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DESIGN AND DEVELOPMENT OF PRONIOSOMAL FILM FORMING GEL OF CRAMP BARK EXTRACT

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ABSTRACT

The aim of present work was to develop, characterize, and optimize the proniosomal film forming gel containing Cramp bark herbal extract for menstrual pain. The effect of span 20 and span 80 on penetration of proniosomal gel. Four formulations are prepared by using span, lecithin and cholesterol. Proniosomal gels was prepared and evaluated for physicochemical parameters like pH, viscosity, spreadability, etc. have been studied. Invitro diffusion studies using Franz diffusion cell. The p^H of the gel is maintained in the range of 6.8 -7 by using triethanolamine to prevent itching and irritation of the skin. Out of four formulations the optimized formulation was selected by entrapment efficiency and diffusion studies. FTIR studies showed compatibility between polymer and extract. From the present studies it is concluded that the film forming gel would help to increase the residence time as well as help in enhancing the permeation of the cramp bark extract and provide around the clock relief from Dysmenorrheoa.

KEYWORDS: Cramp bark, proniosomal gel, Dysmenorrhea, Menstrual pain.

INTRODUCTION

Cramp bark is just one of many herbal medicines and remedies for pms cramps. Cramp bark or Viburnum opulus goes by many other names some of which are Gaitre Berries, Red Elder, Guelder Rose etc.The dried cramp bark is traditionally used as a muscle relaxant and antispasmodic, sometimes in combination with valerian. It is used to treat menstrual cramps. According to an early study published in the Journal of Medicinal Chemistry, the antispasmodic properties of cramp bark are due to the presence of coumarin scopoletin.

Primary dysmenorrhea is defined as cyclic and painful cramps pelvic, occurring just before or during menstruation which deranges daily activities.[1] Primary dysmenorrhea is one of the most common gynecologic disorders in young women which may affect more than half of menstruating women.[2-4] Prostaglandin production by ovulation is the main cause of primary dysmenorrhea.[5,6] Digestive disorders including nausea, vomiting and diarrhea are the symptoms associated with primary dysmenorrhea, which are known due to intestinal spasms during menstruation.[7] The prevalence of dysmenorrhea in different populations is 50 - 90% and in Iran it is 74 - 86.1% (8, 9). Primary dysmenorrhea is a common cause of absenteeism from work, education, or referral to physician, which may lead to decreased efficacy of occupation and education. Although dysmenorrhea is not life threatening, it could have adverse effects on quality of life.[10]

ANTI-SPASMODIC

Cramp bark relieves spasms of all kinds. It Is considered one of the best female regulators and relaxants of the ovaries and uterus, and is highly effective in preventing abortions due to nervous affections during pregnancy. It will speedily quiet the uneasiness and relieve the pains of uterine and abdominal cramps. In 1833 a meeting of the Materia Medica Society of New York was held, and this drug was discussed, though no conclusive evidence was adduced; however, it was said to be urgently advocated as a very powerful uterine sedative, as well as a remedy for neuralgic dysmenorrhea and for the commonly associated spinal irritation. Indeed, the herb has been accredited for augmenting as well as diminishing the menstrual flow. It is used for regulating the flow after birth or after miscarriage as well. For women who have convulsions during pregnancy, high cranberry bark will safely relieve them. It allays uterine irritation tending to end in hysteria.

The development of topical gel systems has received considerable attention over the past few years (Kumar, P., et al. 2013). Now a day's number of topical gel systems are formulated and used on many patients for various biomedical applications.

The topical drug delivery is the convenience means of administration, which deliver the accurate dose and prolong residence time of drug in contact with skin membrane. It is the most promising means of drug delivery system. Various synthetic and natural polymers are been used in the formulation of topical gel (Tomita, T., et al. 2003).

To get the desired characteristics of a particular proniosomal gel formulation, it is important to select the surfactant of suitable HLB in the formulation of proniosome gel (Alsarra.I.et al2005).

