Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env.Pharmacol. Life Sci., Vol11 [4] March 2022 : 18-29
©2022 Academy for Environment and Life Sciences, India
Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD

ORIGINAL ARTICLE **OPEN ACCESS**

Design, Development and Evaluation of Honey Loaded Microsponges

Khadkutkar Vijayananda K.[1], Vijayendra Swamy S. M.[1], Wanje Vaijanti V.[1], Nagoba Shivappa N[1].*
[1]Channabasweshwar Pharmacy College, Latur, Maharashtra, India.
Email: vijayendraswamy@yahoo.com
*Corresponding Author

ABSTRACT

Microsponges are polymeric delivery systems composed of porous microspheres. They are tiny sponge-like spherical particles with a large porous surface. Moreover, they may enhance stability, reduce side effects and modify drug release favourably. Microsponges are porous, polymeric microspheres that are used mostly for topical use and have recently been used for oral administration. Microsponges are designed to deliver a pharmaceutical active ingredient efficiently at the minimum dose and also to enhance stability, reduce side effects, and modify drug release. Microsponges gel may increase the solubility, permeability and efficacy of poorly soluble drugs. Emulsion solvent diffusion method was adopted for preparation of Microsponges which provides ease of formulation. Preparation of honey loaded microsponges was prepared by using different formulations, from which F9 formulation was optimized. In vitro permeation of Manuka honey was studying by using dialysis membrane, through which Manuka honey is release in controlled and sustain manner. Formulation variables namely concentration of EC and PVA significantly affect the rate and extent of permeation of Manuka honey from Microsponge gel. Honey loaded Microsponges drug delivery is safe and effective delivery for ocular delivery of poorly soluble and poorly permeable drug to treat bacterial corneal ulcer.

Keywords: *Drug delivery, microsponges. PVA, bacterial corneal ulcer.*

Received 12.02.2022 Revised 13.03.2022 Accepted 22.03.2022

INTRODUCTION

The Microsponge Delivery System (MDS) is a porous, polymeric microspheres system used for prolonged administration. They are tiny sponge like spherical particles that made of number of interconnecting spaces between a non-collapsible structure with a large porous surface through which active ingredient are released in a controlled manner. The outer surface is porous, allowing a sustained flow of substance out of the sphere [1]. Microsponges show acceptable stability over pH ranging from 1 to 11 and at high temperatures i.e up to 130°C. The microsponge technology was developed by Won in 1987 and the original patents were assigned to advanced polymer system. The size of microsponge ranges from 5-300 µm in diameter and a typical 25 sphere can have up to 25000 pores and an internal pore structure [2-4].
The microsponges are having capacity to entrap wide range of pharmaceutical active ingredients such as fragrances, essential oils, sunscreens, emollients and anti-infective which serve to be a topical drug delivery system. Finally the use of the porous microsponges with addition to active ingredients can be formulated into various dosage forms such as creams, lotions and powders.[2] Microsponges are prepared by several methods as emulsion systems and liquid-liquid suspension polymerization methods. Emulsion systems include water in oil in water (w/o/w) emulsion solvent diffusion, oil in oil emulsion solvent diffusion and quasi emulsion solvent diffusion (ESD) method. Quasi emulsion solvent diffusion (ESD) method is the most common emulsion system used with microsponges preparation [3, 5].
Microsponge delivery systems are used to enhance the safety, effectiveness and aesthetic quality of topical prescription, over-the-counter and personal care products. It offers the formulator a range of alternatives to develop drug and cosmetic products. Microsponges are designed to deliver a pharmaceutical active ingredient efficiently at the minimum dose and also to enhance stability, reduce side effects and modify drug release [6-10]. The aim of present investigation was to design, development and evaluation of honey loaded microsponge gel for treatment of bacterial corneal ulcer

MATERIAL AND METHODS

DRUG AND EXCIPIENTS PROFILE [11]:

A) Drug profile:

Manuka Honey(Methylglyoxal)

Chemical name: 2-oxopropanal

Structural formula of Methylglyoxal :

Chemical formula :$C_3H_4O_2$

Molecular mass :72.06g/mole

Family : Myritaceae

Melting Point: <25 c

Category: Antibacterial

Therapeutic use: Bacterial infection, treatment for Bacterial corneal ulcer

Bioavailability: Orally 37-97%

PH:3.2-4.5

Chemical constituents: Methylglyoxal, dihydroxyacetone

Description: Colour-pale yellow liquid

Odour-pleasant

Taste-sweet and faintly acrid

Solubility: Soluble in water, insoluble in Alcohol

Dosage: Apply a sufficient amount to the affected areas once daily for 2 weeks

B) Excipients profile:32, 34,35

1. ETHYLCELLULOSE (EC)

Chemical name: Ethyl cellulose, Aquacoat, Ethocel, Surelease.

Molecular formula: $C_20H_{38}O_{11}$

Structural formula:

Molecular weight:454.513g\mol

Description:

Ethyl cellulose is a tasteless, slightly hygroscopic, free-flowing, and white to light tancoloured powder.

Melting point: 151ºC

Solubility: Ethyl cellulose is practically insoluble in glycerine, propylene glycol, and water. Ethyl cellulose that contains less than 46.5% of ethoxyl groups is freely soluble in chloroform, methyl acetate, and tetrahydrofuran, and in mixtures of aromatic hydrocarbons with ethanol (95%). Ethyl cellulose that contains not less than 46.5% of ethoxyl groups is freely soluble in chloroform, ethanol (95%), ethyl acetate, methanol, and toluene.

METHODS:

PREFORMULATION [12]

Preformulation is defined as the branch of pharmaceutical science that utilizes biopharmaceutical principles in the determination of physicochemical properties of the drug substance. It refers to the study of physico-chemical properties of drugs- whether single or combined, in order to develop a safe and efficacious medicine for use. It is the first step in the rational development of dosage forms of a drug substance.

