Research Article

Formulation and Evaluation of Gel-Loaded Microsponges of Curcumin for Topical Drug Delivery

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ABSTRACT

The novel drug delivery system enables the introduction of a therapeutic substance in the body and increase its rate of release, safety, efficacy, release time and place of release of drug in the body. Curcumin which is active ingredient obtained from the powdered dry rhizomes of the plant Curcuma longa. Curcumin loaded microsponge were synthesised using Quasi emulsion techniques by using ethyl cellulose and PVA as carriers. The microsponge were characterized by Fourier transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM), UV Visible Spectroscopy, Photomicroscopy and antibacterial studies followed by determination of total drug content and entrapment efficiency. A minimum inhibitory concentration of curcumin microsponge was determined by using positive and negative bacterial strains and was compared to that of curcumin. The prepared microsponges then loaded into Carbopol gel and assessed for its pH, viscosity, solubility and spreadability to ensure its suitable for topical application. Moreover, the antimicrobial efficacy of the developed microsponge gel also assessed against the microorganism *Staphylococcus aureus* and *Escherichia coli*. The prepared Carbopol gel-loaded microsponges of curcumin were found to be promising as new-fangled delivery system offering enhanced stability and significant antimicrobial activity and, hence, would be more useful than conventional formulation therapy.

Keywords: Curcumin, Microsponges, Quasi-emulsion techniques.

INTRODUCTION

The new approaches for the drug delivery other than convention method is a Novel drug delivery system. It improves the drug release with increased prolonged effects and its potency.[1] The drug delivery system which defined as formulation or preparation or device that enables the introduction of a therapeutic agent in the body and which increases its safety and efficacy by controlling its time, the site were the drug released, and its release time[2].when we converted the existing drug molecule from its conventional dosage form to new novel delivery system it can significantly increases their performance, safety, efficacy and the patient compliance. The existing drug molecule get a new profile in the form of a novel drug delivery system. The novel drug delivery system can be used for solving the problems regarding the release of the drug at specific site with specific rate. [3] The novel dug delivery system using carriers, which maintain the concentration of drug in appropriate ranges for prolonged time [4]

The Phytosome, Liposomes, Niosomes, Microspheres, nanoparticles are the recent developments in novel drug delivery system. One of the latest, new technology is microsponge based drug delivery system (MDS) Which gives site specific and controlled release of active ingredients. The microsponges are highly porous and cross linked in nature and made up of a polymer. It will decrease the side effect, improves the stability, efficacy and safety when use for topical application. Also, the topical application can skip the first pass metabolism and improves its bioavailability. The polymers like Eudragyt RS 100, Eudragyt RSPO, Eudragyt S 100, Polylactic acid, Hydroxy propyl methyl cellulose, Ethylcellulose are some of examples for polymers used in the fabrications of microsponges. After the preparation of microsponges with polymer it can be incorporated into formulations like capsule, tablet, gel, ointment and powders etc.[5]

The naturally occurring Curcumin is a yellow-coloured compound obtained from the rhizomes of Curcuma longa belongs to the family Zingiberaceae. It is one of the polyphenol compounds. It is mainly used as anti-inflammatory agent, antimicrobial agent, antineoplastic agent, flavouring agent, natural pigment, lipoxygenase inhibitor, a contraceptive drug etc.it is a nontoxic compound even at higher doses.it has proven efficacy against number of conditions but the curcumin has poor bioavailability when topically applied, poor absorption, rapid metabolism, which limit the therapeutic efficacy of curcumin.[6]

The present study mainly focused with the objective to enhance the absorption properties, solubility and stability of the formulation. The Quasi emulsion solvent diffusion technique is used to prepare the curcumin containing microsponges using Ethylcellulose as a polymer. The FTIR, SEM, Photomicroscopy, Antibacterial activity test are used to characterize the microsponges. Finally, the prepared microsponge was incorporated into the Carbopol gel and the percentage entrapment efficiency, consistency, Washability, viscosity of the gel was determined.