The modification in the niosome converts into proniosomal delivery systems. "Proniosomes are the carrier which is coated with the surfactant, which can be diluted in hot water with agitation." (Mishra.A.et al.2011) Proniosomes are the carrier system, in which the vesicles are made up of different non ionic based surfactants and other additives.

MATERIALS AND METHODS

Procurement of Raw Material

Herbal extract, Cholesterol, lecithin, PEG ,Span 40, Span 60 and Span 80, Methanol and sodium chloride extra pure LR). Potassium dihydrogen orthophosphate Dialysis membrane 150, Diethyl ether, hydroxyl propyl methyl cellulose (HPMC K4M) and sodium chloride Sodium hydroxide pellets LR Glycerin. Purchased from Unicorn scientific, Navi Mumbai.

Compatibility studies

FTIR spectroscopy was carried out to check the compatibility between drug extract and surfactants used. IR spectra of drug extract, and surfactant mixture was studied using FTIR instrument.

Niosomal gel preparation:(Table 1)

Proniosomal gel was prepared by using different composition of surfactants in different ratio which is listed in Table 4. Using Amber coloured vial with tight rubber closure, 100 mg of drug extract with surfactant, Lecithin, and cholesterol was mixed with 2.5 mL of ethanol. Then vial is closed and warmed in water bath at 65 ± 3°C for 5 min. Then 1.6 mL of pH 7.4 Phosphate buffer was added and mixture was further warmed in water bath for 2 min so that a clear solution was obtained. The mixture was converted to proniosomal gel.[11,12]

Evaluation of niosomal gel

Drug content and Entrapment Efficiency

Drug content was determined by disrupting the niosomal formulation by propane-1-ol, diluted suitably using phosphate buffer pH 6.8 and analysed for the drug content spectrophotometrically at 430 nm. The free drug was determined by subjecting the niosomal formulation to centrifugation at 7000 rpm for 30 min to separate the free drug. After centrifugation, the supernatant was collected, and further centrifuged at 7000 rpm for 30 min. A clear solution was separated and the settled niosomes were collected. The collected supernatant was analysed for the drug content spectrophotometrically at 430 nm.[15,16]

Entrapment efficiency calculated by using the following formula

% Entrapment efficiency = Entrapped drug/ Total drug × 100

Vesicle Size

Vesicle size of selected niosomal dispersion was determined by optical microscope and vesicle size, shape and surface property of the selected formula was studied using Scanning Electron Microscope.(Figure 1)

In vitro diffusion study: (Figure 2)

The in vitro drug diffusion study was conducted by using Franz diffusion cell assembly. Niosomal formulation was placed on dialysis membrane between donor and receptor compartment of diffusion assembly. The receptor compartment was filled with (Phosphate buffer pH 6.8) which was maintained at 35° ± 1° , magnetically stirred at 50 rpm. The drug content was determined by collecting the receptor fluid (1ml) every h for 24 h, the volume withdrawn was replaced with 1ml of fresh buffer. After suitable dilution, the samples were analyzed at 430nm.

Formulation of carbopol gel

As a vehicle for incorporation of niosomes for skin delivery, Gel was prepared using carbopol-934 as gelling agent. Required quantity of gelling agent was weighed and dispersed in sufficient quantity of distilled water. This dispersion was neutralized by drop wise addition of triethanolamine till a clear gel was obtained. A 2.5% w/w gel was obtained by dissolving extract in propylene glycol, and treated in the same way as explained above.Formula of gel is given in Table 2). Incorporation of niosomes to gel base optimized formula was incorporated into gel base by gentle mechanical mixing at 25 rpm for 15 min.[12]

Evaluation of Extract Niosomal Gel

Physical examination the prepared gel formulations were inspected visually for colour, homogeneity, consistency, grittiness and spreadability. pH The pH of gel was determined using digital pH meter (Digisun Electronics)[13,14]

Drug entrapment efficiency: Table 3

Viscosity

Viscosity was determined using Brookfield viscometer by selecting suitable (T-F) spindle by trial and error method at 10 rpm. The viscosity in cps was directly read.[17,18]

Spread ability: The Spread ability of the gel formulations was determined by taking two glass slides

of equal length. On one glass slide, 1 gm gel was applied. To the other glass slide, weights were added and the time taken for the second glass slide to slip off from the first glass slide was determined Spread ability coefficient was determined by the formula

SC= M*l/t,

Where, SC=spredability coefficient=Mass in gm, l is the length, t is time in min.