Physicochemical characterization:

i. **Organoleptic properties:** This includes the physical characteristics that can be examined merely by sense organs such as colour, odour, taste and touch.

ii. **Purity:** This is another important aspect for preformulation studies. For every compound, depending on its dose and toxicity, the limit of impurity is defined. Until and unless the purity of the drug is assured other studies like stability, degradation and toxicity cannot be performed. Various parameters which are considered to find the purity of the drug substance are pesticide residue, TLC, HPLC, UV absorption, IR spectra.
The purity of Manuka honey is determined by Thumb test, water test.

iii. **Solubility**: The solubility of drug is an important physicochemical property because it affects the bioavailability of the drug, the rate of drug release into the dissolution medium, and consequently, the therapeutic efficacy of the pharmaceutical product.
Soluble in water, insoluble in Alcohol.

iv. **Stability**: Honey stored in sealed containers can remain stable for decades and even centuries. However, honey is susceptible to physical and chemical changes during storage. Processed honey should be stored between 64–75 °F (18–24 °C).1 Honey can be exposed to higher temperatures for brief periods.

v. **Fourier Transform Infrared Spectroscopy (FT-IR) [13]:**

The pure sample of manuka honey was filled in the sample holder and placed in the FTIR spectrophotometer. Samples were scanned over a wave number range of 4000 to 400 cm-1. The spectral analysis was done, by comparing test sample spectra with the standard spectra of Manuka honey and also by comparing the absorbance peaks with standard absorbance of the functional groups**.** The spectral range used by this technology is from 2,500 to 25,000 nm (4,000 to 400 cm-1). Attenuated total reflectance (ATR) is a technique used in conjunction with IR spectroscopy whereby solid and liquid samples can be analysed directly without any preparation.

Analytical method development and validation:

A. UV-Visible Spectrophotometric method [14]:

Preparation of stock solution (100 µg/ml):

An accurately weighed 0.1 g of Manuka honey was added to 100 ml volumetric flask. 10 ml of Ethanol or PBS (pH 7.4) was added into volumetric flask with shaking for about 2 min. The volume was adjusted up to the mark with respective solvent to obtain solutions of concentration 1000 µg/ml. Aliquot (1 ml) from above solution diluted to 10 ml to obtain standard solution of concentration 100 µg/ml.

Preparation of working standards for calibration:

Appropriate aliquots from the stock solution (100 µg/ml) were transferred to 10 ml volumetric flasks. The aliquots stock solution was diluted up to the mark with respective solution to obtain the concentration range of 1 - 12 µg/ml.

Preparation of Quality Control (QC) samples:

The stock solution (100 µg/mL) was prepared by dissolving 10 mg of the drug in ethanol or PBS (7.4) in a 100 mL volumetric flask. From the stock solution, solutions containing 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20 µg/mL of the drugs were prepared by appropriate dilutions.

Determination of λmax:

To determine the ʎmax of Manuka honey, a solution of strength 100 µg/ml was prepared in Ethanol and PBS(7.4). The absorbance were scanned over a wavelength range of 200-400nm on UV-ViS Spectrophotometer. The ʎmax of Manuka honey was found to be 266 nm in Ethanol and PBS.

B. Drug-excipients compatibility studies:

Drug-excipients compatibility studies were carried out for one month. The drug with excipients ethyl cellulose, PVA in the ratio of 1:1 were subjected to storage at room temperature and elevated temperature at 45°C/ 75% RH in stability chamber for one month. After 7, 14, 21 and 30 days the samples were taken to check the following parameter.

Physical change: The samples were checked for physical changes such as discoloration, odor etc.

C. Drug-excipients compatibility studies:

Compatibility study was carried out using different samples i.e. Manuka honey, excipients and 1:1 physical mixture of Manuka honey with excipients and their combination.

D. Infra-red spectra (IR):

Three month compatibility study was done on physical mixture at 8°C, R.T. and 40°C/75% RH. IR spectra of physical mixture of Manuka honey and excipients were recorded to study the interaction of drug and polymer after every month. FTIR spectrum of that resultant product was taken and compared with the spectrum of Manuka honey.

FORMULATION DEVELOPMENT:

Formulation of Microsponges [15]:

The Microsponges were prepared by using Quasi emulsion solvent diffusion method. In this method appropriate quantity of Ethyl cellulose (EC) was dissolved in 20 ml of Dichloromethane (DCM) and Manuka honey was added and stirred using magnetic stirrer todissolve. This was considered as organic internal phase. Then internal phase was added drop by drop with the help of syringe using 100 ml to aqueous external phase which contained appropriate quantity of PVA in 100 ml Distilled water and stirred for 3 hrs using magnetic stirrer at 1000 rpm. The resultant dispersion was filtered and desiccated for 24 hrs at 40^0-50^0c. Then the dried microsponges were stored in vacuum dessicator to remove the residual solvent.

Screening of levels of excipients:

The concentrations of EC and PVA varying from 1-2 g and 1-2 g were screened so as to obtain highest entrapment efficiency (EE) and % yield at minimum possible concentration. Lowest possible concentration of EC with PVA that exhibited optimum EE and % Yield was selected for further studies.

Design of experiment:

A 3^2 full factorial design was employed in the present study. In this design 2 factors were evaluated, each at 3 levels and experimental trials was performed for all 9 possible combinations.

The concentration of EC (X1) and concentration of PVA (X2) were chosen as independent variables in 3^2 full factorial design, while Particle Size (Y1), % Drug entrapment (Y2), Time

 ©2022 AELS, INDIA

Development of Microsponges gel [18]

Gel forming polymer i.e. carbopol soaked in water for 2 hrs and dispersed by agitation approximately 600 rpm with the aid of magnetic stirrer to get smooth dispersion. The stirring was stopped and dispersion was allowed to stand for 15min to expel entrained air. To this aqueous solution Triethanolamine (2%w/v) was added with agitation. At this stage, microsponges and permeation enhancer i.e. PG incorporated into the prepare base as ethanolic solution.

