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FORMULATION AND EVALUATION OF NATURAL POLYMER BASED CURCUMIN MAGNETIC MICROSPHERES

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Abstract:

The drug delivery system has been advanced to release the drug according to the body requirement during the entire period of treatment and also for the delivery at the targeted site. Now days, several targeted treatment systems including magnetic field, electric field, ultrasound, temperature, UV light and mechanical force are being used in many disease treatments (e.g. cancer, nerve damage, heart and arrayment-diabetic, eye and other medical treatments). Magnetic microsphere is an alternative to traditional radiation methods. As the traditional radiation methods use highly penetrating radiation that is absorbed throughout the body and cause side effects hence its use is limited. Magnetic microspheres are one of the new novel drug delivery system in pharmaceutical field due to their biocompatibility, easy of surface modification and magnetic properties. They hold great result for reaching the goal of controlled and site-specific drug delivery. Therefore, a safe and effective alternate is needed like magnetic microsphere. The main aim of present study was to formulate and evaluate the Curcumin magnetic microspheres using natural polymers like Albumin and Chitosan in different ratios. The formulations were prepared by using Emulsion solvent diffusion evaporation technique. The prepared Curcumin magnetic microspheres were evaluated for Percentage yield, Drug loading and Entrapment efficiency, In-vitro Swelling index and In-vitro Dissolution studies. FT-IR studies showed significant compatibility between the drug and the polymer. Evaluation studies of swelling indicate an increase in swelling index with increase in concentration of polymers due to more uptake of solvent. The in vitro studies indicated that the rate of Curcumin release from magnetic microsphere decreased with increase in the amount of polymer. The study results proved that curcumin magnetic microspheres can be used for controlled drug delivery due to sustained drug release characteristic of polymers that used. The optimized formulation AMMS2 showed diffusion controlled sustained drug release mechanism and therefore can have benefits such as reduction in total dose and frequency of administration.

Keywords: Magnetic microspheres, target drug delivery, Curcumin, Albumin, Chitosan

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INTRODUCTION:

Earlier patients have been using conventional dosage forms like Tablet, Capsule to treat the acute and chronic diseases, but these conventional dosage forms have to be taken several times in a day for maintaining the peak plasma level concentration. Hence to overcome these problems controlled release drug delivery system were developed. Controlled drug delivery system (Microspheres) releases the drug in controlled rate and overcome the problems of conventional drug delivery system and enhances the therapeutic efficacy of a given drug. [1-4] .The main purpose of Controlled drug delivery system is to ensure optimum plasma drug concentration, thus enhancing efficacy, safety and bioavailability of drug with improved patient compliances [5-7]. Controlled release refers to the use of drug delivery with the objective of releasing the drug into the patient at a predetermined rate or controlled rate at specific times or with specific release profile. With the problems like hygroscopicity of drug as in case of capsule and bioavailability problems associated with tablet, various advancements have been done to overcome the problems of conventional dosage form and microsphere is one of them. Microsphere is small spherical particle having the particle size range 0.1-200µm, and made up of biodegradable and non-biodegradable material and can be injected by 18 or 20 number of needles [8-10] .Drug absorption and side effects due to the irritating drugs against the gastrointestinal mucosa is improved because of small particle size of microspheres which get widely distributed throughout the gastrointestinal tract.[11-13]