MATERIALS AND METHODS

Collection of materials

The extracted curcumin was purchased from Kanton Laboratories, Kannur, India and Ethyl cellulose was purchased from Prowess Marketing CO. Pvt Ltd, Palakkad, Kerala. All other chemicals used were of analytical grade and purchased from Nice chemicals Pvt Ltd, Kochi, India.

PREFORMULATION STUDY

A specific dosage form is needed for to achieve therapeutic efficacy. Here, in this study the preformulation studies conducted are solubility analysis, physical characterization like colour, odour etc

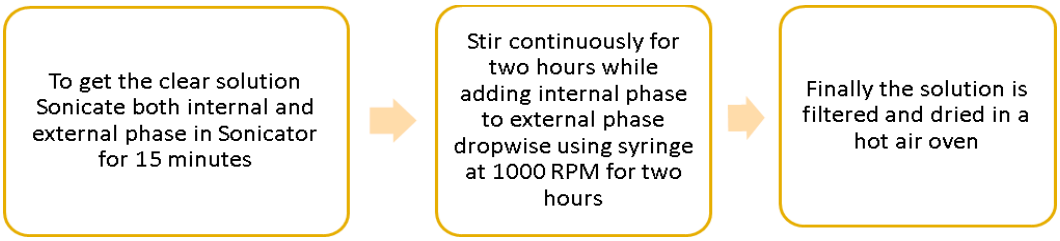
- **Organoleptic properties**

The curcumin pure drug subjected to characterization like colour, odour etc

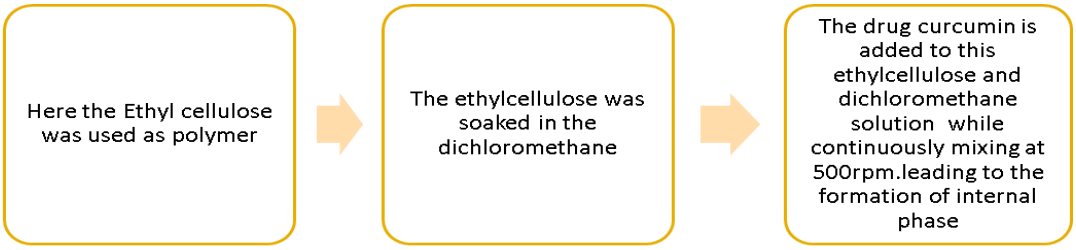
PREPARATION OF CURCUMIN LOADED ETHYLCELLULOSE MICROSPONGES

Here, **Quasi Emulsion Solvent Diffusion Technique** is used for the preparation of curcumin loaded microsponge preparation. Which contains two phases, the two phases are immiscible with each other. The internal and external phase which contains surfactant and reduces interfacial tension by using surfactant. The method which contain mainly 3 steps. In the first step inner phase was prepared and in second step outer phase was prepared.[7]

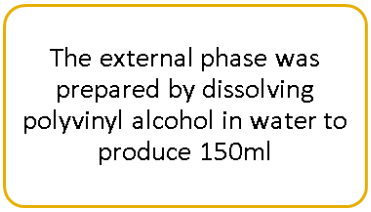
Step 1: Preparation of internal phase



Step 2: Preparation of external phase



Step 3: Preparation of microsponges



Materials and its quantity for the preparation of microsponges:

Table 1: Composition of curcumin microsponge

Formulations	Curcumin (mg)	Ethyl cellulose (mg)	PVA (mg)	Dichloromethane (ml)	Water (mg)
F1	200	100	300	25	150
F2	200	200	300	25	150
F3	200	400	300	25	150

EVALUATION OF CURCUMIN LOADED MICROSPONGES

Percentage Entrapment Efficiency

10mg of curcumin microsponge dissolved in 10ml of methanol with stirring to dissolve free drug and measure the absorbance at 428 nm, M will be the absorbance of total drug. Prepared curcumin microsponge solution were centrifuged at 12000 RPM for 1 hour. The supernatant was collected and Measure the absorbance of the supernatant solution obtained after centrifugation. The m will be the absorbance of free drug. The entrapment effiency calculated by using following formula[8]

$$\%\textit{Entrapment Efficiency} = \frac{\mathbf{M(Total\ drug)\ -\ m(Free\ drug)}}{\mathbf{M\ (\ Total\ drug)}}\ \boldsymbol{x\ 100}$$