Table no 1-Formulation table of Microsponges gel

Ingredient	G1	G2	G3
Microsponges (F9)	100mg	100mg	100mg
Carbopol 934	0.5gm	1gm	1.5gm
Triethanolamine	2ml	2ml	2ml
Propylene glycol	10ml	10ml	10ml
Distilled water	q.s (100ml)	q.s (100ml)	q.s (100ml)

EVALUATION OF MICROSPONGES:

Determination of Production Yield and Loading Efficiency [16]:

The production yield of the microparticles was determined by calculating accurately the initial weight of the raw materials and the last weight of the microsponge obtained. The loading efficiency (%) of the microsponges can be calculated according to the following equation:

$$\textbf{Drug loaded} = \frac{\textbf{weight of the drug in microsponges}}{\textbf{weight of the microsponges}} \times \mathbf{100}$$

$$\textbf{Production yeild} = \frac{\textbf{weight of microsponges}}{\textbf{total weight of polymer} + \textbf{drug added}} \times \mathbf{100}$$

Assay:

Honey loaded microsponges (10 mg equivalent) was diluted to 100 ml with PBS (pH 7.4). Aliquot (1 ml) from above solution was further diluted up to 10 ml (10 µg/ml), which was analysed using validated UV-Vis Spectrophotometric method.

Particle Size Analysis:

Particle size analysis of prepared microsponges was carried by using Malvern Particle Size Analyzer Hydro 2000 MU (A). Microsponges were dispersed in double distilled water before running sample in the instrument, to ensure that the light scattering signal, as indicated by particles count per second, was within instrument's sensitivity range.

In vitro permeation:[16]

In vitro permeation was carried out on jacketed vertical glass Franz diffusion cells (with the 15 ml of acceptor compartment volume) using dialysis membrane (mol. wt. 12000-14000) with effective surface area 3.14 cm2. The mounting of the membrane was done by placing circular rubber above the permeation barrier and in between the acceptor and donor compartment and supported with clips at the brim of the compartments to avoid leakage of the test sample. The temperature of the acceptor compartment containing PBS was controlled at 37 ± 1°C under continuous stirring with teflon coated magnetic bar at constant rate, in such a way that the dialysis membrane surface just flushes the PBS. Membrane was allowed to stabilize in both the compartment for 15 minutes with continuous stirring on magnetic stirrer. After 15 min stabilization, microsponges were added in donor compartment. Aliquots (0.5 ml) were withdrawn at predetermined time interval from sampling port of acceptor compartment and replaced with the fresh PBS. Studies were carried out for 24 hr (every hr till 12 hrs then at 24 hrs directly). The aliquots were diluted suitably and analysed using validated UV method and concentration of Manuka honey permeated was determined.

Scanning Electron Microscopy [17]

For morphology and surface topography, prepared microsponges were coated with platinum at room temperature so that the surface morphology of the microsponges could be studied by SEM. The SEM, a member of the same family of imaging is the most widely used of all electron beam tools. The SEM employs a focused beam of electrons, with energies typically in the range from a few hundred eV to about 30 keV, which is rastered across the surface of a sample in a rectangular scan pattern. Signals emitted under this electron irradiation are collected, amplified, and then used to modulate the brightness of a suitable display device which is being scanned in synchronism with probe beam.

***IN-VITRO* RELEASE STUDY OF MICROSPONGES [19]**

Accurately weighed honey loaded microsponges (5 mg) were placed in 50 ml of ethanol in 100 ml glass

bottles. The later were horizontally shaken at 37°C at predetermined time intervals. Aliquot samples were withdrawn (replaced with fresh medium) and analysed UV spectrophotometrically at 266 nm for manuka honey. The contents of drugs were calculated at different time intervals up to 6hrs.

Stability Profile of Microsponge Formulation

The purpose of stability testing is to provide evidence on how the quality of an active substance or pharmaceutical product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light.

Optimized formulation was subjected to stability as per ICH guidelines at the following conditions (ICH, 2003).

Samples were kept in stability chamber at following conditions for 3 months

1. 40± 2°C and 75 ± 5% RH (Accelerated temperature)
2. Room temperature Formulations were analysed at 1, 2 and 3 months.

EVALUATION OF MICROSPONGE GEL:

General appearance:

Microsponge gel was evaluated for organoleptic properties such as color, consistency, homogeneity, extrudability and presence of any foreign particles.

pH:

The pH of the various gel formulations was determined by using digital pH meter. 1% aqueous solution of gels was used for measuring the pH.

Spreadability:

It was determined by wooden block and glass slide apparatus. Weight of about 50g of honey loaded microsponge gel was added to the pan and the time (seconds) was noted for upper slide (movable) to separate completely from the fixed slide. Spreadability was then calculated by using the formula:

$S = M.L / T$

Where, S = Spreadability;

M = Weight tied to upper slide;

L = Length of glass slide;

T = Time taken to separate the slide completely from each other.

Measurement of Gel Strength:

A sample of 50 gm of honey loaded microsponges gel was placed in a 100 ml graduated cylinder and gelled in a thermostat at 370 C. The apparatus for measuring gel strength was allowed to penetrate in gel. The gel strength, which means the viscosity of the gels at physiological stimuli was determined by the time (seconds), the apparatus took to sink 5cm down through the prepared gel.

***In vitro* diffusion study:**

In vitro studies of the gel were carried out by using honey loaded microsponges gel. The receptor compartments were filled with phosphate buffered saline (PBS) pH 7.4.Franz diffusion cell with 30 ml receptor compartment and effective area 4.52 cm^2 was placed on a thermostatic magnetic stirrer and the temperature was maintained at 37°C throughout the study. Selected batches of drug microsponge gel (G1,G2,G3.) were used for the diffusion study using diffusion cell. Aliquots, each of 1 ml volume were withdrawn at specific intervals and replaced by an equal volume of the receptor medium. The aliquots were suitably diluted with the receptor medium. Release studies were carried out over a period of 12 hr at regular intervals. Samples were withdrawn and analyzed by UV spectrophotometer at 266 nm.