Basically each particle is the mixture of drug that is dispersed in a polymer and release pattern of drug follow the first order process. The release of drug is controlled by dissolution or degradation of matrix. Microsphere offers the Ball bearing effect due to their size & shape. Microspheres vary in quality, sphericity, uniformity of particle and particle size distribution. The appropriate microsphere needs to be chosen for each unique application. To control the drug administration, various opportunities are there for the preparation of microspheres. It facilitates the accurate delivery of small amount of potent drugs and reduced drug concentration at the site other than the target site and protection of labile compound before and after the administration and prior to appearance at the site of action. By coupling the drug with carrier molecule we can change the behavior of drug in-vivo. The behavior of carrier molecule can affect the clearance kinetics, tissue metabolism & cellular interaction of drug. The exploitation of these changes in Pharmacodynamics may lead to enhanced therapeutic effect. [14-16] The goal of this controlled drug delivery system is to provide a therapeutic amount of drug at the required site promptly and after achieving therapeutic level, to maintain the desired drug concentration at the site of action. Oral route is the most convenient and commonly employed route for most of the drugs. Some Drugs that are easily absorbed by the G.I.T. and having short t1/2 are eliminated quickly from the blood circulation. Controlled Drug delivery System can avoid the problems of conventional drug delivery system by releasing the drug slowly into the G.I.T. and maintain a constant drug concentration in the serum for longer period of time.[17-19] The number and chemical diversity of drugs has increased; new and updated strategies are required to be developed for orally active therapeutics. Thus, gastro retentive dosage forms, which prolong the residence time of the drug in stomach and improve their bioavailability, have been developed. [20-24]

The aim of the present study was to enhance the efficiency of drug delivery at a rate directed by the needs of the body during the period of treatment which can be achieving by specific targeting of a particular cell, organ or tissue.

MATERIALS:

All the materials used in formulation, evaluation are given below.

Table1: List of materials used

S.NO	USE	MATERIALS	SOURCE
1	Drug	Curcumin	Sun pure extracts, New Delhi
2	Excipient	Magnetite	SDFineChemicals
3	Polymers	Albumin	SDFineChemicals
		Chitosan	SDFineChemicals
4	Solvents	Dichloromethane	SDFineChemicals
		Methanol	SDFineChemicals
		Polyvinylalcohol	SDFineChemicals
5	Buffers	Phosphatebuffer	SDFineChemicals

Preformulation studies:

Before formulation of drug substances into a dosage form, it is essential that drug and polymer should be chemically and physically characterized. Preformulation studies give the information need to define the nature of the drug substance and provide a framework for the drug combination with pharmaceutical excipients in the fabrication of a dosage form.[25-27]

i. **Physical characteristics:** Model drug **c**urcumin physical characteristics like the color, form reaction with alkali and acid, odor and taste was determined by appropriate procedure.

ii. **Determination of Melting point:** Melting point of the drug was determined by capillary fusion method, taking a small amount of drug in a capillary tube closed at one end and was subjected to melting using melting point apparatus, and temperature at which hydrogels was noted.

iii. **Solubility studies:** The spontaneous interaction of two or more substance to form a homogeneous molecular dispersion is called as solubility. A semi quantitative determination of the solubility was made by adding solvent in small incremental amount to a test tube containing fixed quantity of solute or vice versa. After each addition, the system vigorously shaken and examined visually for any undisclosed solute particles. The solubility was expressed interns of ratio of solute and solvent. The approximate solubilities of substances are indicated by the descriptive terms in the accompanying table. Solubility profile of drug was carried out by using different solvents such as water, acetone, methanol, ethanol, DMSO, phosphate buffer pH7.4.

iv. FTIR [Fourier Transform Infra-Red Spectroscopy]:

FTIR is most powerful technique for qualitative identification of compound. Itgivestheinformationaboutthefunctionalgroupprese ntintheparticularcompound.ThemainapplicationofF TIR-spectrophotometeristhedetermination of the identity of a compound by means of spectral comparison with that of reference spectra and verification of the presence of functional group in an unknown molecule. The Infrared (IR) spectra were recorded using FTIR by the KBr pellet method and spectra were recorded in the waveleng the region between 4000 to 400 cm^{-1} scanning range and the observed spectrum was compared with reference FTIR. FTIR of Curcumin was determined by FTIR Instrument of Shimadzu, Tokyo, Japan using Micro Labsoftware. Spectrum of drug and polymers will be performed to checkany incompatibility present between drug and polymer. The spectra for Curcumin and physical mixtures of Curcumin with polymers were evaluated.

v. **Absorption maxima (λ_{max}):** An absorption maximum of curcumin was determined withPhosphate buffer pH 7.4 using UV spectroscopy. A 10µg/ml containing curcumin stocksolutionwaspreparedwithmethanolanditsa liquotsweretransferredtodifferentvolumetric flask in varying fractions to prepare standard solution. The spectrophotometricdetectionwascarriedoutbet weentheabsorptionmaximumof200nmto600nm usingmethanolassolvent.

vi. **Construction of calibration curve of Curcumin:**

The standard solution was prepared by dissolving 10 mg of Curcumin in 10 ml of phosphate buffer pH 7.4 and the volume was made up to 100 ml using phosphatebufferpH7.4.