Photomicroscopy

By using the optical microscope, the curcumin microsponges were observed. One drop of aqueous suspension was applied on the surface of the glass slide, and it was covered with a coverslip and observed it under a 40X magnification lens.[9]

Determination of particle size, shape, and surface morphology by scanning electron microscope (SEM)

To get the morphology of the microsponge and its surface, the microsponge formulations were visualised by scanning electron microscope (SEM).[10]

Fourier Transform Infrared Spectroscopy (FTIR)

To identify the chemical compounds and understand their molecular interaction the FTIR spectroscopy can be used. When applied to curcumin microsponges, FTIR can confirm the encapsulation of curcumin, characterization of its chemical structure, and assess any interaction between curcumin and the polymer ethyl cellulose.[11]

Evaluation of antibacterial activity

Well diffusion method:

Here we used Streak plate method to isolate the bacterial strain. The inoculating loop was sterilised by heating it in a flame until red hot, then allow it to cool. Dip the cooled, sterilized loop into the microbial sample. Gently streak the loop back and forth across a small section of the agar surface. The antimicrobial study was done by well diffusion method. Then by using borer make wells on the petri plate. Then add the curcumin microsponge and curcumin drug into the well. The pure drug curcumin is used to compare the antimicrobial activity of the curcumin microsponge. Incubate all the Petri dish for 24 hrs. Observed the Zone of inhibition, which is suggested by the clear area around the well. [12]

PREPARATION OF MICROSPONGE LOADED GEL

Table 2: Composition of microsponge loaded gel

Sl.no	Ingredients	Weight of ingredients
1	Curcumin microsponges	1g
2	Carbopol 940	0.35g
3	Triethanolamine	5 ml
4	Propylene glycol	15 ml
5	Ethanol	15 ml
6	Methyl paraben	0.5g
7.	Water	q.s 100ml

Preparation of gel containing curcumin loaded ethyl cellulose microsponges

Soaked the Carbopol 940 in water for 2 h and by agitation and it dispersed homogeneously 600 rpm using magnetic stirrer. Curcumin containing microsponges were then uniformly dispersed in Carbopol gel. To neutralize the pH Triethanolamine was added. To this add, propylene glycol and ethanol as permeation enhancers. Here Methyl paraben is used as preservative agent.[11]

EVALUATION OF GELS

Physical appearance

The prepared formulation was evaluated for their clarity, colour and smell

- **Visual inspection**

Observe the visual appearance of the curcumin microsponge gel. Note the transparency and presence of any particulate matter

- **Odour examination**

Open the container or remove the lid to expose the sample, and determine its odour by sniffing the sample. Note the aroma and intensity of the smell

- **Consistency examination**

Evaluate the consistency and texture of the microsponge gel, for this gently touch the gel with clean hand and note the feel, smoothness, grittiness and stickiness. Also assess its spreads on the skin easily

Determination of pH

The pH of the prepared gel was measured using pH meter (standardized using buffer, pH 7 before use) by putting the tip of the electrode into the gel and after 2 min the result was recorded. The measurement of pH of formulation was done in triplicate and the mean value was calculated.[12]

Determination of viscosity

Viscosity of microsponge gel was determined using Brookfield viscometer (LVDV-E Mode) using spindle No. 64 at different rpm at room temperature. It was carried out with 10 g of sample. The base level of instrument was set up using level indicator. The spindle used was cleaned and attached to the instrument. Then the spindle was rotated in the gel until a constant reading is displayed in the viscometer. The method was repeated in various RPM 20,30,50,60, 100.Finally viscosity of the gel formulation was calculated at various shear rates[13]

Spreadability testing

The spreadability of the curcumin loaded microsponge gel was measured by spreading of 0.5 g of the gel on a circle of 2 cm diameter premarked on a glass plate and then a second glass plate was employed. 50g of weight was permitted to rest on the upper glass plate for 5 min. The diameter of the circle after spreading of the gel was determined. [14]