Drug Content
Niosomal gel formulation equivalent to 100 mg drug extract was dissolved in 25 ml phosphate buffer pH 6.8, by mechanical shaking for 2 h, diluted suitably and analyzed for drug content spectrophotometrically.[15,16]

In vitro Diffusion Study :(Figure 3)
The in vitro drug release studies were conducted by using Franz diffusion cell assembly. A 100 mg drug equivalent niosomal formula was placed on dialysis membrane between donor and receptor compartment of diffusion cell assembly. The receptor compartment was filled with phosphate buffer pH 6.8 which was maintained at 35° ± 1°, magnetically stirred at 50 rpm. The drug content was determined by collecting 1ml of receptor fluid every h. The volume withdrawn was replaced with equal quantity of fresh buffer. After suitable dilution, the samples were analyzed spectrophotometrically.[18]

Zeta potential:
The zeta potential value of prepared niosome was found to be 43.9 mV. Higher the zeta potential more is the stability of colloidal system. In vitro diffusion study: The release study suggests that 50% of drug was released in 12 h which may be due to improper bursting of niosome vesicles. After that the release was controlled because the niosome began to obtain stability.

The release also depends on the entrapment efficiency. Formulations with more entrapment efficiency showed more release percentage compared to formulations with less entrapment efficiency.[17,18]

Evaluation of Niosomal Gel Physical evaluation:
The observations are given in Table 6.

pH of the gel The prepared gel formulations were inspected visually for their color, homogeneity and consistency. The pH values of the prepared gels were measured by a pH (pico) meter (Lab India instruments Pvt ltd.).

Drug content. Content uniformity was determined by following procedure: gel formulations (100 mg) was dissolved in phosphate buffer pH 5.5 and filtered and the volume was made to 100 ml with phosphate buffer. The resultant solution was diluted with phosphate buffer and absorbance was measured using Shimadzu-1700 UV Visible spectrophotometer.

Spreadability: Spredability excess of sample is applied in between two glass slides and was compressed by using 1000g weight for 5min. Weight (50gm) was added to pan. The time required to separate the two slides, was taken as measure of Spreadability (S).

S=ML/T

S=spredability

M=weight on upper slide

L=length moved on glass slide

Viscosity
Viscosity measurements. Viscosity measurements were carried out at temperature (25–27^{o} C) using a Brookfield DV-1 viscometer with shear rate ranging from 10 to 100 s ^{1}. A specific amount of the formulation (20 ml) was used and the speed of the spindle was adjusted to 100 rpm.

In vitro drug release
An in-vitro drug release study was performed using modified Franz diffusion cell of capacity 60 ml. Dialysis membrane (molecular weight 12 kD) was placed between receptor and donor compartments. Niosomal gel equivalent to 1 g was placed in the donor compartment and methanolic phosphate buffer (pH 5.5) was used as receptor compartment. Donar cell compartment is maintained at 37+- 2^{o}C. Magnetic stirring 100rpm throughout the experiment. About 1 ml of aliquots were withdrawn at different time intervals up to 24 h from receiver compartment and replaced with the same amount of fresh methanolic PBS to maintain the sink conditions. The samples were analyzed using UV spectrophotometry. In vitro diffusion study The drug release from niosomal gel was 78.9% at the end of 12 h in (Figure 2)

Tables and Figures
Composition of herbal extract noisome: Table 1.

Formulation code	Drug (mg)	Span 60	Span 80	Lecithin(mg)	Cholesterol (mg)	Alcohol (ml)	0.1% Glycerol solution(ml)
F1	100	1800	-	1800	200	2.5	1.6
F2	100	-	1800	1800	200	2.5	1.6
F3	100	1800	-	900	200	2.5	1.6
F4	100	1800	-	1800	200	2.5	1.6

Composition of carbapol gel: Table 2.