Viscosity:

Viscosity of honey loaded microsponges gel was determined on Brookfield viscometer using RV (spindle no. 6) and T-type helipath spindle (spindle no. F) at room temperature and 5 rpm.

Stability:

Optimized formulation was subjected to stability as per ICH guidelines at the following conditions (ICH, 2003).

Samples were kept in stability chamber at following conditions for 3 months-

1. 40± 2°C and 75 ± 5% RH (Accelerated temperature)
2. Room temperature

Formulations were analyzed at 1, 2 and 3 months for following tests-

i) Visual appearance
ii) PH
iii) Consistency
iv) Spreadability
v) Assay
vi) *In vitro* permeation

RESULT AND DISCUSSION
PREFORMULATION:
Physicochemical characterization:
Description-

i. Colour-pale yellow liquid
ii. Odour-pleasant
iii. Taste-sweet and faintly acrid

Solubility- solubilityof Manuka honey is Soluble in water, insoluble in alcohol.

FTIR spectrum interpretation:

The peaks were observed in FTIR spectra of Manuka honey (Fig.10) at wave numbers 3248.03, 2936.26, 1643.58,1421.21,1372.56,1332.50,1248.71,1208.67,1152.17,1105.18,1046.41,1023.56,1011.32,914.79,850.90,817.24,769.91,559.05,511.39 cm-1. In this FTIR spectra of Manuka honey, characteristic peak at wave number 1046.41cm-1 indicates presence of si-o-sitetrahydral, 559.05 cm-1 indicates presence of alkyl halides, 2936.26 cm-1 indicates C-H stretch, sharp peak at 1332.50 and 1372.56 cm-1 indicates C-O , peak at 1208.67 indicates C- O stretch of alkyl amine and 1421.21 cm-1 indicates Carbonate group. Occurrence of only expected peaks for functional group at their respective wave number assured the purity of Manuka honey.

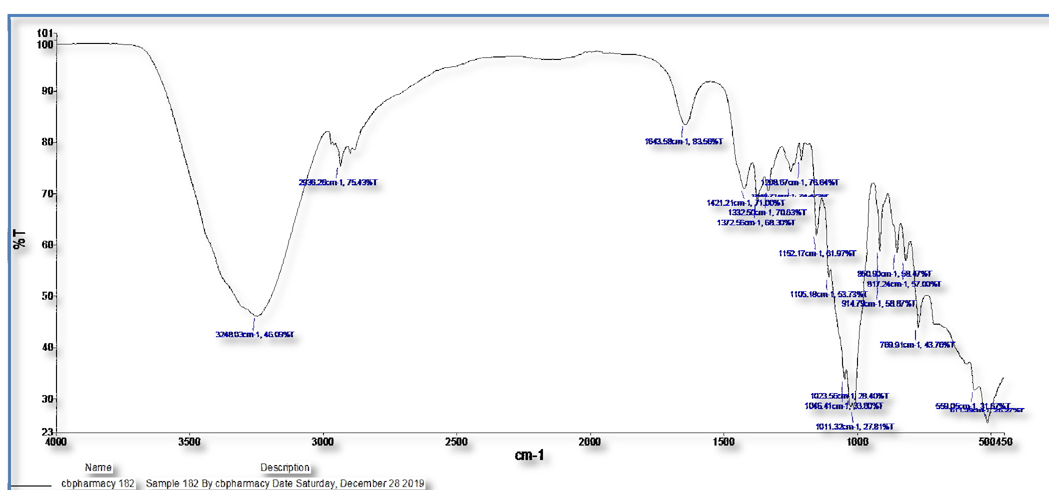

Fig 2. FTIR spectra of Manuka honey

Analytical method development:

The development of analytical method is most important part of Preformulation study of drug. It helps in analysis of drug in the sample obtained from dissolution, permeation and assay.

UV-VIS Spectrophotometric method:

Selection of solvent:

PBS (pH 7.4) were selected as solvents for development of UV-VIS Spectrophotometric method.

Selection of analytical wavelength (λmax):

UV-Vis spectra of Manuka honey showed maximum absorbance at 266 nm in PBS (pH 7.4), therefore this wavelengths was considered as λmax for Manuka honey.

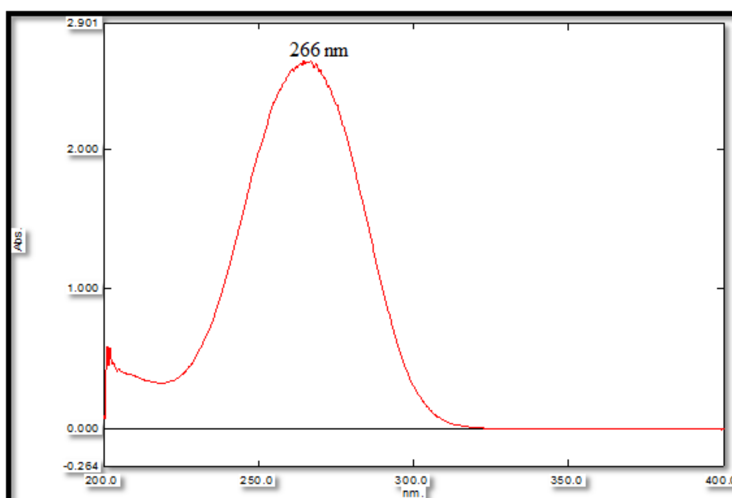

Fig-3. UV-Vis spectra of Manuka honey in PBS (pH 7.4)

Drug-excipients compatibility:

FTIR:

As per ICH guidelines, compatibility study was carried out with different excipients and the samples were analysed using FTIR spectrophotometer. After three month, FTIR spectra of each excipient were compared with the FTIR spectra of pure Manuka honey. All peaks for the functional group of Manuka honey were observed similar as pure Manuka honey spectra, which indicate the compatibility of Manuka honey with the excipients.

