Journal of Pharmaceutical and Scientific Innovation

www.jpsionline.com (ISSN : 2277 -4572)

Research Article

CURCUMIN LOADED CHITOSAN NANOPARTICLES FOR TOPICAL DELIVERY: FORMULATION DESIGN, IN VITRO EVALUATION, KINETICS AND STABILITY STUDIES

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DOI: 10.7897/2277-4572.102204

Received on: 18/03/21 Revised on: 09/04/21 Accepted on: 14/04/21

ABSTRACT

The main objective of this research is to evaluate a new approach for the preparation of bio adhesive nanoparticles and to design an innovative topical delivery system for curcumin which is able to enhance the drug anticancer activity. Curcumin encapsulated nanoparticles were prepared by ionic gelation method. The nanoparticles were found to be discrete, spherical with free-flowing properties and evaluated for particle size analysis, shape (scanning electron microscopy), drug encapsulation efficiency, FTIR, DSC studies and in vitro release performance. The best selected nanoparticles formulation (FS5, containing drug: polymer ratio 1:5) was incorporated into gels with a bio adhesive polymer. The Nanoencapsulated topical gels were evaluated for pH, spreadability, extrudability, viscosity, in vitro drug release, drug release kinetics, bio adhesion test, accelerated stability of selected gel formulation. In vitro drug release rate for selected Nanoencapsulated bio adhesive topical gel (FS3 gel, containing 1 % w/w of drug loaded nanoparticles and 0.6 % w/w of Carbopol 934) was found to control curcumin release over 12h. The results were then compared statistically and obtained a satisfactory correlation. Thus, in conclusion preparation protocol of Nanoencapsulated topical gel study may be adopted for a successful delivery of Curcumin for topical use.

Keywords: Curcumin, Topical Gel, Carbopol, Carcinogenic activity

INTRODUCTION

Skin cancer is the most commonly diagnosed cancer. More than 1 million cases of SCC are diagnosed in each year. The latest figures show that more than 15,000 people die due to squamous cell carcinoma of the skin, more than twice as many as from melanoma. More than 5,400 people worldwide die of non melanoma skin cancer every month[1]. There have been concerns related to the conventional topical dosage forms such as lotions, creams, ointments and powder in terms of drug diffusion or release from the vehicle and delivery through the skin[2]. Creams and Lotions often provide poor bioavailability of the drug because they rapidly get cleared from the skin and poorly release the drug from base. Medicated powders for topical application have short time of residence on the skin. Curcumin is also been known to counter inflammatory responses similarly to the action of steroids, but without side effects. Oral administration is poorly absorbed and only the traces of compound appear in blood. It undergoes extensive first pass metabolism and hence is a suitable candidate for topical gel formulation[3]. The use of gel as a delivery system can increase the time of residence of drugs on the skin and consequently enhance bioavailability. Gel delivery systems have several advantages such as non-greasy, ease of administration, patient compliance, high residence time on the skin and better drug release[4].

MATERIALS AND METHODS

Curcumin was provided as a gift sample from Natural Remedies, Bangalore560100.

Preparation of Curcumin Nanoparticles[5-7]

Chitosan nanoparticles were made by ionic cross-linking chitosan solution with TPP anions. Chitosan was dissolved in acetic acid (0.25 v/v) aqueous solution at concentrations of 0.1, 0.2, 0.3, 0.4, and 0.5 mg/ml. At room temperature, 5 ml of 0.84 percent (w/v) TPP aqueous solution was added drop by drop into 10 ml chitosan solution containing 10 mg of Curcumin using a syringe needle. 0.1 M NaOH was used to change the pH to 0.6. After that, the stirring was kept going for another 5 minutes. The nanoparticles suspensions were then homogenized at 8000rpm for 20 minutes. The interaction between the negative groups of the TPP and the positively charged amino groups of chitosan resulted in the nanoparticles formation. (Table 1)

Preparation of Curcumin Nanoparticles Topical Gel[8]

Selected batches of prepared Nanoparticles were then incorporated in gels prepared by mechanical stirring with polymer Carbopol 934 with different concentrations and other formulation additives. The experimental design of the gel formulated was expressed in (Table 3)

Characterization of Formulations[9-11]

The pH, homogeneity, spreadability, viscosity, drug content, skin irritancy, in vitro drug release, and stability studies of the prepared curcumin gels were all visually verified.

