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The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.03
TPI 2021; 10(1): 01-05

www.thepharmajournal.com
Received: 02-11-2021
Accepted: 05-12-2021

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Curcumin loaded deformable drug carrier for the disease of posterior segment of eye: Diabetic retinopathy

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DOI: https://doi.org/10.22271/tpi.2020.v9.i12d.5442

Abstract
Diabetic Retinopathy (DR) is one of the most common complications of diabetes mellitus that affects theblood vessels of the retina, leading to blindness. The current approach of treatment based on anti-inflammatory, anti-angiogenesis drugs and laser photocoagulation are effective but also shows adverse affect in retinal tissues and that can even worsen the visual abilities. Thus, a safe and effective mode of treatment is needed to control or delaying the DR. Based on the earlier evidence of the potentiality of natural products as anti-oxidants, anti-diabetic and antitumor, medicinal plants may constitute a good therapeutic approach in the prevention of DR. Curcumin, constituents of dietary spice turmeric, has been observed to have therapeutic potential in the inhibition or slow down progression of DR. In this review, we summarize the therapeutic potentiality of curcumin in the delaying the DR through antioxidant, anti-inflammatory, inhibition of Vascular Endothelial Growth and nuclear transcription fac-tors. In period of time. Curcumin, the major extract of termuric, has been widely used in many countries for centuries both as a medicine. In the last decade, researchers have found the beneficial effects of curcumin on mutiple disorders are due to its antioxidant, anti-inflammatory, and antiproliferative properties, as well as its novel function as an inhibitor of histone aectyltransferases. In this review, we summarize the recent progress made on studying the benificial effect of curcumin on mutiple retinal diseases, including diabetic retinopathy, glaucoma, andage-releated macular degeneration. Recent clinical trials on the effectiveness of phosphatidylcholine formulated curcumin in treating eye diseases have also shown promising results, making curcumin a potent therapeutic drug candidate for inflammatory and degenerative retinal and eye diseases.
Posterior segment dieases, including age-related macular degeneration (AMD), diabetic retinopathy, diabetic macular edema (DME), retinal vein occlusion(RVO), uveitis, and endophthalmitis, are responsible for causing visual impairment and blindness worldwide. The purpose of this study was to evaluate the therapeutic potential of opthalmic curcumin in the preventionand treatment of posterior segment of eye.

Keywords: Curcumin, Transfersome, topical drug delivery

Introduction

Materials and Methods

Materials - Chloroform, di-potassium hydrogen phosphate, potassium dihydrogen orthophosphate and sodium hydroxide pellets (AR grade) were procured from S.D. Fine Chemicals Ltd. (Mumbai, India). Rhodamine Red-X (RR) was obtained from Molecular Probe (Eugene, OR). Flonida cream 5% w/w as marketed formulation (marketed product) was purchased from local medical shop. Span-60, Span-80 and Tween-80 were purchased from Himedia (Mumbai, India). HPLC grade methanol and water were procured from Sigma-Aldrich (Mumbai, India).Ethanol and acetone were obtained from Avarice Laboratories Pvt., Ltd. Dialysis membrane with molecular weight cut off value of 12 000–14 000 Dalton was procured from Himedia. In this study, all other reagents were of analytical grade. Double distilled water and Milli-Q water (Millipore, Bedford, MA) were used throughout the experiments.

Methods / Preparation of Transfersome

The transfer some were prepared by modified hand shaking, lipid film hydration technique. The composition of Drug (curcumin), polymer (lecithin) (PC) and edge activator (tween-80, span-80) were dissolved in ethanol: chloroform (1:1) mixture in a round bottem flask. Organic solvent was removed by rotary film evaporator under reduced pressure at 60 °C ± 2 °C and 60

rpm to get a homogeneous lipid film. A thin lipid film was formed inside the flask wall with rotation. The thin film was kept overnight for complete evaporation of solvent. The film was then hydrated with phosphate buffer (pH 7.4) with gentle shaking for 15 minute at corresponding temperature. The transfersome suspension further hydrated up to 1 hour at 2-80 C to obtained multilamiller (MLVs). The resulting MLVs were kept overnight at 4 °C to allow the complete hydration of the vesicles. The MLVs were then subjected to probe sonication at 4 °C for 2 min using ultrasonic sonicator to get small unilamellar vesicles (SUVs). The SUVs were then passed 10 times through 0.45 and 0.20 µm hydrophilic syringe filters to get uniform sized nanovesicles which were kept at 4 °C for further characterization. A similar methodology was used for the preparing blank transfersomes without curcumin. Similarly, CUR loaded liposome formulations were also prepared using lacithine and surfactant in 85:15 ratio that was used as a control formulation for *in vitro* release study experiments

Results and Discussion

- Preformulation studies
- Test for identification of the drug

Physical appearance: The organoleptic properties like general appearance etc. were performed by visual observation. A small quantity of drug was taken on butter paper and viewed in well-illuminated place. The taken curcumin sample is a Orange-yellow crystalline powder.