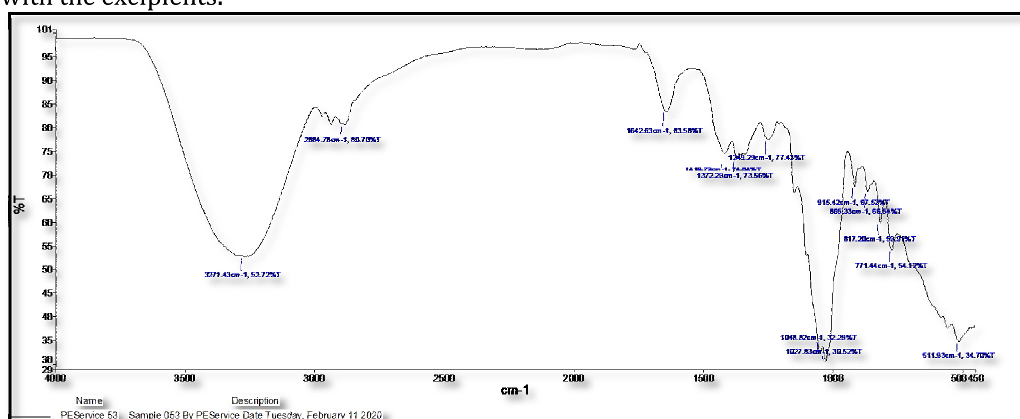

Fig 4. FTIR spectra of Manuka honey + ethyl cellulose

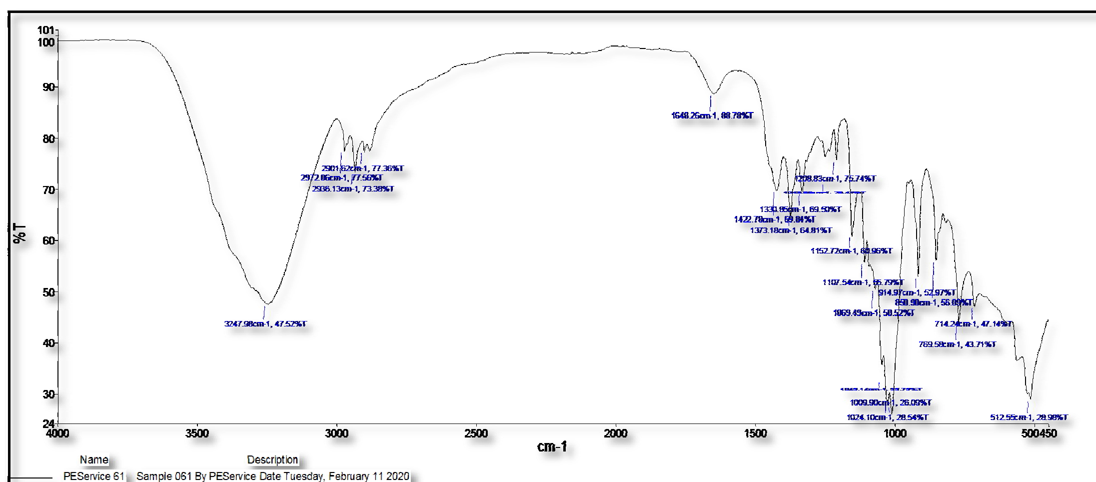

Fig 5. FTIR spectra of Manuka honey + propylene glycol

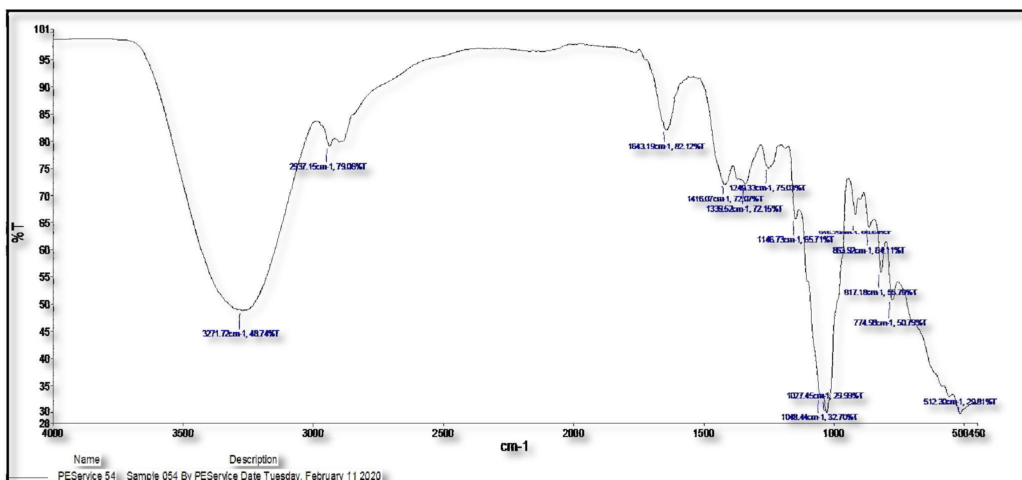

Fig 6. FTIR spectra of Manuka honey + polyvinyl alcohol

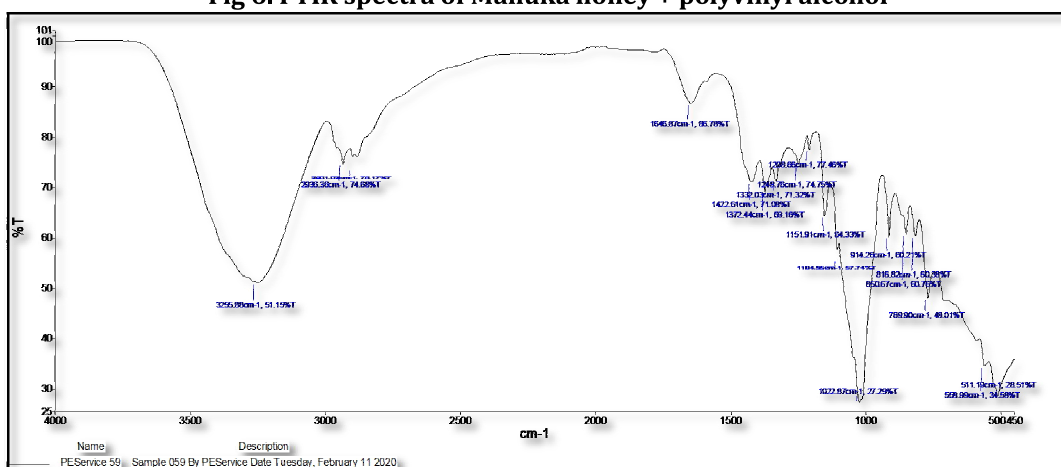

Fig 7.FTIR spectra of Manuka honey + Triethanolamin

Absorbance of Manuka Honey in PBS (pH 7.4):

The calibration curve was found to be linear in the concentration range 1-10μg/ml with R2 = 0.998.

Table.2-Absorbance of Manuka Honey in PBS (pH 7.4):

SR.NO	CONC(μg/ml)	ABSORBANCE
1	1(μg/ml)	0.521
2	2(μg/ml)	0.535
3	4(μg/ml)	0.621
4	6(μg/ml)	0.775
5	8(μg/ml)	0.871
6	10(μg/ml)	0.981

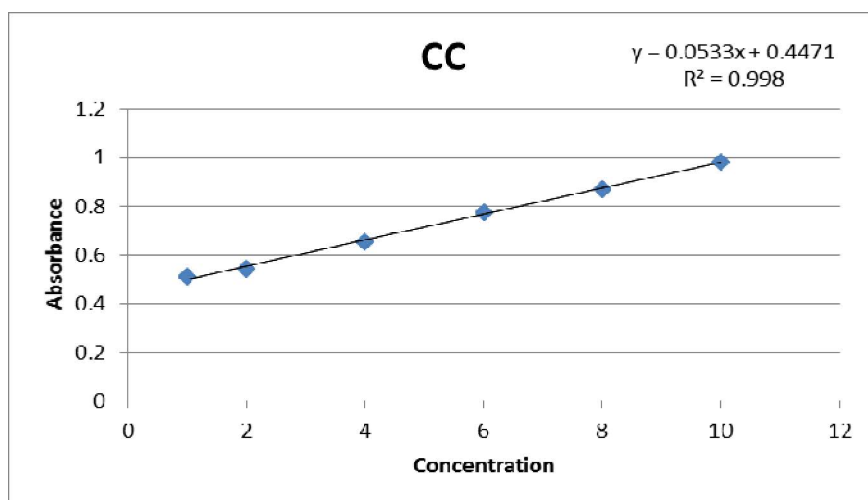

Fig 8. Calibration curve of Manuka honey in PBS 7.4

FORMULATION DEVELOPMENT:

Screening of levels of excipients:

On trial and error basis, different batches (A-J) of microsponges formulations were prepared by varying concentration of EC and PVA as reported in Table no.3. EC and PVA were selected as organic and aqueous phase polymer respectively because of their high compatibility, non-toxicity, ability to form microsponges by emulsion solvent diffusion. The concentration of EC and PVA selected for study was above the concentration which is required to diffuse from solvent, so as to form microsponges. DCM was used organic solvent.

All batches were evaluated for entrapment efficiency and % yield. Batch D, E, I and J showed the good EE and % Yield. As batch E showed the optimum EE and % yield at lowest possible concentration i.e.400 %w/v EC and 200 %w/w PVA, it was selected for further design of experiment.

Table no. 3.Screening of levels of excipients

Ingredients	A	B	C	D	E	F	G	H	I	J
MANUKA HONEY	100	100	100	100	100	100	100	100	100	100