Determination of pH

The pH of the carbapol gels were determined by a digital pH meter (Model MK- VI, Kolkata). 1g gel was dissolved in 25 ml of distilled water and the electrode was then dipped into gel formulation and reading was noted. The pH measurements of each formulation were replicated three times.

Viscosity Measurements

A Brookfield Rotational Digital Viscometer DV II RVTDV-II was used to measure the viscosity (in cps) of the gels. The spindle was rotated at 10 rpm. Samples of the gels were allowed to settle over a period of 30 min at the assay temperature (25 ± 1°C) before the measurements were taken.

Spreadability

It is measured in seconds the time it takes for two slides to detach from the gel and be put in between the slides under the impact of a particular load; the shorter the time it takes for two slides to separate from the gel, the greater the spreadability. Spreadability is calculated using the formula S = M. L / T, where M is the weight attached to the upper slide. L stands for the duration of the glass slides. T is the amount of time it took to separate the slides. The pH of each gel was determined using a pH meter that had been calibrated with standard buffer solutions at pH 4, 7, and 9 before each use. After that, the electrode was placed into the sample for 10 minutes until the reading was taken at room temperature.

Homogeneity

All the developed gels were tested for its homogeneity by visual inspection once after the gels have been set in the container. They were tested for their presence of any aggregates and appearance.

Drug Content Studies

By dissolving an appropriately weighted quantity of gel (about 100 mg) in about 50 ml of pH 7.2 phosphate buffer containing 20% v/v ethanol, the drug content of the gel formulations was calculated. The solutions were quantitatively transferred to volumetric flasks and dilutions were carried out using the same buffer solution. After that, the solutions were filtered through a 0.45 m membrane filter before subjecting the solutions to spectrophotometric analysis for CUR at λmax of 427 nm. Drug content was calculated from the linear regression equation obtained from the data of calibration study.

In Vitro Release and Release kinetics

The in vitro release studies were carried out by using Franz-diffusion cells apparatus from different formulations. An exact number of formulations (1.0 g) was spread out on membrane between the donor and receptor compartments with an available diffusion area. The receptor compartment was filled with pH 6.8 phosphate buffer and continuously stirred with a small magnetic bar at a speed of 150 rpm during the experiments to ensure homogeneity and maintained at 37.2±0.5ºC. The samples were withdrawn at various interval of time and replaced with the same volume of phosphate buffer solution. Sink conditions were met in all cases. The samples were analyzed spectrophotometrically at 427 nm (Shimadzu UV-Visible-1800).

In order to study the exact mechanism of drug release from the nanoparticles-containing gels, drug release data were analyzed according to zero order, first order, Higuchi square root, Korsmeyer-peppas equation.

Stability study

For the evaluation of stability studies, maintaining the formulations at an ambient condition over a period of three months. The physical appearance, rheological properties, pH value, drug content, drug release studies were determined periodically.

RESULTS AND DISCUSSION

The formulation design of curcumin nanoparticles has been presented in (table 1). From the batch of prepared nanoparticles, the FS-5 formulation was considered as ideal formulation and was incorporated in gels by mechanical stirring. (Table 2)

The prepared formulations of gel shared a smooth and homogeneous appearance. The Carbopol curcumin gels were transparent, dark yellow gummy with smooth and homogeneous appearance. All preparations were spreadable easily, with good bio adhesion and fair mechanical properties.

pH

The pH values ranged from 6.8 to 7 for all the formulations which were in acceptable range to avoid skin irritation after application to the skin. (Table 4)

Viscosity

Viscosity is an important physical parameter which will reflect the consistency in case of topical preparations, and it also affects the rate of drug release. High viscosity is due to high polymeric entanglements; therefore, the resistance to deformation will be increased and it will lead to more rigid structure. The highest viscosity was found for FTG-1 formulation (11639.7) due to high polymer concentration and FTG-3 showed (6500.3) low viscosity. (Table 4)

Spreadability

FTG-1 formulation showed the lowest spreadability, due to the high polymer concentration. The ability of the gel to spread has decreased due to high polymeric entanglements, FTG-3 shows high spreadability. (Table 4)

