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Formulation and Evaluation of the Curcumin Hydrogel Under the Influence of Natural Chemical Enhancer

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Abstract: *Curcumin (CUR) is a natural compound extracted from turmeric (Curcuma longa L.) used to cure acne, wound healing, etc. Nanoemulsion (NE)-based drug delivery systems have gained popularity due to their advantages. This study aimed to optimize a CUR-NE-based gel and evaluate its physicochemical and biological properties. A NE was prepared using the catastrophic phase inversion method and optimized using the Design Expert 12.0 software. The CUR-NE gel was characterized in terms of visual appearance, pH, drug release, antibacterial and wound healing effects.The aim of the present investigation was to develop and study topical gel delivery of Curcumin for its anti-inflammatory effects. Carbopol 934P (CRB) and hydroxy propyl cellulose (HPC) were used for the preparation of gels. The penetration enhancing effect of menthol (0–12.5% w/w) on the percutaneous flux of Curcumin through the excised rat epidermis from 2% w/w CRB and HPC gel system was investigated. The percutaneous flux and enhancement ratio of curcumin across rat epidermis was enhanced markedly by the addition of menthol to both types of gel formulations. Both types of developed topical gel formulations were free of skin irritation. In anti-inflammatory studies done by carrageenan induced rat paw oedema method in wistar albino rats, anti-inflammatory effect of CRB, HPC and standard gel formulations were significantly different from control group (P < 0.05) whereas this effect was not significantly different for CRB and HPC gels formulations to that of standard (diclofenac gel) formulation (P > 0.05). CRB gel showed better % inhibition of inflammation as compared to HPC gel.*

Keywords: curcumin, nanoemulsions, optimization, wound healing, gel

I. INTRODUCTION

The present investigation involved preparation of hydrogel nanoparticles using a combination of hydroxyl propyl methyl cellulose and polyvinyl pyrrolidone. The objective was to exploit the size and hydrophilic nature of the formulated nanocarriers to enhance absorption and prolong the rapid clearance of curcumin due to possible evasion of the reticulo-endothelial system. Reproducible nanoparticles of size around 100 nm, a fairly narrow distribution and encapsulation efficiency of 72%, were produced by the solvent emulsion-evaporation technique. This optimized system was further subjected to freeze-drying. The freeze-dried product was readily reconstituted with distilled water. The reconstituted product exhibited a size and distribution similar to that before freeze-drying, drug content of greater than 99% and presence of amorphous drug when analyzed by differential scanning calorimetry (DSC) which may result in possible improved absorption of curcumin. In vivo anti-malarial studies revealed significant superior action of nanoparticles over curcumin control suggesting the possibility of the formulation being employed as an adjunct anti-malarial therapy along with the standard therapy. Acute and as an adjunct anti-malarial therapy along with the standard therapy. Acute and subacute toxicity studies confirmed the oral safety of the formulation.

A battery of genotoxicity studies was conducted to evaluate the nongenotoxic potential of the developed formulation thus indicating the possibility of the formulation being employed for prolonged duration. The optimal formulation contained CUR, Capryol 90 (oil), Labrasol:Cremophor RH40 (1:1) (surfactants), propylene glycol (co-surfactant), and water. The NE had a droplet size of 22.87 nm and a polydispersity index of 0.348. The obtained CUR-NE gel had a soft, smooth texture and a pH of 5.34 ± 0.05. The in vitro release of CUR from the NE-based gel was higher than that from a commercial gel with nanosized CUR (21.68 ± 1.25 µg/cm2, 13.62 ± 1.63 µg/cm2 after 10 h respectively). The

CUR-NE gel accelerated in vitro antibacterial and in vivo wound healing activities as compared to other CUR-loaded gels. The CUR-NE gel has potential for transdermal applications.

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The study aims to investigate a transdermal hydrogel formulation containing curcumin, which would attenuate the low bioavailability associated with oral administration of the drug. Carboxypolymethylene was used to develop topical hydrogel formulations of curcumin with different concentrations of penetration enhancers. Rheological properties, drug content, skin irritation, stability and in-vitro permeation studies were conducted. Permeation experiments were performed on silicon membrane and excised abdominal rabbit skin using Franz Diffusion Cell. All the prepared hydrogel formulations containing Curcumin showed good consistency, homogeneity, spreadability and has wider prospect for topical preparation. The formulation containing Curcumin (2 % w/w gel) and olive oil (2 % w/w, as enhancer) was found to have good permeation of the drug across artificial skin as well as rabbit skin. The anti-inflammatory activity of 2 % w/w Curcumin hydrogel in the rat hind paw edema model revealed that the drug was delivered to the inflammation site at a controlled rate over a desired period of about 3 h, using carboxypolymethylene as gel forming polymer and olive oil and tween 80 as penetration enhancers.