EC	50	100	200	300	400	50	100	200	300	400
PVA	200	200	200	200	200	300	300	300	300	300
DCM	20	20	20	20	20	20	20	20	20	20
Dist. Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
EE(%)	39.4	52.9	74.4	**86.6**	**94.2**	43.7	48.9	73.4	**87.4**	**90.3**
Yield (%w/w)	56.7	68.5	76.4	**80.7**	**85.3**	59.4	67.7	78.9	**81.6**	**89.7**

Formulations (Qty. in %w/w)

CHARACTERIZATION

Evaluation of Microsponges:

Percentage yield: All batches (F1-F9) were exhibit the percentage yield from 79% to 90% (Table no.4). F6 to F9 batches showed more than 85% yield which shows optimum utilization of polymers.

Table.no.4. Entrapment efficiency, percent yield and drug content.

Batch(%)	Enteraptment efficiency(%)	Yield(%)	M.honey assay
F1	73.45	81.48	99.23
F	277.21	71.15	99.09
F3	79.59	83.67	99.63
F4	84.77	79.86	95.05
F5	88.28	83.34	98.23
F6	86.78	85.82	98.42
F7	91.87	89.22	98.78
F8	91.87	89.22	98.78
F9	93.43	90.10	97.35

 ©2022 AELS, INDIA

Percentage encapsulation efficiency and dug loading:
EE for all batches (F1-F9) were found to be 73% to 93% (Table 4). F7 to F9 batches showed more than 90% EE which shows optimum encapsulation and drug loading into microsponges.
Assay: The assay (%) for all the prepared microsponges formulations was analysed by validated UV method. The assay was found to be in the range of 95.85 to 100.23 % of the labeled claim (Table no.4). The assay values are well within the acceptable limits (95-105 %) of labeled claims.
FTIR:
An FTIR spectrum of honey loaded microsponges was carried out by using FTIR spectrophotometer, which is compared with FTIR spectra of pure Manuka honey. Peaks for the functional group of Manuka honey were observed similar as pure Manuka honey spectra, which indicate the compatibility of Manuka honey with the excipients as per following figures.

