results suggested that the presence of this vetiver oil into the cross-linked alginate-gellan gum polymeric matrix. Also, vetiver oil was found apparently stable in the microcapsules, and any interaction with alginate-gellan gum polymeric matrix not revealed.

DSC analysis

DSC analysis is valuable for the study of the thermostability of encapsulated vetiver oil in the alginate-gellan gum microcapsules. Figure 4 a and represents the DSC thermogram of pure vetiver oil and vetiver oil encapsulated microcapsules (Formulation F5). The pure vetiver oil showed a sharp

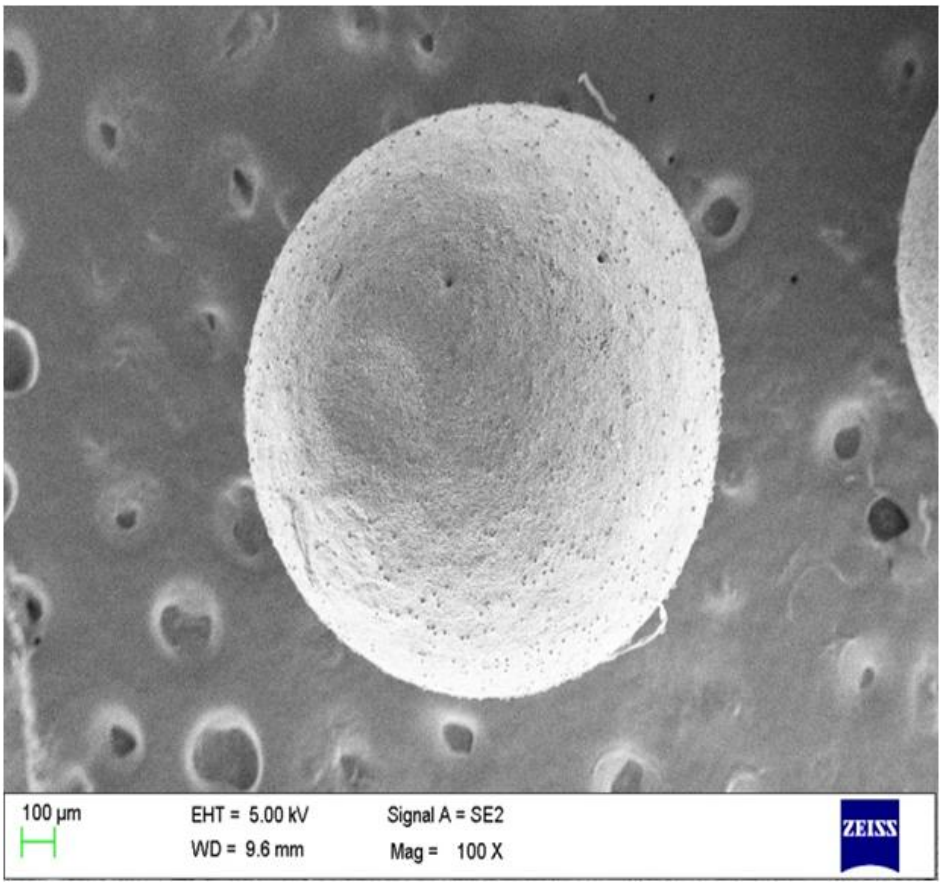

Figure 5: Surface morphology of vetiver oil encapsulated microcapsules

exothermic peak at 223.74°C (Figure 4 a). However, the DSC thermogram of vetiver oil encapsulated microcapsules (Formulation F5) did not show a sharp peak at the same temperature, but it showed a peak at 241.70 °C (Figure 4 b), which can be related to the auto-oxidation of samples. The tested formulations showed improved antioxidant property than its pure form. The modified antioxidant activity of vetiver oil encapsulated microcapsules by this technology shows that proper control of variations in the process parameters could allow the formation of a link between alginate-gellan gum polymeric matrixes.

SEM analysis

The surface morphology of vetiver oil encapsulated microcapsules was characterized by SEM analysis. The SEM micrograph of vetiver oil encapsulated microcapsules (Formulation F5) demonstrated spherical shaped microcapsules with almost smooth external surfaces (Figure 5).

Particle size analysis

Mean particle diameter of the vetiver oil encapsulated microcapsules formulations ranged in the micrometre range (656-769 μm). This result indicated a slight increase in size, which might be due to increasing of the number of dispersed phase droplets size of the primary emulsion cross-linked in a fixed volume of the aqueous phase. Which increases vetiver oil encapsulation in the microcapsules.

Flow properties

The flow property results indicated that these vetiver oils encapsulated microcapsules had excel-

lent flow property. The oil encapsulated microcapsules were found to exhibit higher packing properties. The improvement in flow properties clearly suggested that the vetiver oil encapsulated polymeric microcapsules can be easily handled during processing.

In vivo animal study by rota rod assembly apparatus

Rota-rod assembly apparatus was used to determine motor coordination in the in vivo animal study using Swiss albino mice. The effects of the different formulation on sleep duration and latency time induced were assessed. Vetiver oil at the dose of 150 mg/kg body weight, radically augmented total sleep duration in contrasted with the control ($p < 0.05$) and this effect was less than the standard drug diazepam (3 mg/kg), while vetiver oil (2 ml/kg) extensively increased the sleep duration in contrasted all groups and it is insignificant in contrast to diazepam group ($p > 0.05$)(Table 2). Effect of vetiver oil (150 mg/kg) was found significant as compared to the control, whereas it was found to be increased ($p > 0.05$) as compared to diazepam and vetiver oil. Vetiver oil has revealed equivalent efficacy with standard drug diazepam.

CONCLUSION

In conclusion we can suggest that vetiver oil may be used via cross-linked polymeric microcapsules. It is prepared by the ionotropic gelation method, and it is prepared in the alginate-gellan gum blends cross-linked microcapsules suitably and repeatedly. Prepared vetiver oil-loaded microcapsules were of spherically shaped and size. FTIR and DSC analyses suggested no chemical interaction occurred between the encapsulated vetiver oil within the microcapsules made of alginate-gellan gum blends. This cross-linked vetiver oil encapsulated microcapsules made of alginate-gellan gum blends were found capable of providing a prolonged release of encapsulated oil in a sustained manner, indicating the potential for the sustained release sedative application.

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