Washability

Microsponges gel formulation was applied on the skin surface. Waited for some time and placed under tap water for 10min. After the specified time the skin is visually examined and ensured that any of product remained on the skin[15]

Antibacterial activity of drug loaded microsponge

Well diffusion method:

Muller-Hinton agar media was used here and we used Streak plate method to isolate the strain. sterilize the inoculating loop by heating it in a flame until red hot, then allow it to cool. Dip the cooled, sterilized loop into the microbial sample. Gently streak the loop back and forth across a small section of the agar surface. The antimicrobial study was done by well diffusion method. Then by using borer make wells on the petri plate. Then add the prepared microsponge gel into the well. Incubate all the Petri dish for 24 hrs. Zone of inhibition then observed, which is suggested by the clear area around the well.[11]

RESULTS AND DISCUSSION

PREFORMULATION STUDY

Organoleptic properties

Colour: Brilliant Yellow colour

Odour: Aromatic odour -Earthy, Mustard like aroma

Preparation of curcumin loaded ethylcellulose microsponges

Here we prepared 3 formulations of microsponge by altering the amount of polymer. The microsponge prepared by Quasi emulsion solvent diffusion technique.

Figure 1: Dried microsponge

EVALUATION OF CURCUMIN LOADED MICROSPONGES

- **% Entrapment efficiency**

EE in different formulations were estimated by UV spectrophotometric method. The total drug content and entrapment of the drug depend on the successful molecular association of the drug with the polymers. The value EE were found maximum for the formulation F3 having the drug to polymer ratio of 1:2.

F1	30.8%
F2	47.36%
F3	82.1%

Photomicroscopy

Figure 2 shows, the photomicroscopy images of the curcumin microsponges. In these images, the microsponges shows spherical image. By comparing the photomicroscopy image of three formulation (F1, F2, F3) the photomicroscopy image of formulation F3 Shows more porous and spherical shape. F3 satisfied the required microsponge characteristics and was taken for further studies

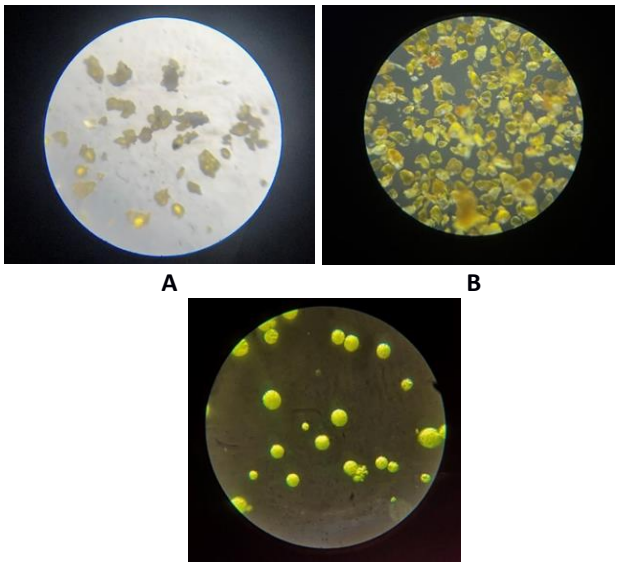


Figure 2: A) Formulation F1, B) Formulation F2, C) Formulation F3

Determination of particle size, shape, and surface morphology by scanning electron microscope

Figure 3, exhibits the SEM showing surface morphology of curcumin microsponge prepared by using Quasi emulsion technique's micrograph displayed that microsponges formed are predominantly spherical and porous in nature. In the SEM images of curcumin microsponges the curcumin crystals are not seen.