II. MATERIALS AND METHODS

2.1 Materials

Curcumin was received as a gift sample from Dabur India Limited, Ghaziabad, India. GO was purchased from Sigma-Aldrich Pvt, Ltd. Tripalmitin was purchased from scientific traders, Shastri Marg, Prayagraj. Dimethyl sulfoxide (DMSO) was purchased from BASF SE Ludwigshafen, Germany. Cholesterol was obtained from LobaChemiePvt. Ltd., Mumbai, Maharashtra. Dihydrogen sodium hydrogen phosphate was purchased from LobaChemiePvt. Ltd., Mumbai, Maharashtra. Potassium dihydrogen phosphate was obtained from Thomas Baker (Chemicals) Pvt. Ltd, Marine Drive, Mumbai, Maharashtra. M/s Bengal Chemicals Ltd. Provided absolute ethanol (Kolkata, India). All other substances used in this study were of analytical purity, and double distilled water was employed.

2.2 Methods

Determination of λmax of Curcumin in DMSO

CUR was scanned using the ultraviolet–visible (UV–vis) spectrum range of wavelengths 200 to 800 nm (Thermo electron corporation model NO Gensys 10.s). Each sample was diluted with 1.5 mL of DMSO before being maintained in a quartz cell. The double-beam UV–vis spectrophotometer sample was used for the UV scan of CUR, which covered wavelengths from 200 to 800 nm. The spectrometer was calibrated for around 20 min before the cuvette was filled with samples and positioned in the right orientation. (22) A cover was used to keep out any light or scattering so that the absorbance could be maximized. The equipment was allowed to scan through various wavelengths, and the absorbance spectrum was obtained by comparing it to the blank sample and its absorbance graph. (22)

2.3 Solubility Studies

Solubility of CUR was quantified by using various lipids, solvents, and solvents. The drug's solubility was tested by diluting a small amount of the drug in several test tubes and adding various solvents. Organic solvents such as methanol, ethanol, acetone, and DMSO are used to dissolve CUR. The solubility of GO organic solvents was also observed in various abovementioned solvents. CUR/GO was also put into each aforesaid vehicle and swirled constantly at 25 ± 1 °C for 72 h to remove any surplus.

Mayer's test: To 1ml of filtered extract 2 drops of Mayer's reagent is added from the walls of the test tube. The presence of white or creamy precipitate includes for the alkaloid presence.

Wagner's test: To 1ml of filtrate 2mlof Wagner's reagent was added from the walls of the test tube. Presence of reddish-brown precipitate confirm positive for the above test.

Dragendroff's test: To the 1ml of filtered extract2mlof Dragendroff's reagent isadded.Formation of yellow color precipitate confirms were positive

GLYCOSIDES Borntrager's test:- Prepared curcumin extract was boiled with dilute H2SO4, filtered and the addition of chloroform was done and shaken well. The separation of organic layer was observed to which ammonia is added slowly. The appearance of pink or red ammonical layer indicates positive for the test.

TERPENOIDS

Salkowski test:- To the extract add 2ml of chloroform and 3ml of concentrated H2SO4 was added carefully. A reddish brown color formation indicates presence of terpenoids.

FLAVONOIDS: To the extract 1.5mlof 50% methanol was slowly added. The above solution is warmed and magnesium metal was added onto it. To this, addition of concentrated sulphuric acid and red color was observed indicating for the presence of flavonoids.

TANNINS: To 0.5ml of extract ,water and few drops of ferric chloride was added. Presence of blue color indicates for tannins presence.

SAPONINS: The processed curcumin extract was shaken with 5ml of water and then heated for boil. Frothing shows up for saponins presence.

ASSESSMENT OF ISOLATED CURCUMIN BY HIGH PERFORMANCE THIN LAYER CHROMATOGRAPHY EXPERIMENTAL:

Extraction of the curcuminoid from *Curcumalonga* was carried out with two different solvents and then the isolation of curcumin from the other two components of curcuminoid.

Preparation of sample:0.5gm of *Curcuma longa* was dissolved in 10ml of ethanol, filtered, concentrated and was collected.

Developing system:

Ethyl acetate: n-hexane 3:7solvent system was made into use for the development of HPTLC fingerprint profile of terpernoids. Sample application: Test solution of the curcumin extract(2and standard solution of the standard curcuminoid extract(3µl) were filled in Hamilton syringe for 5mm band length on per coated silica gel G aluminum plate 60F 254(E MERCK Germany) (3×10cm) using the applicator connected to AETRON HPTLC system installed and programmed with SPRAYLIN.