From this standard solution, a series of dilutions containing 0.2, 0.4, 0.6, 0.8, 1,1.2 mlwere pipette out and subsequently diluted to10 ml with phosphate buffer pH 7.4 to give 2,4,6,8,10,12µg/ml respectively.

The absorbances of the dilutions were measured using UV spectrophotometer at421nmusingphosphate buffer pH 7.4asblanksolution.

Formulation of Curcumin Magnetic Microspheres:

Method of preparation of Curcumin Magnetic Microspheres:

Emulsionsolventdiffusionevaporationtechniquewas employedtopreparecurcuminloadedmagneticmicros phereswithdifferentnaturalpolymers.

Magnetic microspheres of curcumin containing albumin (1:1) were prepared as follows:

- Accurately weighed quantities of drug and albumin (1:1) were dissolved in Dichloromethane: methanol (1:1) as an internal phase (10ml).
- Thepolymericsolutionwasthenincorporatedwit hspecifiedamountofmagnetitewhichactsasprim aryingredientofmagneticmicrospheres.
- So formed magnetite polymeric solution (organic phase) was poured drop-wiseto polyvinyl alcohol (0.5%w/v) in water as an external phase volume (EPV100ml)with vigorous stirring over amechanical stirrer.
- Highstirringratesofapproximately4000rpmwer eemployedtoobtainmicrosphere of smaller size.
- Both phases initially forms a dilute emulsion and the resultant mixture was stirred constantly with a propeller type of agitator up to eight hours until complete volatile organic solvent (IPV) DCM and methanol gets evaporated.
- The emulsion breaks down to form tiny

microspheres which are subjected to set a side and allow settling down.

- There sulting microspheres were collected by filtration.
- Then, several washings with excess of distilled water and dried overnight at roomtemperature[51,52].
- In the similar manner, several batches of curcumin magnetic microspheres werepreparedbyvaryingdrug-polymerratioofvaryingratios(aspertable7), keeping all other formulation factors constant.

Table 2: Composition of Formulation

Formulation code	Drug (mg)	Polymer(mg)	Drug: Polymer ratio	Magnetite (mg)	IPV (ml)	PVA% W/V	EPV (ml)
AMMS1	200	Albumin(200)	1:1	50	10	0.5	100
AMMS2	200	Albumin(400)	1:2	50	10	0.5	100
CMMS1	200	Chitosan(200)	1:1	50	10	0.5	100
CMMS2	200	Chitosan(400)	1:2	50	10	0.5	100