Table 1: Description of Organoleptic properties of drug

Drug	Test	Observation
Curcumin	Color	Orange powder
Curcumin	Taste	Acrid
Curcumin	Odour	Odorless

Melting point - The melting point of sample of curcumin was determined as per procedure given in materials and methods part. The performed melting point were 180ºC.

Table 2: Melting point of Curcumin

Drug	Apparatus	Specification	Result
Curcumin	Vegus	179-185˚C	184-185˚C

Solubility- Solubility study of Curcumin was performed using shaking method in different vehicles and the observed results were solubility in water 0.012±0.012, in acetone 20±0.231, in ethanol 10±0.121. The drug was observed to be having very low solubility in water and showed good solubility respectively in remaining four solutions. Such measure confirmed the poorly aqueous soluble nature of Curcumin.

Table 3: Solubility of Curcumin in various solvents

S/no.	Drug	Vehicles	Solubility mg/ml
1	Cur cumin	Water	0.012±0.012
2	Curcumin	Acetone	20 ± 0.231
3	Curcumin	Ethanol	10 ± 0.129
4	Curcumin	Dichloromethane	05 ± 0.327
5	Curcumin	PBS 7.4	0.081 ± 0.014

Standard curve- The standard curve was obtained by plotting data of absorbance v/s concentration (µg/ml).

Table 4: Absorbance values for standard calibration curve in ethanol

Concentration in µg/ml	Absorption at λmax 412 nm
2	0.178
4	0.395
6	0.617
8	0.768
10	0.984
12	1.112

Calibration curve of Curcumin in Acetone

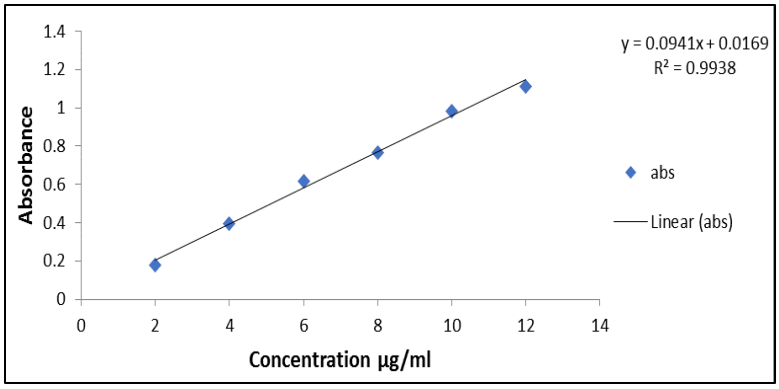

Fig 1: Standard curve of curcumin in acetone

Drug excipients interectio: FTIR analysis measures the selective absorption of light by the vibration modes of specific Chemical bonds in the sample. The Observation of vibration spectrum of Curcumin, different Excipients, physical mixtures allows evaluating the kind of interaction Occurring between the drug and polymer, because the vibration of atoms involved in this Interaction can suffer alteration in frequency and intensity. FTIR analysis was conducted to verify the occurrence of chemical bonds between drug and excipients. Figure shows the FTIR Spectrum of Curcumin PLGA and physical mixtures.

The spectral analysis indicates that the specific functional group of the Curcumin and physical mixture has almost the same characteristics as that of pure drug and polymer combinations. The study suggests that molecular interactions did not occur that could alter the chemical structure of Curcumin.

Hence the chemical structure is likely to be unaffected during physical mixture and due to the low content of drug in the formulation, its detection would have been difficult in the

FTIR experiments and the characteristics band of Curcumin would have been masked by the polymer absorptive band at the same position, which therefore would conceal any possible interactions such as hydrogen bonding.