Development of chromatogram: The developed chromatogram was dried at room temperature and then placed in AETRON document chamber and visualized less than 254nm and image of the chromatogram were obtained with an EOS utility, after quantification was done by using the SPRAYLIN

Storage Temperature	**Zero Time**		**1 Month 4º C**
Formulation	**NCR1**	**Coated NCR-F3**	**NCR1**
Size (nm)	272.1 ± 15.32	312.1± 15.32	289.7± 15.32
PDI	0.315± 0.06	0.489± 0.098	0.504± 0.054
Content	91.5± 5.34	96.66± 2.5	89.80± 3.87

Preparation of cucumin nanocrystals (CR-NC) :

In this study, nanocurcumin formulations were prepared utilizing a modified antisolvent nanoprecipitation technique as previously reported (Abdelbary et al., 2015). Briefly, CR was dissolved in ethanol (organic phase). The antisolvent phase was prepared by dissolving the stabilizer combination of PVPK30 with (Poloxamer 188, Tween 80, HPβ-CD and Brij®35) at a ratio of 1:2 (CR: stabilizer combination, w/w) with PEG200 (costabilizer) (1 ml) in distilled water (Table 1). At a temperature of 25 °C, the organic phase was added slowly at a rate of 1 ml/min into the antisolvent phase and stirred on a magnetic stirrer for 20 min. Instantly, nanodrug particles precipitated from the antisolvent. Then,

nanocurcumin dispersions were placed in a rotary evaporator at 40 °C for 15 min for complete evaporation. The developed nanocurcumin formulations were stored at −80 ± 1 °C in the refrigerator before freeze-drying. The composition of the developed formulations is listed

Evaluation of the developed hydrogel formulations :

Curcumin hydrogel in different formulations was elegant, clear, while the hydrogel of free CR was found to be opaque. No lumps or air bubbles were observed. The content of CR in the different prepared hydrogel formulations ranged from 97.5 ± 1.5 to 99.0 ± 1.8%. Hence, these matches with theoretical limits (100 ± 5) indicate high homogeneity and uniformity of the fabricated hydrogel formulation. Furthermore, pH determination results showed that all the developed hydrogel formulations exhibited pH values ranging from 6.9 to 7.2 that were acceptable for skin application, which confirmed the compatibility of these formulations. (Kumar et al., 2022). The higher pH values might be related to the addition of triethanolamine during hydrogel preparation. Viscosity is a crucial parameter for hydrogel characterization that influences the release of drugs. Table 10 shows the viscosity measurements of the prepared hydrogel formulation; they showed an acceptable range for topical administration. It is clear that the viscosity value was significantly increased by using nanocurcumin and chitosan-coated nanocurcumin, this might be attributed to the incorporation of polymer stabilizer (PVP-Poloxamer) and chitosan in nanocurcumin and coated nanocurcumin, respectively. These findings were consistent with previous reports (Salem et al., 2020). The skin irritation study exhibited that the prepared hydrogel formulations did not demonstrate any sign of edema or erythema (null irritation). This result indicated the compatibility of the developed formulations with the skin.

Curcumin Delivery Mediated by Hydrogels :

Various plant-derived natural products have been used for human applications as drugs or supplementary agents. (78−86) The biological activity of curcumin was first reported by Schraufstätter and Bernt, where they showed the anti-bacterial activity of the compound against Staphylococcus aureus. (87) Despite promising biological properties, low cost, and availability in bulk, a limited number of human clinical trials have been reported for curcumin and its derivatives. (68,88) The major challenge for human application of curcumin is its poor bioavailability resulting from low solubility and stability. (61) Following the administration of substantial doses of curcumin, its plasma level becomes negligible within hours. (89,90) Considering the unique properties of hydrogels, they can improve the bioavailability, solubility, and stability of curcumin for medical applications.

Formulation development of curcumin-honey hydrogel

Chitosan (1%) solution was prepared in 0.5% (w/v) acetic acid solution with continuous stirring. The drug and polymers (Curcumin, Honey and Collagen) at different ratios (Table 1) were mixed in previously prepared Chitosan solution by vortexing for 1 h and poured into glass moulds. They were then frozen at −20 °C for 18 h and then thawed at room temperature for 6 h for three consecutive cycles. After three F–T cycles, the hydrogel samples were dried for 6 h at 50°C under vacuum. They were then soaked in distilled water for 24 h up to a constant weight to remove the soluble parts. The gels were then dried again at 50°C under vacuum (Cho et al., 2010).