Table 2: Composition of Formulation

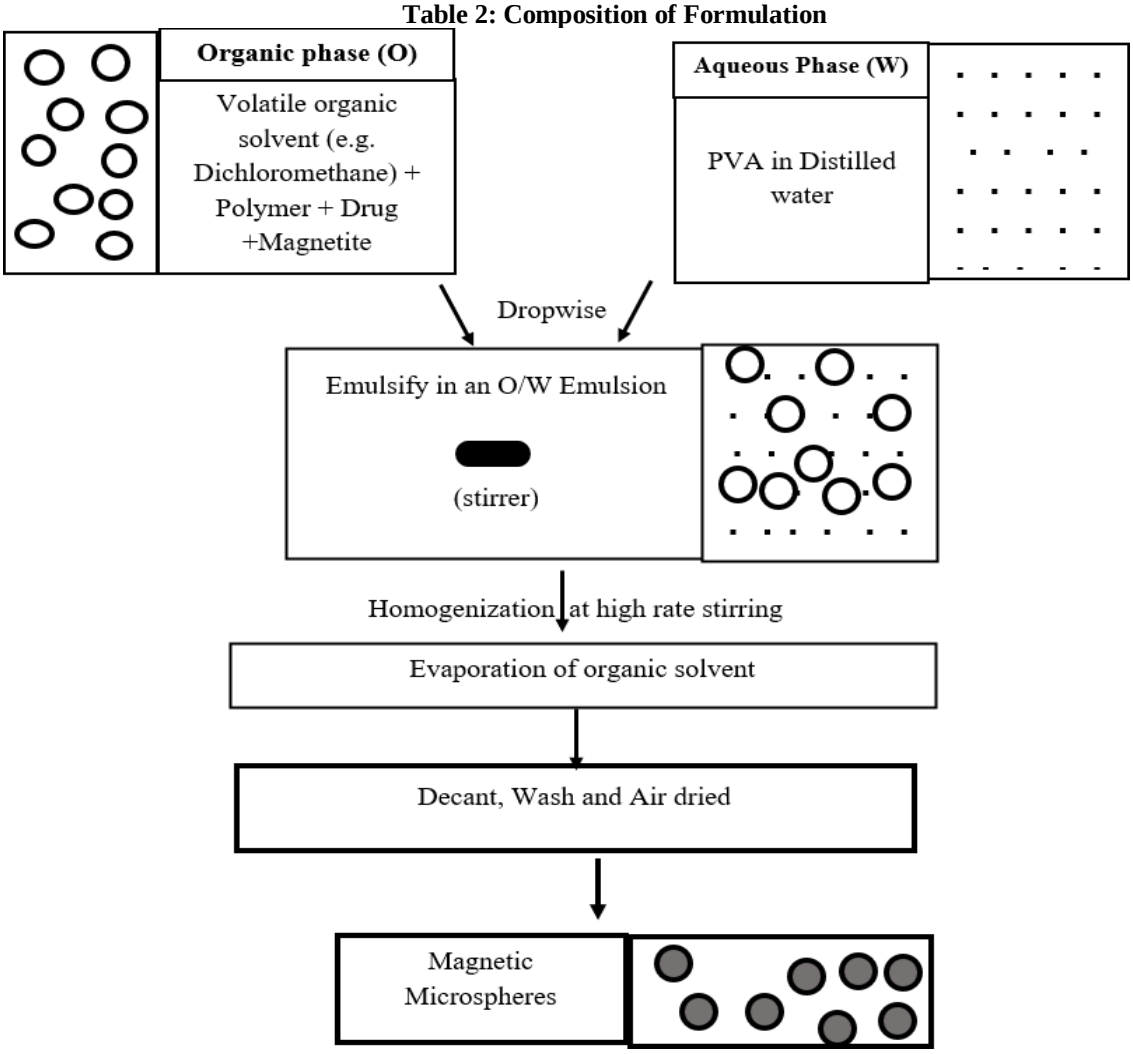

Figure 1:Schematic diagramofOil-in-Water(O/W)emulsionsolventevaporationdiffusionmethod for preparation of Magnetic Microspheres.

Evaluation of curcumin magnetic microspheres: [28-31]

Determination of percent yield of magnetic microspheres:

The percent yield (% PY) of prepared magnetic microspheres was calculated based on mass of curcumin and polymer (non-volatile excipients) added.

The actual weight of obtained microspheres divided by the sum of amount of all non-volatile material that was used for the preparation of the Microspheres multiplied by 100 gives the percentage yield of magnetic microspheres.

Determination of drug loading and entrapment efficiency:

100 mg of prepared magnetic microspheres were first crushed with the help of glass mortar pestle followed by dispersion in 100 ml of methanol and kept for overnight for the extraction of drug. The supernatant was shaken using mechanical shaker for few hours and using UV spectrophotometer, absorbance wasmeasuredat421nm.Afterthattheamountofcurcumininmicrosphereswascalculatedbycalibrationcurve.

Using following equation, drug loading (DL) and entrapment efficiency (% EE) were determined.

