WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Curcumin Loaded Liposomes for Brain Delivery

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A B S T R A C T

The aim of the present work to the explore the potential or the efficiency of the nanoparticle technology to improve the characteristic of dissolution of the curcumin the sparingly soluble drug contain a high therapeutic value. Mainly work on the preparation and evaluation of the curcumin loaded liposomes in the brain delivery. Curcumin show a variety of biological activity due to the low aqueous solubility , absorption poor and rapid metabolism . curcumin loaded liposome preparation by different ratio by the film hydration method because this method is easy to perform and the calculation of high encapsulation rate of lipid . IN the liposomal formulation mainly evaluated of the zeta potential, calibration curve, higuchi plot Drug release kinetics ,encapsulation efficiency , polydispersity index bioavailability determined on the rat,. There are some main benefits regarding this work will be as follows :

- Reduced frequency dose
- Bioavailability of drug is improved
- Avoided the first pass metabolism
- Decreased the dose of the drug administered
- Reduced the frequency of dosing

The investigated the effects of these NPs in slowing down or disrupting the aggregation process in vitro through kinetic studies performed with the Aβ1-42 peptide . The dissolution drug properties as a dosage form release further impact in properties of bioavailability. Solubility in a challenging condition in the industry of a pharmaceuticals in a formulation of a pharmaceutical product .

Evaluation Of Curcumin Nanoparticle -Particle Size Distribution and Zeta Potential Measurements PNP and SLN mean size, polydispersity index (PDI) and zeta potential (ZP) were determined 1 h after sample preparation by PCS . The experiments were carried out at a detection angle of 90°, at 25 °C with a 4mv laser operating at 633 nm as light source. Each value was measured in triplicate. The results are shown as the mean ± standard deviation (SD). . Entrapment Efficiency The amount of free Cur in the PNP was calculated to determine the entrapment efficiency (EE%). PNP were centrifugated at 12,000 rpm for 1 h at 8 °C to eliminate unentrapped drug in the supernatant. The amount of Cur in the supernatant was determined spectrophotometrically using a UV-Vis 1601 spectrophotometer at a wavelength of 425 nm.

Differential Scanning Calorimetry (DSC) Analysis DSC scans of raw materials, as well as freeze-dried empty and SLN were performed on a Mettler DSC 12E equipped with a Indium was used to calibrate the instrument. The reference was an empty aluminium pan. Each sample was analysed in triplicate at a scan speed of 5 °C/min in a 25–200 °C temperature range.

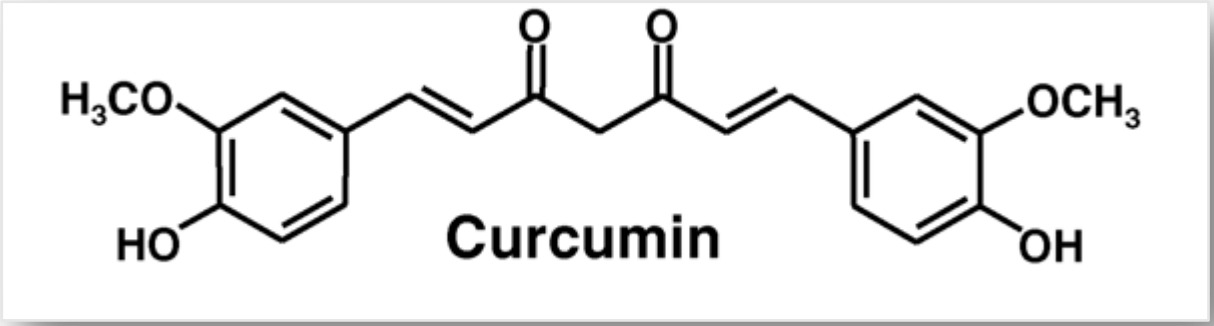
.Keywords: liposome, curcumin , zeta potential, encapsulation efficiency