Extrudability

Extrudability of FTG-1 formulation was found good and extrudability of FTG-3 formulation was excellent. (Table 4)

Drug content and Uniformity

All the formulations have satisfactory appearance, clarity and drug content in the range of 87.5 to 95.6. Formulation FTG-3 showed maximum drug content. Drug content data indicates the suitability of the applied method for semisolid system preparation. (Table 4)

In vitro dissolution profile

In vitro dissolution profile of curcumin gels containing different concentration of Carbopol are shown in Table 4 and Fig. 1. Release profiles of curcumin from various gel formulations across the egg membrane deplicated that drug release decrease with increase in concentration of the gelling agent. The drug

release values were also found lower for the formulation in which polymer concentration was kept high.

Release kinetics

The in vitro drug release data of the formulation FTG-3 was fitted to various mathematical models, it showed linear nature between cumulative percentage drug released and time suggesting that it followed zero order kinetics. The best fit with higher correlation was found with zero order r^2 =0.92. The diffusion co-efficient data indicates that the formulation FTG-3 release the drug by diffusion which follows non-fickian transport mechanism. (Table 5)

Stability studies

The CUR nano gel was found stable upon storage over the period of 6 year. The results of drug content of ideal formulation FTG-3 after 3 months of stability testing at different storage conditions were shown in Fig. 2. It was observed that there was a slight increase in drug content when the formulation was stored at 5º± 3ºC which showed 92.04% and at Room temperature it showed 88.35% and at 40 ± 2˚C/75% there was a decrease in the drug content which showed 56.23%. (Table 6)

TABLE 1: PREPARATION OF CURCUMIN NANOPARTICLES

Sl. No	Formulation code	Drug: Polymer ratio	TPP (ml)	RPM
1	FS-1	1:1	5	8000
2	FS-2	1:2	5	8000
3	FS-3	1:3	5	8000
4	FS-4	1:4	5	8000
5	FS-5	1:5	5	8000
6	FS-6	1:6	5	8000

TABLE 2: EVALUATION PARAMETERS OF PREPARED NANOPARTICLES

Evaluation parameter	FS-1	FS-2	FS-3	FS-4	FS-5	FS-6
%Drug content	46	56	57	63.2	89.5	65
Encapsulation Efficiency (%)	44.6	57.5	62.3	78.4	92.64	81.23
In vitro drug release (12hr study) (%)	43.52%	57.68%	64.98%	76.93%	85.89%	71.43%
Stability studies	5º±3ºC, Room temperature					

TABLE 3: EXPERIMENTAL DESIGNS OF NANOENCAPSULATED TOPICAL GELS

Nanoencapsulated Topical Gels compositions - Amount taken in percentage (w/w)						
Formulation	Nanoparticles	Carbopol 943	Triethanolamine	Alcohol	Propylene glycol	Distilled Water
FTG1	1	0.2	0.5	20	10	q. s.
FTG2	1	0.4	0.5	20	10	q. s.
FTG3	1	0.6	0.5	20	10	q. s.
FTG4	1	0.8	0.5	20	10	q. s.

TABLE 4: EVALUATION PARAMETERS OF PREPARED CURCUMIN NANOPARTICLES TOPICAL GEL

Formulation code	FTG-1 (0.2)	FTG-2 (0.4)	FTG-3 (0.6)	FTG-4 (0.8)
Drug content (%) (X±S.D)	87.5	93.2	98.9	95.6
Drug content uniformity	*	**	***	**
pH	6.9	6.95	6.8	7
Extrudability	*	**	***	**
Spreadability (g.cm/sec)	5.9	6.1	8.5	7.3
Viscosity(cps) (X × 104)	11639.7	9040.67	6500.3	7900.07
Invitro drug diffusion (%) (12h study)	64.98±1.25	46.95±1.97	41.22±0.75	57.68±1.12
Bio adhesive strength (kg)	3.5	6.3	7.9	5.2
Bio adhesion Time (hr)	10-12	15-17	35-37	22-24

*(Good), ** (Very Good), *** (Excellent)

TABLE 5: MATHEMATICAL MODEL RELEASE KINETICS OF OPTIMIZED BATCH

MODEL NAME	r^2
Zero order	0.92
First order	0.90
Higuchi square root	0.99
Korsmeyer and peppas	0.51
n	0.85