In-vitro Dissolution studies:

In-vitro release study of developed formulations was performed in USP dissolution- II (paddle type, Electro lab) in phosphate buffer pH7.4. The temperature was maintained at37 ± 0.5°Cand the rotation speed of 100rpm. At regular time intervals 5 ml of samples were withdrawn and replenished with equal amount of the fresh medium to maintain sink condition. The samples were analyzed by UV spectrophotometerat421nmanddetermine the amount of drug release.

RESULTSANDDISCUSSION:

The results and discussion are arranged in the order of the experimental methods performed.

Preformulation studies

Preformulation studies were done to deliver all obligatory data, like physiochemical properties and compatibility of drug and excipients

Physical properties (Organoleptic characteristic evaluation of curcumin): Color: Orange-yellow in color, which is crystalline powder in nature and gives brownish-red color with alkali; light-yellow color with acids.

Odor: Mildly aromatic

Taste: Pungent, Bitter

Melting point:

The melting point of Curcumin was determined by using Capillary fusion method. The observed melting value of the drug was found to be with the range of reference value. The results are as follows:

Apparatus	Observed Value	Reference value
Meltingpoint apparatus	181ºC	179-183ºC

Table3: Melting point of Curcumin

Solubility studies:

ThesolubilitystudiesofCurcuminwereperformedindifferentsolventsanditssolubilityprofile as follows:

S.NO	SOLVENT	SOLUBILITY
1.	Distilled water	Practically insoluble
2.	Acetone	FreelySoluble
3.	Methanol	FreelySoluble
4.	Chloroform	FreelySoluble
5.	DMSO	FreelySoluble
6.	pH7.4phosphatebuffer	SlightlySoluble

Table4: Solubility profile of curcumin in different solvents

Drug-polymer interaction studies by FTIR

Drug polymer compatibility studies were performed by FTIR (Fourier transform infrared spectroscopy). Literature survey indicates no significant interaction between Curcumin and other components of the experiment, eventhough it was cross verified by conducting drug to excipient interaction by using FT-IR analysis.

Drug-Excipients compatibility was carried out for drug, drug with magnetite, drug with albumin and drug with chitosan FTIR analysis.

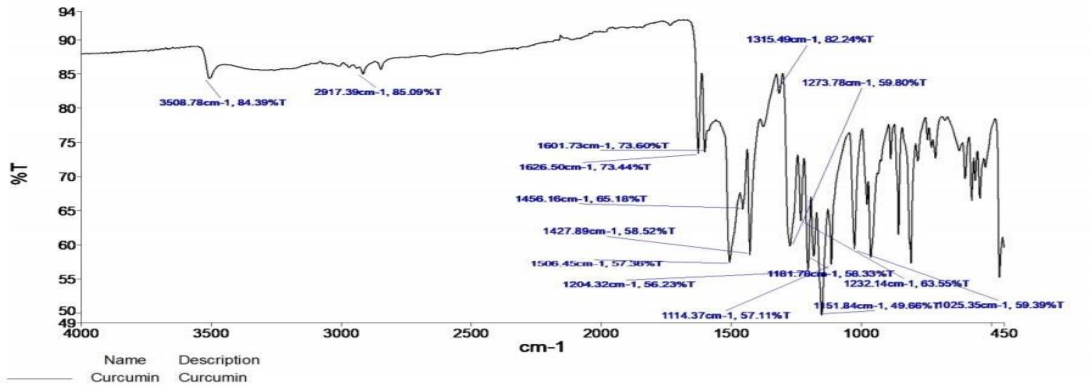

Figure 2: FTIR Spectra of pure drug (Curcumin)