Introduction

Liposome is a nanostructure for a encapsulation and a delivery of a bioactive agents. Many bioactive materials are incorporated into liposomes includes cosmetics , food ingredients and pharmaceuticals. It possesses particular properties such as biocompatibility, in the form of nanoform have a potential application in nanomedicines, cosmetics and a food industry. Nanoliposome offer a technology chances for food technology in field include a encapsulation and a controlling a release of food ingredients and then enhanced bioavailability and

stability of a sensitive material. Advance technology carry an active molecules in the site for an action in a various clinical trial used in the active form. Nanoliposomes in these days opportunities exciting for food technologists areas example such a encapsulation and release of food materials increase a bioavailability, stability and a ingredients self- life in a sensitive form. Nanoliposome new technology develops for the encapsulation and agent delivery in the bioactive form. Nanoliposomes has ability to enhancing the performance of a bioactive agents by improvement of solubility and the bioavailability in vitro and in the stability in vivo form , well prevent their unwanted interaction with a different molecules. Liposomes consists of one or more vesicles and a layer of phospholipid microcarriers used in disciplines in scientific form. Nanoliposomes ability to protection provide form release of food grade bioactive materials sustained form. It is utilized for the encapsulation are different types of bioactive materials such as drug , vaccines , antioxidant, antimicrobials, preservative ,minerals for the fortification in a different food and formulation of nutraceuticals formulation for manufacturing in a functional product. Many issues unique in the nutraceutical in a food industry resolve an application in a complete manner. Curcumin as a hydrophobic polyphenol is extracted from the rhizome of Curcuma longa. Curcumin is widely used as a dietary spice and a topical medication for the treatment of inflammatory disorders in Asia. This compound also possesses remarkable anti-inflammatory and neuroprotective effects with the ability to pass from the blood brain barrier. Based on several pharmacological activities of curcumin, it has been introduced as an ideal candidate for different neurological disorders.

Curcumin is a component of the Indian spice turmeric, and is extracted from the rhizome of Curcuma longa, which is widely cultivated in south and southeast Asia, especially Ch India. Commercial curcumin refers to curcumin complex, which is composed of curcumin (77%), desmethoxycurcumin (17%), and bisdemethoxycurcumin (3%). Curcumin is the major component of three curcuminoids that give turmeric its distinctive yellow colour, and is used as a food colorant, flavouring, and additive.



2. Methodology

TABLE 1 List of chemical used with grade

sno	Materials used	Grade
1	CURCUMIN	API
2	HPMC	LR
3	METHANOL	LR
4	SUCROSE	LR
5	CHITOSAN	LR
6	SODIUM ACETATE	LR
7	CHROLOFORM	LR
8	ETHANOL	LR
9	TWEEN 80	LR
10	ACETONITRILE	LR
11	PVP K-30	LR

A. METHODS

PREFORMULATION STUDIES

It is a study in which a initiated phase a new molecule is seeded one it deals with studies of physical, chemical, properties analytical and pharmaceutical properties related to the molecule and provide idea about suitable modification in molecule shows a better performance , in order to develop a better safe and effective dosage form .

Solubility analysis

solubility analysis of curcumin was determined in the phosphate buffer , DMSO and the PH remain the 7.4

3 MELTING POINT DETERMINATION

Melting point of the curcumin was determined by the melting point apparatus .

Compatibility studies

The drug compatibility was performed under the TLC METHOD WHICH IS WORKING A TLC PLATE AND the stained of the curcumin drug and the selection of the polymer different drug and the TLC plate heated at the temperature 100-120^{0}c at the hot air oven check the polymer compatibility depend upon solubility of drug

some polymer helps to enhance the solubility of the drug .

Determination of Lambda max

The solution of the curcumin contain the concentration 10ug/ml preparation in the methanol a uv spectrum at the range of 200-400nm

Development of calibration curve

Calibration development by the UV spectrometric method 1mg /ml solution standard solution prepared in methanol from this 0,1,2,4,6 dilution prepared and measured at 425nm graph shown in fig 6.1