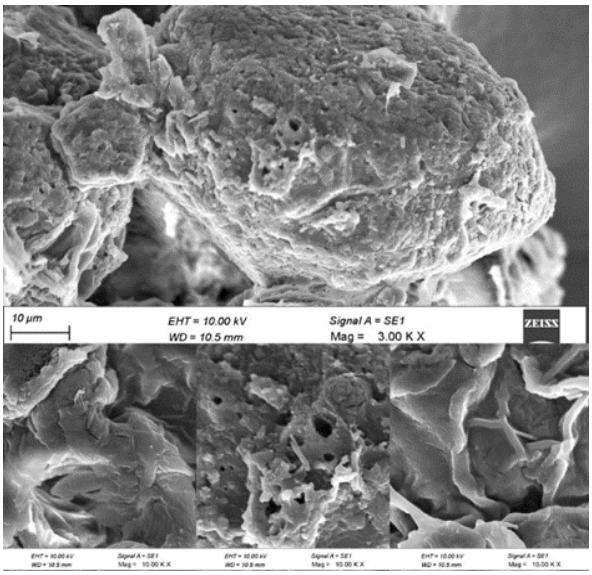


Figure 3: SEM image of Curcumin microsponge

FTIR spectra of Curcumin, Ethylcellulose and Curcumin Microsponge

Figure 4 exhibits the FTIR spectra of Curcumin, Ethylcellulose and Curcumin microsponge. Fig.18a, show the several absorption peaks in range of 2974–2872 cm^{-1} and 1300–800cm^{-1} represent the ethoxyl groups. In spectra of CUR, as shown in Fig. 18b, the characteristic transmittance bands were observed at 1596, 1541, 1076, cm^{-1} corresponding to stretching –C=C vibrations of benzene, aromatic –C–O stretching of (–OMe and –OH), and –C–O–C stretching (–OMe). Fur ther, characteristic bands for phenolic –OH and conjugated ketonic –C=O vibrations were observed at 3400 cm^{-1} while the spectra of CUR microsponges show broadening of band at around 3400 cm^{-1} and characteristic bands in the range 1597–800 cm^{-1}. However, comparison of the spectra demonstrated no new characteristic peaks in the microsponge which indicated no physical or chemical interactions between curcumin and carrier polymer.

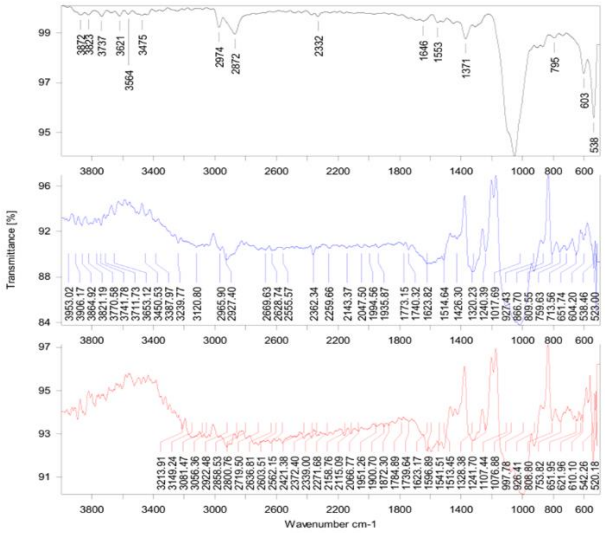


Figure 4: FTIR spectra of Ethylcellulose (a), Curcumin(b) and Curcumin Microsponge

EVALUATION OF ANTIBACTERIAL ACTIVITY

The invitro antimicrobial study was performed by measuring the diameter of zone of inhibition (mm) for the microsponge formulation. The zone of inhibition is the circular spot on the antibiotic in which the bacteria colonies do not grow. The zone of inhibition can be used to measure the susceptibility of the bacteria towards the antimicrobial agent.

Table 3: Antibacterial activity of curcumin v/s curcumin microsponges

Microorganism	Curcumin (A)	Curcumin Microsponge (B)
S.aureus	4mm	10.1mm
E.coli	2mm	5mm

The antimicrobial activity measured individually against *S.aureus* And *E.coli* by using curcumin pure drug (A) and curcumin microsponge (B) and the zone of inhibition was found.