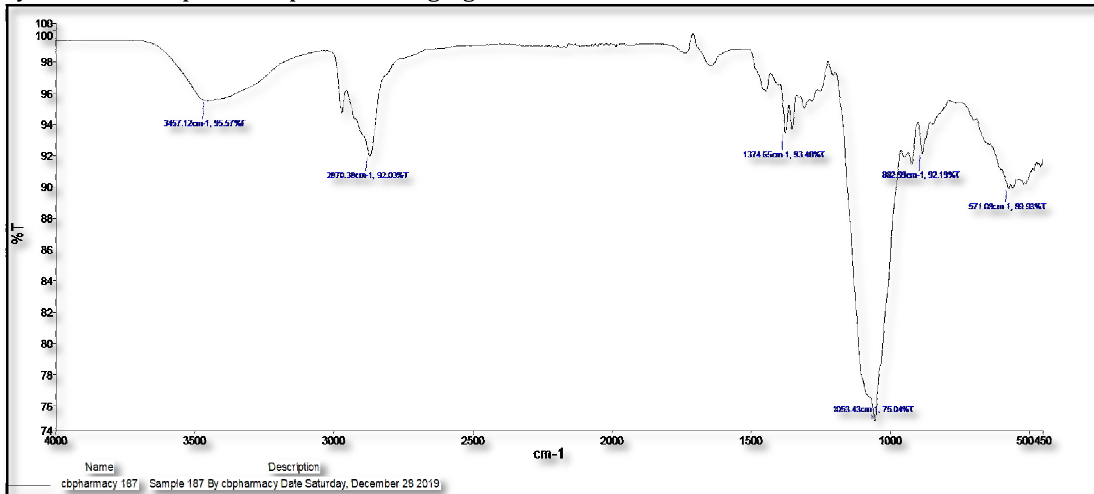

Fig.9. FTIR spectra of honey loaded microsponges

***IN VITRO* PERMEATION**
In vitro permeation was carried out using dialysis membrane upto 24th h. Cumulative amount of Manuka honey permeated was calculated (Table 5). In vitro permeation of all batches was found to be 69.1% to 90.5 %. Permeation was decrease, because increase particle size. Comparative Manuka honey permeation of all formulations and comparative average flux from in vitro permeation of all formulations.

Table.no.5: In vitro permeation of Manuka honey from different batches of microsponges

SR.NO	TIME	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2	1	3.7	3.5	2.1	3.5	4.1	3.8	3.9	3.0	4.1
3	2	7.9	8.5	8.0	9.3	8.9	10.5	10.1	4.5	10.5
4	3	13.3	14.1	13.1	12.9	12.1	13.7	12.1	9.8	13.7
5	4	15.7	16.2	17.0	19.4	14.5	18.1	14.3	12.1	15.8
6	5	18.5	19.4	19.2	21.5	16.8	21.5	11.6	14.6	17.5
7	6	21.9	25.7	22.5	23.6	20.2	25.6	13.1	15.6	19.1
8	7	25.6	28.5	29.5	30.7	24.6	30.4	25.3	26.9	30.2
9	8	29.5	31.7	33.7	34.8	29.9	34.7	30.1	34.2	35.5
10	9	31.7	35.9	36.6	37.7	32.4	36.1	32.3	36.4	38.4
11	10	35.3	39.8	38.9	42.3	36.2	40.3	36.5	41.5	43.6
12	11	41.8	43.8	45.4	45.8	41.5	42.5	38.7	45.8	48.3
13	12	47.5	49.3	48.3	49.8	46.2	47.1	44.6	49.9	52.6
14	24	80.5	81.7	79.5	82.6	75.9	73.1	78.5	80.2	89.5

EVALUATION OF HONEY LOADED MICROSPONGE GEL:
F9 batch was found to be optimized which is used further for preparation of gel from optimized microsponges and evaluated for following parameters.
Homogeneity or physical appearance:
All the prepared honey loaded microsponge gels was clear transparent without any aggregates, particles, and fibres and free from air entrapment.

pH:
pH values of all the formulation was found to be 6.9±0.019 to 7.3±0.050 (Table 6).This shows that pH values was within the physiological pH range of the eye which is quite important for topical formulations, since the increase in the pH value may cause irritation to eye.

Viscosity:
The viscosity depends upon the type of polymer grade and concentration of polymer used in the formulation. In general, viscosity increase with increasing polymeric ratio, conditions like 0.5%,1%,1.5%(Table no.6). Hence, in the prepared microosponge formulation 1%carbopol 934 was used because of its desired viscosity, spreadability and gel strength. The viscosity for the formulation was found to be 874±0.74%.

Spreadability:
Spreadability is an important factor to consider in formulation of gels. If the prepared gel is too viscous the spreadability is very low, if the prepared gel is of moderate –to low viscosity, the spreadability of the product is high (Table no 11). Thus viscosity and spreadability are inversely proportional to each other. The spreadability of the prepared honey loaded microsponge gel formulation was found to be 2.250±0.103cm (G2), therefore prepared formulation can be considered ideal for topical applications.