3. Formulation development

TABLE 2 formulation development of curcumin drug

S.NO	CODE	DRUG	CHITOSAN	DRUG CARRIER
1	CLL1	100	100	1:1
2	CLL2	100	200	2:1
3	CLL3	100	300	3:1
4	CLL3	100	400	4:1

4 Evaluation of Curcumin Nanoparticle

Particle Size Distribution and Zeta Potential MeasurementsPNP and SLN mean size, polydispersity index (PDI) and zeta potential (ZP) were determined 1 h after sample preparation by PCS . The experiments were carried out at a detection angle of 90°, at 25 °C with a 4mv laser operating at 633 nm as light source. Each value was measured in triplicate. The results are shown as the mean ± standard deviation (SD). . Entrapment Efficiency The amount of free Cur in the PNP was calculated to determine the entrapment efficiency (EE%). PNP were centrifugated at 12,000 rpm for 1 h at 8 °C to eliminate unentrapped drug in the supernatant. The amount of Cur in the supernatant was determined spectrophotometrically using a UV-Vis 1601 spectrophotometer at a wavelength of 425 nm.

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In vitro Curcumin Release from Liposomes

The in vitro drug release profiles of liposomes were studied with the dialysis method. In brief, freeze-dried curcumin loading liposomes were rehydrated in a final volume of 400 µL ultrapure water and vigorously vortexed. To determine the total amount of curcumin available at time t=0 (X1), a 10 µL sample volume was kept for HPLC quantification. In parallel, 50 µL of the sample were taken to quantify free curcumin outside the liposomes. For this, the 50 µL were diluted in 950 µL ultrapure water and centrifuged 15 min at room temperature. The remaining pellet, considered to be free curcumin, was diluted in 1 mL ethanol and the free curcumin content (X2) was quantified via HPLC. Therefore, the difference of concentration between X1 and X2 represents the actual amount of curcumin present inside the liposomes at t=0. Then, the remaining 340 µL of rehydrated samples were and dialyzed against 5 mL ultrapure water containing 20% ethanol and 0.5% Tween-80 (1:50 acceptor/donator volume ratio to obtain sink condition) at 37°C, stirred at 25rpm for 7 days. At certain time points

respectively) 250 µL sample volume was taken from the receptor compartment and replaced by the same volume of fresh receptor compartment media. The concentration of curcumin was then determined via HPLC and the accumulated drug release over the time was calculated taking X2 into account

Dissolution evaluation Dissolution profiles of both NSs and pure curcumin powder were evaluated by apparatus II (at 75 rpm) at predetermined time intervals (5, 10, 15, 30, 60, 120, and 180 mins). The NSs (equivalent of 5 mg curcumin) were released into 900 mL dissolution medium (phosphate buffer saline [0.01 M, pH 7.4] . After mentioned intervals,, 1 mL medium was withdrawn and then centrifugation (14,000 rpm for 15 mins), the supernatant was analysed by HPLC.

Pharmacokinetics study

The ethics committee of Tehran University of Medical Sciences approved the study protocol. The animal welfare care was considered based on the followed guidelines "Handbook of laboratory animal science, An overview of global legislation, regulations and policies on the use of animals for scientific research, testing, or education, and Animal rights according to Quran viewpoints The pharmacokinetics were examined in male rats (250±20 g), which were bred at central animal house of the university, to be used in this research. The rats were kept under standard (2ºC, 60–70% humidity) laboratory settings at 12 hrs dark and light cycle.

he experimental rats (n=18) were randomly grouped in triples and anesthetized generally by injection of a ketamine–xylazine mixture (ketamine 100 mg/kg and xylazine 10 mg/kg) intraperitoneally (IP), followed by insertion of a polyethylene silicone rubber catheter in their right jugular veins according to the standard surgical operation.[46] Curcumin solution, Tween-NS, and TPGS-NS were administered as a 10 mg/kg of curcumin single bolus dose on the next day. The right jugular vein was catheterized to facilitate blood sampling. For pharmacokinetic analysis, blood samples (400 µL) were taken at intervals of 0, 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, and 6 hrs following administration and stored in collection tubes impregnated with lithium heparin. In order to isolate the plasma, the blood samples were centrifuged immediately at 5,000 rpm for 10 mins and stored at −70°C for further analysis.