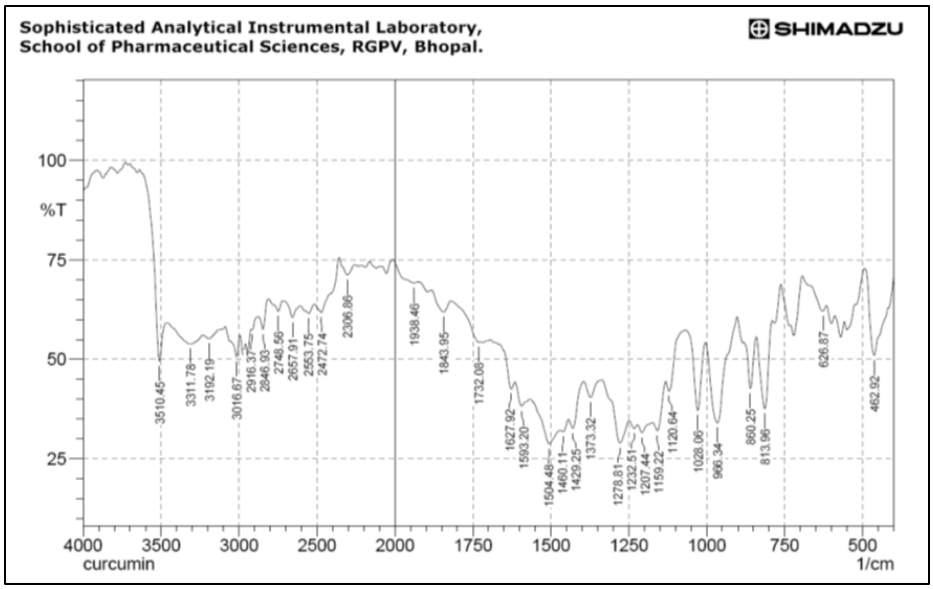

Fig 2: FTIR spectra of Curcumin

Frequency in (cm^{-1})	Functional group
3510.45	OH Stretching (Aliphatic)
3016.67	C=C-H Stretching (alkane)
1504.48	C=C Stretching
1287.81	C-O Stretching
1028.06	C-O-C Stretching

Interpretation

The spectrum of drug sample is shown in fig. The interpretation of FTIR of Curcumin is summarized in table. All the peaks given in the table and there functional groups present in the molecular structure of the Curcumin is shown figure. On the basis of spectra we could sure the sample is pure Curcumin drug.

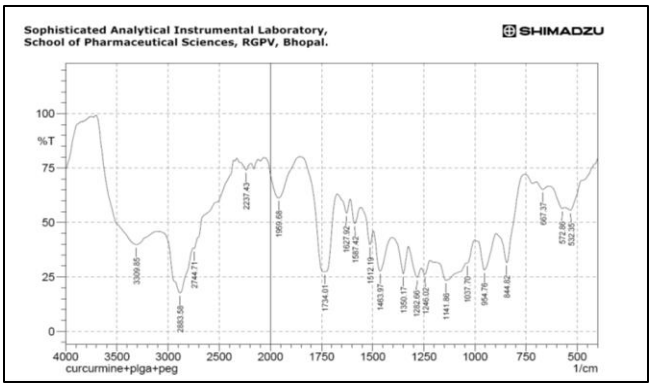

Fig 3: Spectra of Curcumin drug sample

Table 5: Peak and chemical group present in IR spectrum of Physical mixture

Frequency in (cm^{-1})	Functional group
3309.85	O-H Stretching
2883.58	C-C-H Stretching
2237.43	C≡N Stretching
1959.68	C=O Stretching
1734.01	C=O Stretching
1627.92	C=C Stretching

Interpretation

The spectrum of drug and polymer mixture is shown in fig 3.5 the interpretation of major peaks is summarized in table.

From the figure we observed the peak of both Curcumin and lecithin indicate there is no interaction among them. There are no extra peak arises other than peak of Curcumin and lecithin FTIR spectra, it shows there are not any chemical reaction between drug and polymer.

Optimization of transferosomes

There are various process variables which could affect the preparation and properties of the transfersomes. The preparation procedure was accordingly optimized and validated. The preparation of transfersomes containing curcumin involves various process variables such as effect of lecithin: surfactant ratio (95:05,85:15), effect of various solvents (ethanol, isopropyl alcohol) and effect of various surfactants (Span80, Tween80), optimization was done by selecting entrapment efficiency of drug. During the preparation of a particular system, theother variables were kept constant.