Table 1: List of variables employed in 32 factorial designs Factors

Levels
Curcumin (%) Honey (%)
Collagen (%) Chitosan (%)
Final equation in terms of coded factors Gel
Low (-1) High (+1) 0.25
0.5 0.5 1.5
1.0 2 3.0 strength=
0.6945B2 +0.1680C2
Viscosity=+8674.84+342.13A-153.99B+554.06C-0.5500AB-1314.90AC+188.08BC1245.96A2- 2154.18B2-137.33C2
Spreadability = +6.43++0.0000A+0.0200B+0.8725C Drug content = +94.96+1.43A-0.3250 B + 0.1000 C -5750 AB - 0.4750 ac +0.9750 BC

Characterization of hydrogel
pH
measurements pH of selected optimized formulations was determined with the help of digital pH meter
1492 | P a g e +9.56+0.0213A+1.76B+0.1037C-0.0050AC-0.2125BC-0.1720A2-IJFANS International Journal of Food and Nutritional Sciences ISSN PRINT 2319 1775 Online 2320 7876
Research paper © 2012 IJFANS. All Rights Reserved, UGC CARE Listed (Group -I) Journal Volume 11,S Iss 3, Dec 2022
(Guptal et al., 2010). Before each measurement of pH, pH meter should be calibrated with the help of buffer solution of pH 4, pH 7 and pH 9.2. After calibration, the electrode was dipped into the gel and pH of selected formulation was measured and readings shown on display were noted.
Measurement of viscosity Viscosity measurements of prepared topical hydrogel were measured by Brookfield viscometer using spindle no. 63 with the optimum speed of 10rpm; the results of viscosity are shown in table no. 2.
Determination of gel strength The method by which the properties of polymeric system may be conveniently determined is texture profile (TA-XT2 Texture analyzer). The experiment was done by placing the gels in standard beaker below the probe. In this an analytical probe is then immersed into the sample. The Texture Analyzer was set to the 'gelling strength test' mode or compression mode with a test-speed of 1.0 mm/s. An acquisition rate of 50 points per seconds and a trigger force of 5 g were selected. An aluminum probe of 7.6 cm diameter was used for all the samples. The study was carried out at room temperature. The force required to penetrate the gel was measured as gel strength in terms of g.
Drug content Accurately weighed amount of gel formulation equivalent to 10mg curcumin of prepared hydrogel formulation was taken in beaker and added 10ml of methanol. This solution was mixed thoroughly and filtered using 0.45µ membrane filter. Then 0.1mL of filtered solution was taken in 10 mL capacity of volumetric flask and volume was made upto 10 mL with methanol, this solution was analyzed using HPLC method. Drug content of hydrogel formulations are shown in table 2.
Extrudability study Extrudability was based upon the quantity of the gel extruded from collapsible tube on application of certain load. More the quantity of gel extruded shows better extrudability. It was determined by applying the weight on gel filled collapsible tube and recorded the weight on which gel was extruded from tube. The results of Extrudability of gel are shown in table no. 4.
Spreadability of formulation is necessary to provide sufficient dose available to absorb from skin to get good therapeutic response (Contreras and Sanchez, 2002; Rao et al., 2009). An apparatus in which a slide fixed on wooded block and upper slide has movable and one end of movable slide tied with weight pan. To determine spreadability, placing 2-5 g of gel between two slide and gradually weight was increased by adding it on the weight pan and time required by the top plate to cover a distance of 10 cm upon adding 80g of weight was noted. Good spreadability show lesser time to spread.

III. RESULT

The complexation of CUR had an increased solubility up to 103.09 times for 1:3 molar ratio with in vitro dissolution 90.64% for 60 min. The optimized formulation F9 had viscosity of 6500.3 cps and 97.5% in vitro drug diffusion for 8 h which follows zero-order release kinetics. In vitro anti-inflammatory activity studied showed that the CUR gel has a good potency for renaturation and was as effective as standard diclofenac with 76.9% inhibition (p=0.0507). CUR showed approx. 3 mm diameter of zone of inhibition against *C. albicans*and *E. coli.*

IV. CONCLUSION

As a result, in this study, a new formulation was produced based on a simple concept with acceptable quality parameter results promising to be conducted in the industry. Biocompatible polymer-based hydrogels, in film form, have great potential for use in medicine as transdermal systems for skin wounds treatment. In this study, films based on crosslinked polysaccharides, κ-carrageenan and alginate, were prepared. As poloxamer 407 is known to increase hydrophobic drug solubility and encapsulation, this synthetic polymer was also added to the carriers. Different ratios of polysaccharides, different concentration of poloxamer, and glycerol as plasticizer, and different crosslinking times were

examined to obtain carriers with optimal properties. The films with optimal properties were obtained using carrageenan and alginate in a ratio of 8:2 and 5.0% poloxamer concentration.

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