Tissue distribution and sample preparation

The male rats weighing were investigated for organ biodistribution studies designed as three randomly assigned groups of rats with six animals at each time points. General anaesthesia was induced by the IP injection similar to the anesthetic cocktail described above Pharmacokinetics study. Three formulations, TPGS-NS, Tween-NS, and curcumin solution were injected at a dose of 10 mg/kg and blood samples were withdrawn at 0.25, 0.5, 0.75, 1, 2, and 3 hrs after injection. Both injections and blood sampling were done via cardiac puncture.

The rats were then promptly decapitated and the organs (liver, heart, spleen, lung, kidney, and brain) were removed and preserved frozen until the time of drug analysis.

Biodistribution study

it shows the concentrations of curcumin in the tissues after intravenous administration of the curcumin NSs. At the studied time points, the concentrations of curcumin in the tissues from the curcumin-NSs were significantly higher compared with the curcumin solution, which is in agreement with the results observed in plasma.

The spleen, lung, and liver showed higher levels of TPGS-NS (*P*-value<0.05) compared with curcumin solution; this agrees with the results of previous research on tissue biodistribution of curcumin-NS using TPGS as a stabilizer. On the other hand, the lung showed higher levels of Tween-NS (*P*-value<0.05). The pegylation and block copolymers on the NPs surface may delay, but not prevent, the clearance from the blood. However, the RES (liver, spleen, and lung) may have been unable to capture the NPs coated with TPGS or Tween 80 due to the lower affinity of the MPS toward the hydrophilic surface and steric repulsion effect, respectively, of the modified NPs, which resulted in the opsonization or rapid clearance of the particles from the body. So in non-RES organs, such as heart and brain, curcumin levels enhanced significantly. As shown in the figures , Tween-NS significantly increased the curcumin concentration in the brain (*P*-value<0.05) compared with the curcumin solution and TPGS-NS. Additionally, the $AUC_{0.25–3}$ in the brain was 57.0, 24.3, and 5.1 ng/g.h for the Tween 80-NS, TPGS-NS, and curcumin solution, respectively (*P*-value<0.05). The interaction of the injected external particles with the plasma proteins and the cells could strongly determine the fate of particles. Polysorbates 20, 40, 60, and 80, poloxamer, poloxamer, and Cremophor EZ, and RH-40 are some surfactants that have been examined as surface-coating candidates for the brain targeting of NPs. However, the most effective surface-coating material for accelerating the delivery of NPs to the brain was reported to be polysorbate 80.

In vivo pharmacokinetic study

A noncompartmental model was used to describe the pharmacokinetics of curcumin-NSs and curcumin solution following i.e. administration in rats. Figure 5 depicts the average plasma concentration of curcumin in rat administered intravenously with both curcumin solution and NS formulations at a single dose of 10 mg/kg. summarizes the pharmacokinetic parameters. The plasma concentration-time profiles indicate that drug NSs could effectively increase curcumin plasma levels in comparison with curcumin solution. The pharmacokinetic profile in the rats showed a sharp reduction in the plasma concentration of curcumin within 1 hr of the intravenous administration of curcumin-NS, which may be due to the rapid uptake of the slowly dissolving curcumin-NS by the RES. Studies have reported that slowly dissolving NSs are ingested by the phagocytes of the MPS, mainly the Kupffer cells found in the liver, spleen, and

lungs. The dissolved NSs are able to pass through the phagolysosome membrane because of their lipophilic character; they leave the cellular vesicle, penetrate the cytoplasm, and then exit the cell by diffusing down the drug concentration gradient. Accordingly, the half-life of curcumin-NSs is increased, which leads to prolonged curcumin-NSs presence after their administration. Maximum concentrations of Tween- and TPGS-NS in plasma were almost 2 and 1.7 fold, respectively, that of curcumin (P-value<0.05). The values of AUC0-inf obtained for Tween-NS and TPGS-NS, respectively) were roughly 2.6 and 1.3 times the curcumin solution. After 6 and 5 hrs of injecting Tween-NS and TPGS-NS, respectively, it was still possible to detect curcumin plasma concentration, while this time was up to 3 hrs for curcumin.