Table 6: Optimization of done selecting entrapment efficiency of drug

Edge activators	Formulation code	LEC:TS	solvent
Tween -80	A	95:05	Ethanol
	B	85:15	
	C	95:05	Isopropyl alcohol
	D	85:15	
Span-80	E	95:05	Ethanol
	F	85:15	
	G	95:05	Isopropyl alcohal
	H	85:15	

LEC-indicate lecithine, TS- indicate Tween-80 and Span-80

Morphological analysis of vehicles

Entrapment efficiency

The values obtained after UV- visible spectroscopy are fitted in formula and results are obtained are: - % EE =entrapped

drug /total drug taken ×100

Table 7: Determination of Entrapment efficiency of percentage

Molar ratio (LEC:TS)	Formulation code	%EE
Tween-80		
95:05	A	69.2±0.065
85:15	B	74.6±0.031
95:05	C	75.3±0.028
85:15	D	78.3±0.076
Span-80		
95:05	E	72.6±0.044
85:15	F	79.0±0.035
95:05	G	83.7±0.022
85:15	H	88.6 ±0.055

***In Vitro* Release Study: Membrane-free Model** -The cumulative amount of drug released after 24 h in case of EV dispersion and EVs incorporated into the hydrophilic ointment base was found to be 1320.62±34.86 and 1085.38 ±36.28 µg, respectively. Both the systems showed first-order release kinetics (r 2 =0.9826 and 0.9759, respectively; Fig. 6).Curcumin is known to be soluble (17.75 ± 0.11 mg/mL) in Labrafac CC (32).

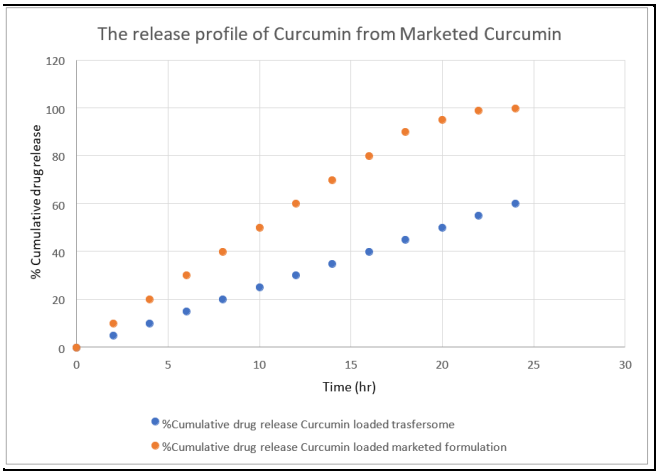

Fig 4: Determined cumulative amount of curcumin drug

Discussion

- Curcumin drug was selected as a suitable drug candidate for this study because it is very bitter in taste. Thus, taste masking is very important for administration in patients mainly diabetic
- Transfersome were prepared by Hand shaking method as it is a cheap, fast method and desired particle size range is achieved. It synthesis was preferred for the formulation of Transfersome because of the reported hazards of adding organic solvent. Thus 0.1 N HCl used as solvent for dissolving drug and polymer. 0.1 N NaOH was used as antisolvent.
- Characterization of Transfersome was done on the basis of taste masking, size and shape, entrapment efficiency, DSC.
- Topical delivery was performed on human volunteers. Based on their responses, it was evident that the prepared Transfersome are absorb in posterior segment of eye Size of were found uniform by optically microscopy. Entrapment efficiency was found to be 78% (85:15) and 88% (85:15).
- Transfersome was formulated due to several advantage. Three polymers were used i.e. Lecithin (1%, 0.5%, 2%), Tween 80 (1%, 0.5%, 2%), Span 80 (1%, 0.5%, 2%).
- Prepared Transfersome was characterized on the basis of parameters like sedimentation volume, degree of redispersibility, flow rate, viscosity. From the results, it was evident that Transfersome containing Span 80 (0.5%) was showing best results among all four formulations.
- From the stability study results it was found that the selected formulation H was found to be stable. There was no significant change from initial readings to final results after 1 month of stability studies.
- Toptical evaluation was performed on human volunteers. Based on their responses, prepared Transfersome was found to be absorbed in posterior segment of eye was successfully done.
- The DSC curve showed the sharp peak at the respective melting point of Curcumin The melting point of curcumin was found to be 100- 150°C. DSC curve of Curcumin show its peak at its reported melting point of 150 °C. Figure 8 shows DSC curve of pure Curcumin. The result of DSC analysis also confirm that drug sample obtained were pure and could be used for further work.
- The DSC curve of Transfersome entrapped with curcumin also showed the peak at respective melting point of Curcumin. The melting point of Transfersome containing curcumin was found to be between 100-150° C. The result of DSC analysis also confirm that drug sample obtained contained entrapped Curcumin. The result also shows that the broad peak of Transfersome entrapped curcumin was due to the transformation of crystalline phase to amorphous phase. This transformation was due to the incorporation of drug inside Curcumin.

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