Gel strength:
Gel strength was determined by visually observing and measuring the time required for travel of 5 g weight upto 2 cm distance through gel. These observations were graded as +++ if time required is more than 4 h, ++ if time is 2.5-4 h and + if time is less than 2.5 h. + indicate low gel strength and the gel may get dissolved and cleared off faster from skin surface, ++ and +++ indicate good and very good respectively and will help to hold drug for prolonged period of time(Table no.6).The gel strength for the formulation was found to be ++ indicates good gel strength which will help desired drug release and may get easily cleared off from skin when required

Table no. 6.Evaluation of honey loaded microsponges gel

Formulation code	pH	Viscosity	Spreadability (cm)	Gel strength*
G1	7.31	98.04%	8.15±0.81	2.219±0.017 +
G2	7.42	99.23%	874±0.74	2.250±0.103 ++
G3	7.49	99.76%	923±0.94	2.135±0.026 ++

*+++ if time required is more than 4 h, ++ if time is 2.5-4 h and + if time is less than2.5 h.

CONCLUSION

Quasi emulsion solvent diffusion method used conventionally to prepare honey loaded microsponges were observed to be compatible with ethyl cellulose. Therefore, in the present study honey loaded microsponges were prepared by simple, reproducible and rapid quasi-emulsion solvent diffusion method. The formulation was characterized by FTIR, In vitro permeation studies.

Stability studies revealed no significant changes in visual appearance, assay and permeability of Manuka honey microspongegel in comparison to initial characteristics. This indicated that the formulation was stable at accelerated stability test condition.

REFERENCES

1. Hans Mansi, Dua Jagdeep Singh, Prasad D.N, Sharma Diksha, Monika, (2019). A Review on Microsponge Delivery System, Journal of Drug Delivery & Therapeutics. 9(3-s):1032-1040.
2. Avinash Darekar1*, Pooja Pawar1, Ravindranath B, (2019). A Review on Microsponge as Emerging Drug Delivery System, Journal of Drug Delivery & Therapeutics. 9(3-s):793-801.
3. Avhad Pawan S.* and Patil Prashant B, (2018). New era in topical formulations – microsponge drug delivery system. International Journal of Pharmaceutical Sciences And Research, 9(1):89-96
4. Parikh B.N., Gothi G.D., Patel T.D., Chavda H.V., and Patel C.N, (2010). Microsponge as novel topical drug delivery system. Journal of Global Pharma Technology, 2(1):17-29
5. Garish Joshi, Rajandeep Kaur, Harpreet Kaur, (2016). Microsponges: A Novel Drug Delivery System .International Research Journal of Pharmaceutical and Biosciences, 3(1):1-11
6. Ayan Kumar Kar, Banhishikha Kar, Hiranmoy Parya, Snehashis Kundu, Rishabh Hirawat, (2018). A Novel Approach on Microsponge : Multifunctional Modern Dosage Form. Int. J. Pharm. Sci. Rev. Res., 51(2), Pages: 64-72
7. Pradhan S. K., (2011). Microsponges as the Versatile Tool for Drug Delivery System, Int J Res Pharm Chem., 1(2): 243-258
8. D'souza J. I., More H. N., (2008). The Microsponge Drug Delivery System: for Delivering an Active Ingredient by Controlled Time Release; Pharmainfo net., 6 (3): 62.
9. Santanu Kaity, Sabyasachi Maiti, Ashoke Kumar Ghosh, Dilipkumar Pal, Animesh Ghosh, Subham Banerjee, (2010). Microsponges: A novel strategy for drug delivery system, J Adv Pharm Technol Res Jul;1(3):283-90. doi: 10.4103/0110-5558.72416. 10

10. Shaha V., Jain H., Krishna J., Patel P., (2010). Microsponge Drug Delivery: A Review, Int J Res & Pharm Sci., 1(2): 212-218.
11. Patidar K., Soni M., Saxena C., Sharma D. K., Soni P. (2010). Microsponge Versatile Vesicular Approach for Transdermal Drug Delivery System, J Global Pharm Tech., 2(3): 154-164.
12. Parida R., Kumar S., Nabin K., Satish V., (2010). Overview of Spherical Crystallisation in Pharmaceuticals, Int J Pharm Biol Sci., 1(3).09-12
13. Ramaiyan Dhanapal and J. Vijaya Ratna, (2012). Ocular drug delivery system – a review. International Journal of Innovative Drug Discovery: 2-1: 4-15
14. Kishore Cholkar, Supriya Reddy Dasari, Dhananjay Pal and Ashim K Mitra , (2009). Eye: anatomy, physiology and barriers to drug delivery Division of Pharmaceutical Sciences, School of Pharmacy, University of Missouri-Kansas City, Kansas City, MO, USA.
15. Julie Milano., Simone Goncalves Cardoso.,(2005). Spectrophotometric Determination of Oxiconazole in Topical Lotion Using Methyl Orange, J Pharm Biomed Anal., 37; 639-642.
16. Rajiv Kumar1*, Mithun Bhowmick1, Balkrishna Dubey., (2012). Polymeric Microsponge Technology – An Overviewon Highly Cross-linked Porous Spherical Particles for Topical Delivery., Inventi Rapid: NDDS Vol. 2012, Issue 2 :1-11.
17. F. Bongomin, S. Gago, R. O. Oladele, D. W. Denning., (2017). Global and Multi-National Prevalence of Fungal Diseases—Estimate Precision. Journal of fungi, 2017, vol. 3, P. 1-29.
18. R. C. Rowe, P. J. Sheskey et al. (1996). Methylene chloride (Environmental Health Criteria No. 164). 2nd ed. Geneva: International Programme on Chemical Safety, World Health Organization, Handbook of excipients fifth edition. 2006, P. 51-832.
19. Obert L Stamper MD, Michael V Drake MD,(2019). Aqueous humor formation, in Becker-Shaffer's Diagnosis and Therapy of the Glaucomas (Eighth Edition).

CITATION OF THIS ARTICLE

Khadkutkar Vijayananda K., Vijayendra Swamy S. M., Wanje Vaijanti V., Nagoba Shivappa N. Design, Development and Evaluation of Honey Loaded Microsponges.Bull. Env. Pharmacol. Life Sci., Vol11 [4] March 2022 :18-29.