5. Results

PREFORMULATION DATA

The solubility profile of curcumin found as follows :

Table 3SOLUBILITY OF CURCUMIN

MEDIUM	SOLUBILITY	ACCURATE RANGE	PRACTICAL VALUE
DMSO	SOLUBLE	1/1O	5
WATER	SPARINGLY SOLUBLE	30/100	95
CHLOROFORM	SOLUBLE	1/10	5
ETHANOL/ METHANOL	SOLUBLE	1/10	5
PETROLEUM ETHER	INSOLUBLE	1/10	5
ACETIC ACID	SOLUBLE	1/10	5

The melting point of curcumin found to be 180-183^{0}c

TABLE 4

SNO	CALCULATION			MELTING POINT
1	1	2	3	181^{0}C
	180^{0}C	181^{0}C	183^{0}C	

TABLE 5WAVELENGTH OF CURCUMIN

SLNO	**SOLVENT**	***λMAX***
1	ETHANOL/METHANOL	425.0NM

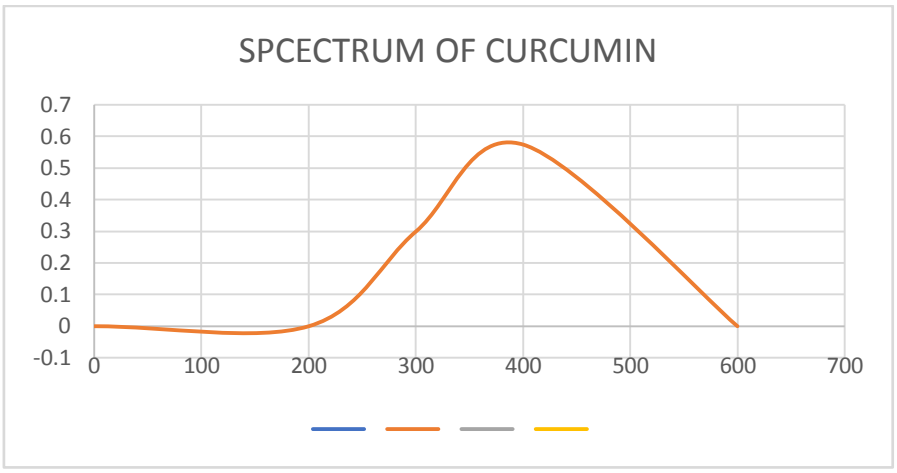


TABLE 6

CALIBRATION CURVE OF CURCUMIN IN METHANOL AT 425 NM

SNO	**CONCENTRATION**	**ABSORBANCE**
	Ug/ml	**425nm**
1	**0**	**0**
2	**1**	**0.156**
3	**2**	**0.3**
4	**4**	**0.578**
5	**6**	**0.897**