It can be concluded that the curcumin microsponge possess antimicrobial activity more than curcumin pure drug

PREPARATION OF MICROSPONGE LOADED GEL

The Microsponge gel was successfully prepared by using Carbopol 940, Triethanolamine, Propylene Glycol, Ethanol, Water and Methylparaben

EVALUATION OF GELS

Physical appearance

The prepared formulation does not contain any particulate matters and shows good clarity

- **Visual Inspection**

The colour of the microsponge gel was visually inspected and was found to be yellow (corn yellow) in colour

- **Odour examination**

The microsponge gel has mild pleasant odour and enhanced the organoleptic characteristics

- **Consistency examination**

The prepared formulation was examined for its consistency and was found to be smooth homogeneous texture and mild glossy appearance.

Determination of pH

The pH of the prepared formulation was found to be 6.6 using digital pH meter, which were within the acceptable limit of topical application which is in the range of 4-7. It is very important that the topical formulations should be in neutral pH

Determination of viscosity

The viscosity measurements are done by using Brookfield viscometer model-LVDV-E and the report showed at an RPM of 20, the viscosity of the gel was found to be 21140 Cp, here we observed the pseudoplastic behaviour that is decrease in viscosity with increase in the RPM. Hence the viscosity of the gel was found to be optimum and can be used for topical application

Spreadability

The spreadability of the gel was considered high by having a low spread of time. The therapeutic efficacy of gels depends on their spread. The gel spreading helps in the uniform application of the gel to the skin, so the prepared gels must have a good spreadability and satisfy the ideal quality in topical application.[53]

Washability

The formulation was applied on the skin and extent of washing with water under tap water for 10 minutes. The formulation was exhibited good Washability and left no

traces of the gel on the skin which indicates that the formulation is easy to remove and hydrophilic in nature

Antibacterial activity of gel loaded curcumin microsponge

The in vitro antibacterial study was performed by measuring the diameter of zone of inhibition (mm) for the prepared microgel formulation.The antimicrobial activity measured individually against *S. aureus* And *E. coli* and the zone of inhibition was found to be 4mm and 3mm respectively[54]

Figure 5: Antimicrobial activity of microsponge gel by well diffusion method

CONCLUSION

The objective of developing polymeric microsponge delivery system was to deliver curcumin in a sustained manner for an extended period of time, to reduce frequency of administration and to improve its bioavailability. Therefore, in the present study curcumin microsponges were prepared by simple, reproducible and rapid quasi-emulsion solvent diffusion method.

The formulation was characterized by its entrapment efficiency, Photomicroscopy, FTIR, and antimicrobial studies. The prepared microsponges were then loaded in Carbopol gel. We prepared mainly three formulations by varying the drug polymer ratio. Varied drug–polymer ratio reflected a remarkable effect on particle size, encapsulation efficiency and the structure of microsponges. The F3 formulation possesses the maximum entrapment efficiency of 82.1%. The photomicroscopy images of curcumin microsponges also revealed that the F3 formulation gives more spherical and better microsponges with porous structure. We also analysed the microsponge v/s pure drug for its antimicrobial activity and the results showed that the microsponges have more antimicrobial activity than the pure drug. Finally, the F3 formulation was incorporated the Carbopol gel.

The Carbopol gel exhibited characteristic colour, pleasant odour, good consistency. The viscosity of the gel was determined and indicated it ease of application and spreadability on the skin. The prepared Carbopol gel have 6.6 of pH and hence ensuring compatibility with the skin and reduces the skin irritation upon topical application. The microsponge gel was also evaluated for its antimicrobial activity against *S. aureus* and *E. coli* by *in vitro* antibacterial studies. The results showed that the gel possess antibacterial activity and can be used for topical bacterial infections.

In conclusion, the findings of this project support the gel loaded curcumin microsponges can be used as topical agents for bacterial infections. curcumin microsponges prepared in this study were found to be promising as new-fangled delivery system offering prolonged release of drug and, hence, would be more useful than conventional formulation therapy in topical drug delivery. Further studies, including bioavailability studies, In vivo studies and clinical trials, would be valuable to assess its efficacy, safety and potential therapeutic benefits.

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