Sr.No.	Ingredients	Quantity(100gm)
1	Drug extract	1gm
2	Carbapol	2gm
3	Polyethylene glycol	9 ml
4	Triethanolamine	q.s
5	Distilled water	q.s

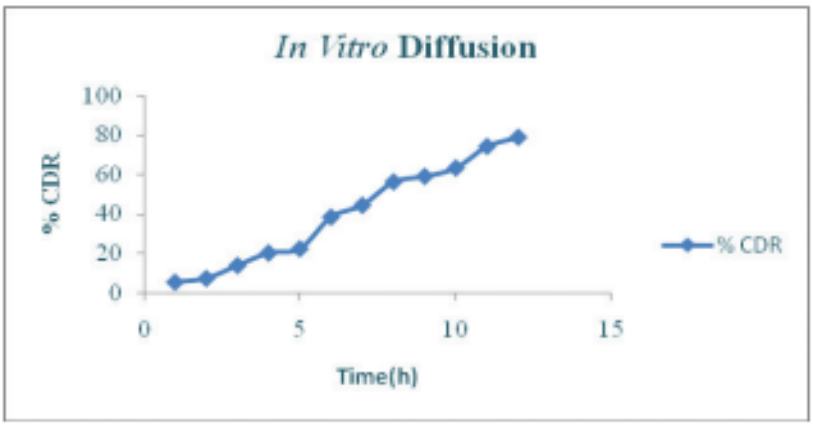
Drug Entrapment Efficiency: Table 3.

Sample code	Drug content	Entrapment efficiency
GF1	98.12 ± 0.20	68.52 ± 0.16
GF2	97.4 ± 0.39	72.59 ± 0.15
GF3	97.45 ± 0.42	69.57 ± 0.24
GF4	98.84 ± 0.34	64.59 ± 0.22

Physical evaluation of gel: Table 4.

Sample code	Drug extract gel	Plain gel
Spreadability	Good	Good
Washability	Washable	Washable
Homogeneity	Yes	Yes
Appearance	Clear	Transparent
Phase Seperation	No	No

(Figure 1): Microscopic view of Niosomal gel.



(figure 2): Invitro diffusion study niosomal gel.

RESULT AND DISCUSSION

Drug content

Drug content was determined for all the niosomal formulations. Average of three readings was considered. The drug content was found to be 98.12 ± 0.20, 97.4 ± 0.39, 97.45 ± 0.42 and 98.84 ± 0.34.The data are presented in Table 3.

Entrapment efficiency
Of all the niosomal formulations, span 80 showed to have higher entrapment efficiency compare to span 60. The data are presented in Table 3

Drug entrapment of the optimized formulation was determined at wavelength of 430 nm with the help of UV spectrophotometer. Entrapment efficiency was found to be 70% ± 3.99.

In vitro drug release study
Drug release of the niosomes was carried out in phosphate buffer pH 6.8 and was found to be 78% after 12 h. The in vitro release profile is depicted in Figure 2

Evaluation of Niosomal Gel
Physical evaluation: The observations are given in Table 4

pH of the gel The pH of the gel was found to be 6.4 which falls in range of the skin pH.

Drug content
The drug content of the niosomal gel was found to be 97.4 ± 0.39.

Spreadability
The spreadability of the formulation was found good.

Viscosity: Viscosity of the niosomal gel prepared using carbopol 934 was found to be 6170 cp.
In vitro diffusion study The drug release from niosomal gel was 78% at the end of 12 h in (Figure 2)

pH of the gel
The pH of the niosomal gel was observed to be 6.4 ± 0.159 which was found to be compatible with the pH of the skin.

CONCLUSION
We reviewed the literature documenting traditional plant use in the study area for dysmenorrheal. The film forming gel would help to increase the residence time as well as help in enhancing the permeation of the cramp bark extract. The film forming gel have good release properties and provide around the clock relief from menstrual cramp and reduce the frequency of dosing and improve patient compliance.

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