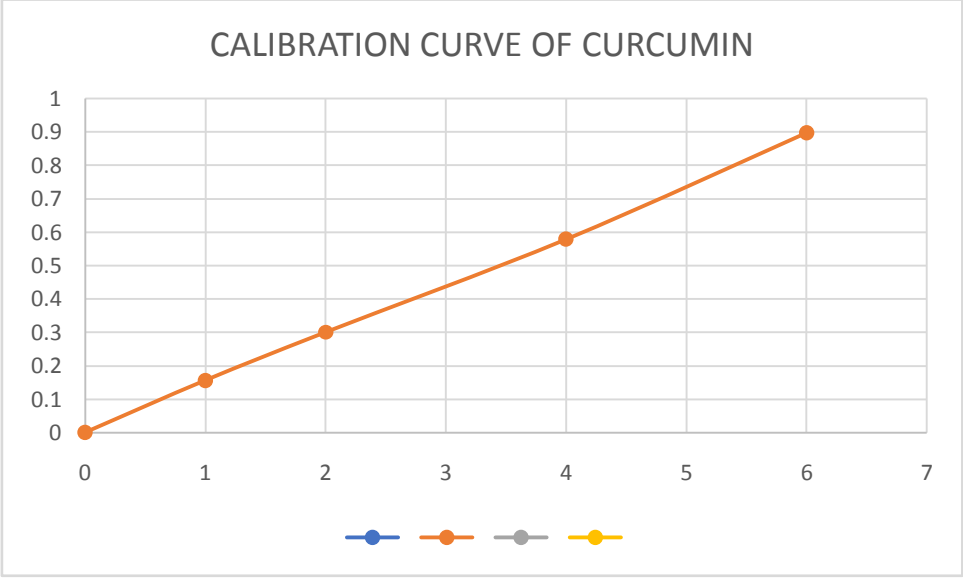


TABLE -7

SNO	formulation	%yield	%DRUG LOADING	%Encapsulation Efficiency
1	CLL1	76.83	26.3	77
2	CLL2	67.4	18.3	80.4