TABLE 6: STABILITY STUDY OF NANO GEL FORMULATION FTG-3 AT 5º± 3ºC, ROOM TEMPERATURE AND AT 40 ± 2˚C/75% RH AFTER 3 MONTHS

Temperature in ºC	% Drug content
5º± 3ºC	92.04
30 ± 2˚C	88.35
40 ± 2˚C/75% RH	56.23

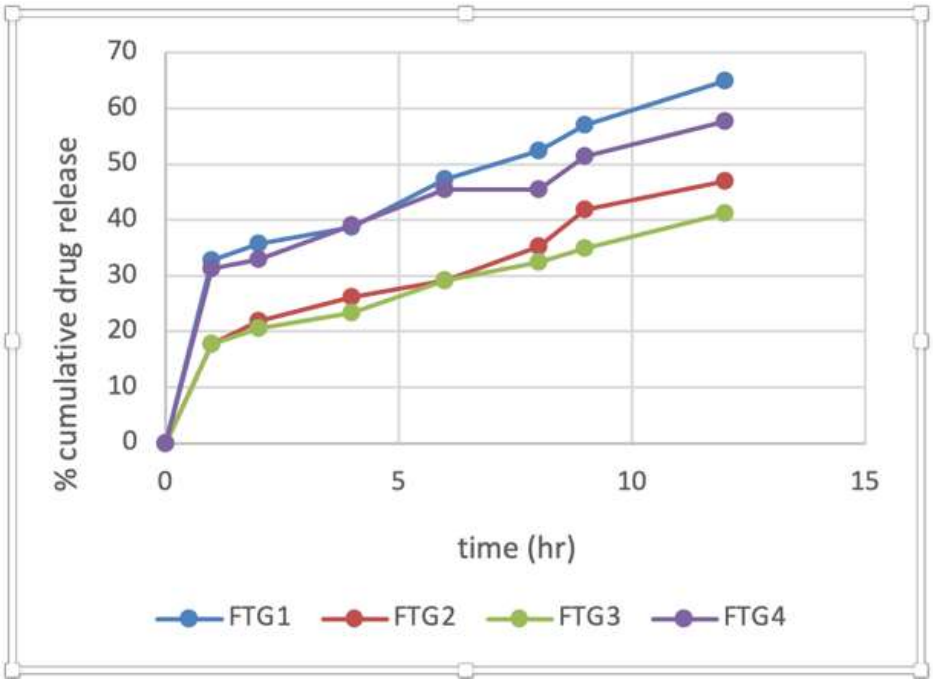

Figure 1: In vitro release profiles of curcumin nanogel formulations

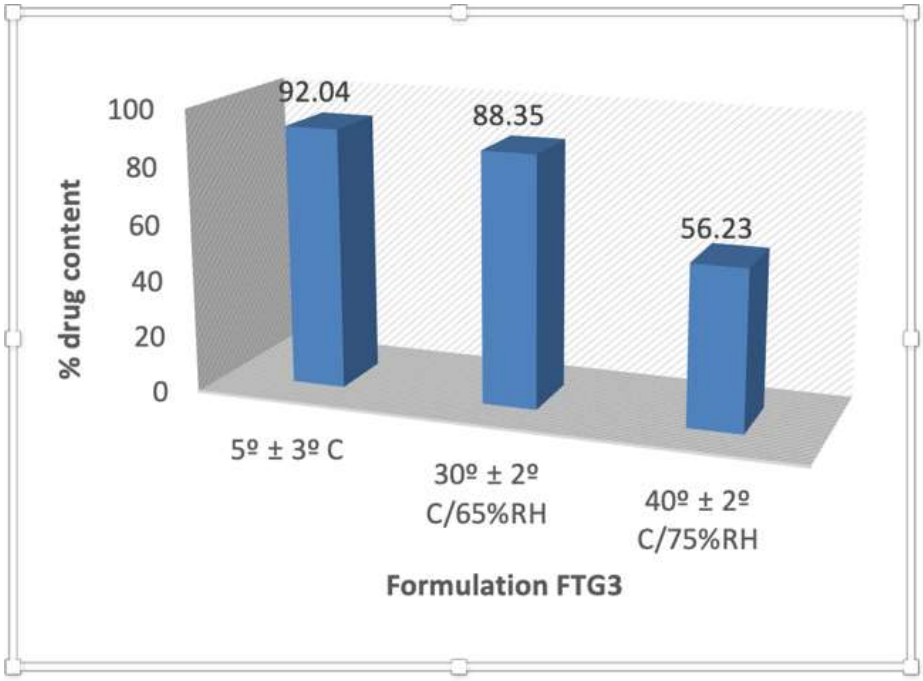

Figure 2: Stability study: comparison of drug content of formulation ftg-3 at 5º± 3ºC, room temperature and at 40 ± 2˚C/75% rh after 3 months

CONCLUSION

Topical route of application has a great potential as an effective and safe way to administer curcumin. To overcome the side effects associated with Curcumin therapy and to have the benefits associated with topical therapy; Curcumin topical gels are prepared in this study. It showed that drug release was decreased with increasing in the concentration of gelling agent because polymer concentration increases, viscosity increases. Drug was absorbed from the site of application as long as it remains with the higher concentration gelling agent. Therefore, with an intention to keep the Curcumin at its site of action, and thus prolonging the time of absorption, gel formulations were prepared. The topical gel formulations of curcumin developed in this study have a lot of potential and are a good choice for managing drug release effectively and safely.

ACKNOWLEDGEMENT

The authors are thankful to Natural Remedies for providing the drug as a gift sample for this work.

REFERENCES

1. Sonavane K, Phillips J, Ekshyyan O, Moore-Medlin T, Roberts Gill J, Rong X, et al. Topical curcumin-based cream is equivalent to dietary curcumin in a skin cancer model. J Skin Cancer 2012; 2012:147863
2. Heng MC. Topical Curcumin: A Review of Mechanisms and uses in Dermatology. Int J Dermatol Clin Res 2017; 3(1):10-7.