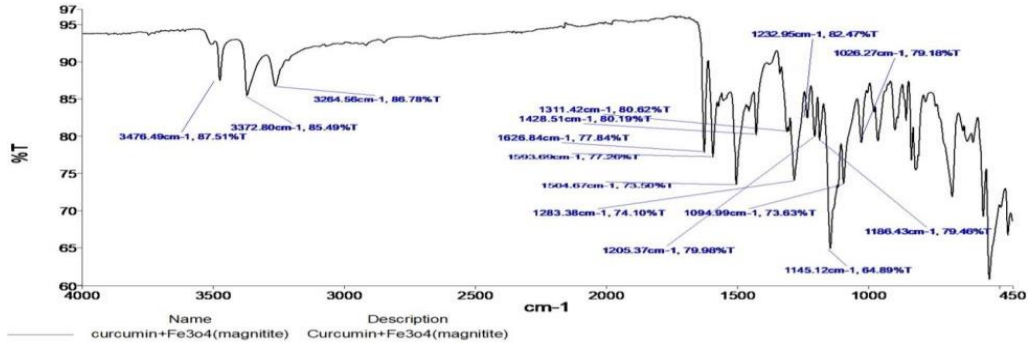

Figure3: FTIR Spectra of physical mixture of Curcumin and Magnetite (Fe3O4)

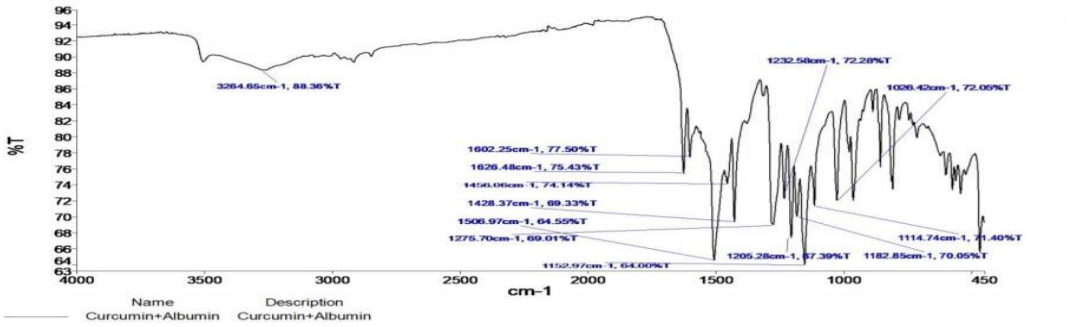

Figure4: FTIR Spectra of physical mixture of Curcumin and Albumin

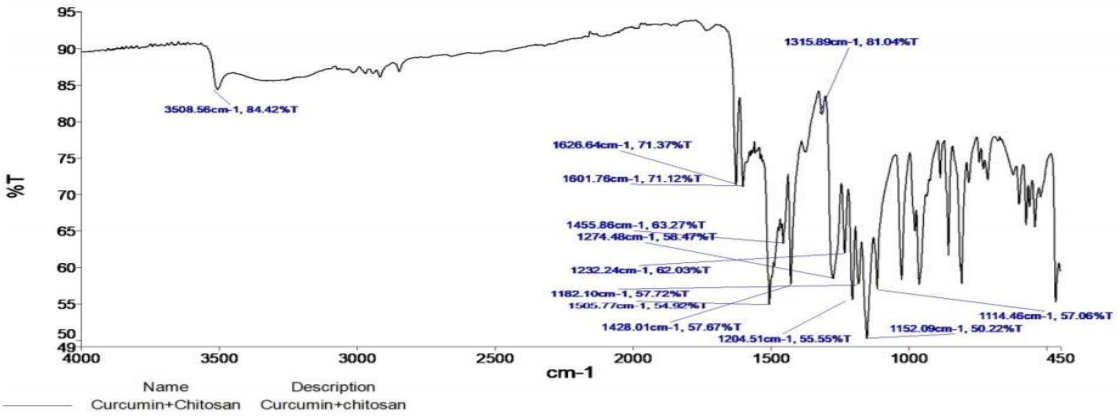

Figure 5: FTIR Spectra of physical mixture of Curcumin and Chitosan

The FTIR spectrum of pure drug was compared with the FTIR spectrum of various physical mixtures of drug and polymers shows no significant interaction between drug and polymers, which shows significant compatibility between the drug and the polymer.

Determination of absorption maxima (λmax):
Determination of absorption maxima **(λ max)** of curcumin was carried out by using pH 7.4 phosphate buffer as solvent and was found to be 421nm.