3	CLL3	91.3	17	83.6
4	CLL4	87.42	13.8	86

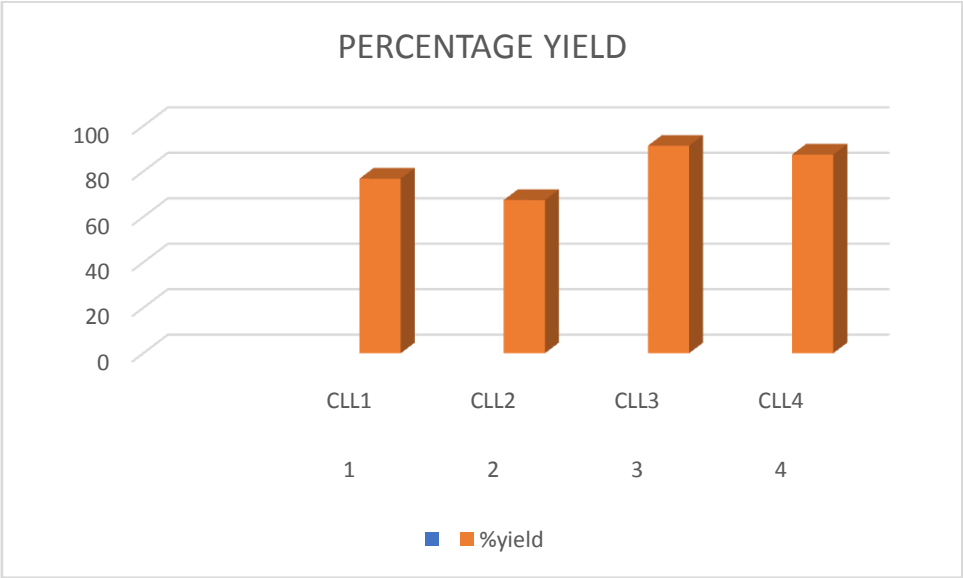
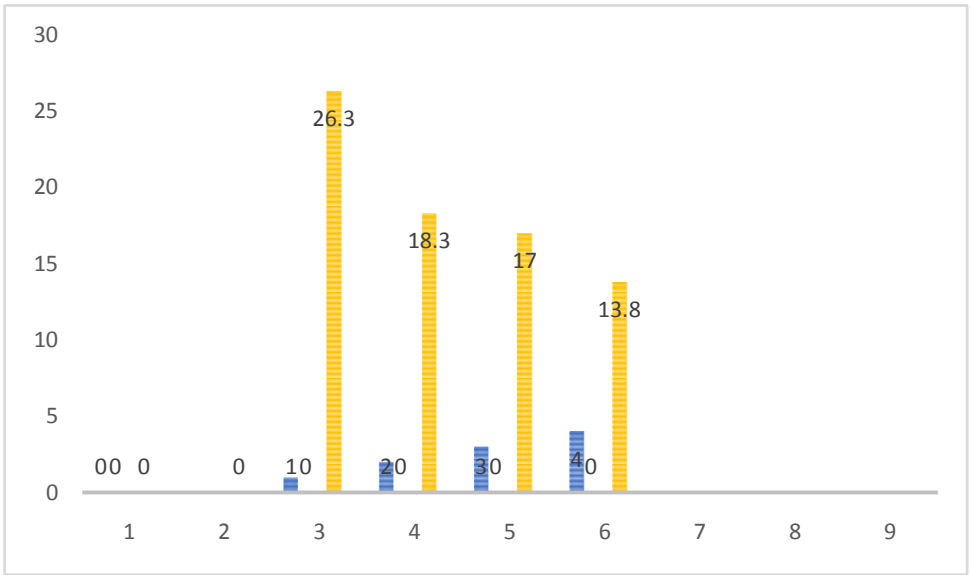
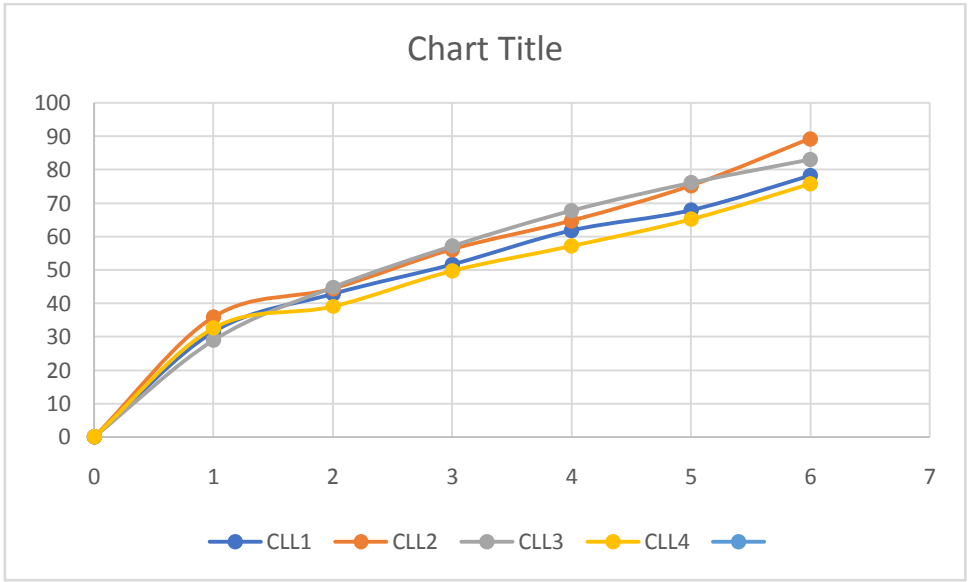