3. Patel NA, Patel NJ, Patel RP. Formulation and evaluation of curcumin gel for topical application. Pharm Dev Technol 2009; 14(1):83-92.
4. Pathan IB, Setty CM. Chemical penetration enhancers for transdermal drug delivery systems. Trop J Pharm Res 2009; 8(2).
5. Wu Y, Yang W, Wang C, Hu J, Fu S. Chitosan nanoparticles as a novel delivery system for ammonium glycyrrhizinate. Int J Pharm 2005; 295(1-2):235-45.
6. Aktaş Y, Andrieux K, Alonso MJ, Calvo P, Gürsoy RN, Couvreur P, et al. Preparation and in vitro evaluation of chitosan nanoparticles containing a caspase inhibitor. Int J pharm 2005; 298(2):378-83.
7. Zengshuan M, Tit Meng L, Lee-Yong L, et al. Pharmacological activity of peroral chitosan insulin nanoparticles in diabetic rats. Int J Pharm 2005; 293:271-80.
8. Bhowmik BB, Nayak BS, Chatterjee A. Formulation development and characterization of metronidazole microencapsulated bioadhesive vaginal gel. Int J Pharm Pharm Sci 2009; 1(1):240-57.
9. Shivhare UD, Jain KB, Mathur VB, Bhusari KP, Roy AA. formulation development and evaluation of diclofenac sodium gel using water soluble polyacrylamide polymer. Digest J Nanomat Biostruc 2009; 4(2).
10. Borgia SL, Schlupp P, Mehnert W, Schäfer-Korting M. In vitro skin absorption and drug release–a comparison of six commercial prednicarbate preparations for topical use. Eur J Pharm Biopharma 2008; 68(2):380-89.
11. Rafiee-Tehrani M, Mehramizi A. In vitro release studies of piroxicam from oil-in-water creams and hydroalcoholic gel topical formulations. Drug Dev Ind Pharm 2000; 26(4):409-14.

How to cite this article:
J. Adlin Jino Nesalin and Preethi Raj M N. Curcumin loaded chitosan nanoparticles for topical delivery: Formulation design, In vitro evaluation, kinetics and stability studies. J Pharm Sci Innov. 2021;10(2):48-52.
http://dx.doi.org/10.7897/2277-4572.102204

Source of support: Nil, Conflict of interest: None Declared