TABLE -8

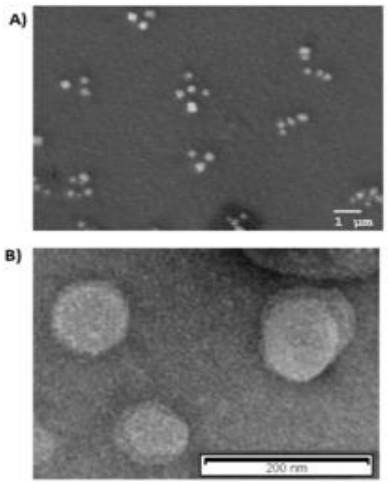
SNO	formulation	%DRUG LOADING
1	CLL1	26.3
2	CLL2	18.3
3	CLL3	17
4	CLL4	13.8



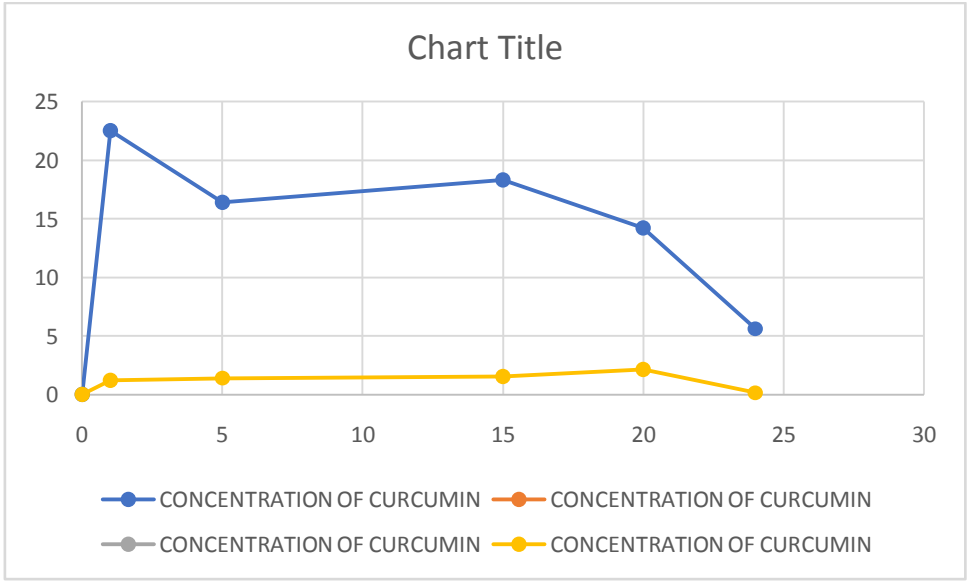
release kinetics of curcumin nanoparticle					
SL-no	TIME	CLL1	CLL2	CLL3	CLL4
1	0	0	0	0	0
2	1	31.45	35.87	28.93	32.53
3	2	42.8	44.35	44.76	39.01
4	3	51.63	56.13	57.1	49.66
5	4	61.81	64.69	67.7	57.1
6	5	67.87	75.18	76.02	65.1
7	6	78.26	89.28	83.01	75.72



4. SEM ANALYSIS



TIME	CONCENTRATION OF CURCUMIN				
	CUR			CUR PURE	
	NANOPARTICLE				
0	0			0	
1	22.5			1.2	
5	16.4			1.4	
15	18.3			1.55	
20	14.2			2.15	
24	5.6			0.14	



5. Discussion

In this study mainly enhanced the bioavailability of drug curcumin by formulating its nanoparticle . curcumin nanoparticle is prepared by solvent emulsification method , evaporation method , the ratio of drug to polymer 1:1,1:2,1:3,1:4

Preformulation studies

In the formulation studies it found that the lambda max of curcumin by uv spectroscopic method was found to be 425 nm

Standard calibration curve of curcumin in methanol by taking absorbance and concentration.

- The solubility of curcumin in chitosan , organic solvent, aqueous solution in the curcumin
- Curcumin is a good drug solubility good in mixture of DCM and methanol.

6. -CONCLUSION

Our liposomal formulation of curcumin can effectively reduce glial scarring associated microglia and astrocyte reactions in human cell culture models as well as murine acute brain slices. Liposomal curcumin is suitable for long-term storage (≤6 months), well tolerated by healthy cells in relevant concentrations and at least as effective as free (soluble) curcumin in alleviating glial scarring reactions in human astrocytes and microglia as well as in murine acute brain slices.

In this study, Cur was efficiently encapsulated in homogeneous PNP and SLN nanosuspensions with suitable properties for potential intranasal administration. Drug encapsulation in both NPs overcomes its chemical instability as revealed by Cur content (>70% and >90% for PNP and SLN, respectively) after 135 days of storage at room temperature as freeze-dried form. The delivery of the drug through PNP and SLN enhanced OEC viability grown in normal and hypoxic conditions compared with the control and even compared to free Cur after 24 h, indicating the enhanced drug protective effect against injured cells suggesting an increase in Cur antioxidant effect

7. SUMMARY

- The anatomy and function of the blood-brain (BBB) and blood-cerebrospinal fluid barriers are reviewed.
- Exposure routes to bypass the BBB (convection-enhanced delivery and uptake from the nasal cavity by cranial nerves) are described.
- Visual and procedural methods to determine nanoparticle (NP) brain and brain parenchymal entry are presented.
- Criteria are proposed to classify levels of experimental result evidence that demonstrate NP bulk brain or brain parenchymal entry.
- Studies of NP brain entry or distribution across the BBB are summarized, critiqued and evaluated using the classification levels to interpret if the study shows NP bulk brain or brain parenchymal entry.
- NP or component persistence in the brain after systemic or intranasal administration compared with blood and peripheral organs and direct infusion by convection-enhanced delivery into the brain are compared with interpret support for NP distribution beyond the brain vasculature, into brain parenchyma.

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