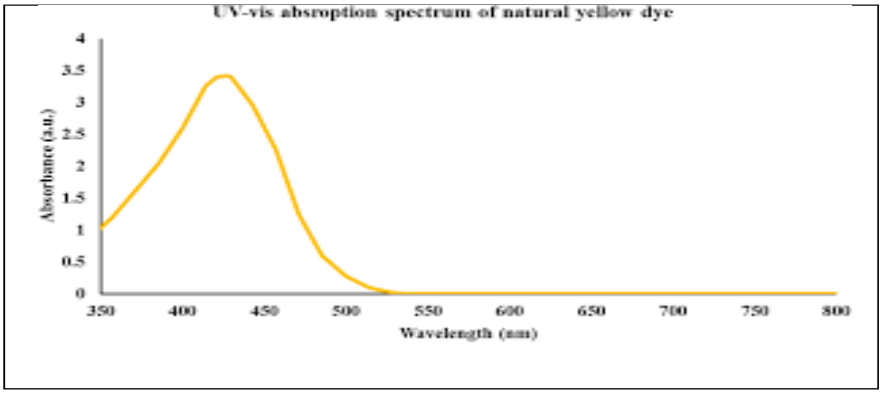

Figure6: Absorption maxima of curcumin

Construction of Calibration Curve of curcumin:
The absorbance was measuredbytaking2µg/ml,4µg/ml,6µg/ml,8µg/ml,10µg/mland12µg/ml,as the serial concentrations spectrometricallyat421nm.

Table5: Spectro photometric data for the estimation of Curcumin

S.No	Concentration(µg/ml)	Absorbance(nm)
1	0	0
2	2	0.153
3	4	0.312
4	6	0.473
5	8	0.631
6	10	0.789
7	12	0.942

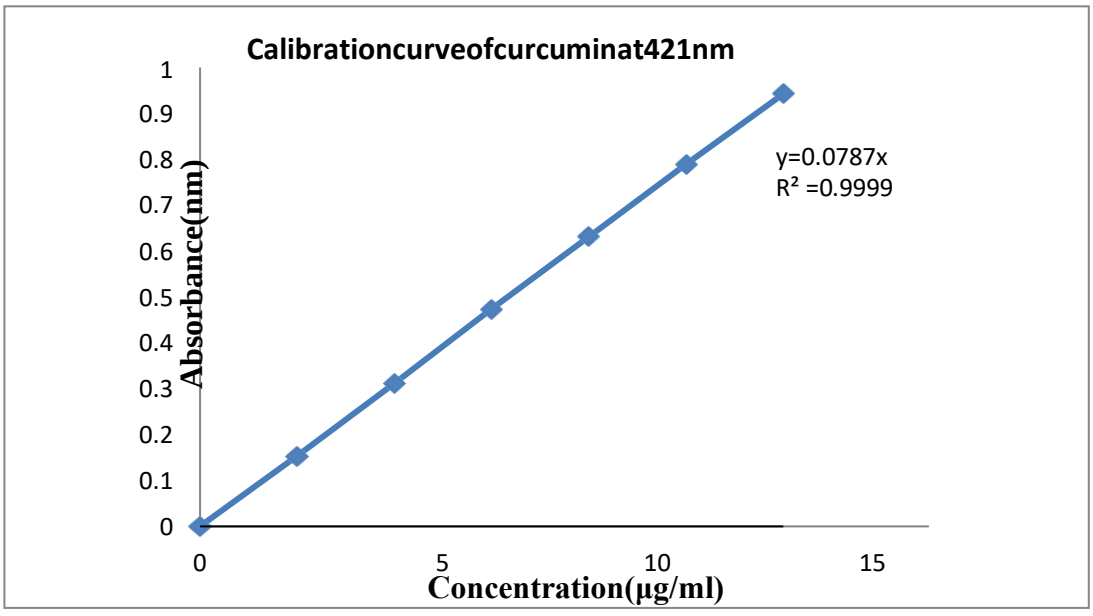

Figure 7: Calibration curve of Curcumin

Formulation of curcumin magnetic microspheres:

Curcumin magnetic microspheres were prepared by emulsion solvent diffusion evaporation technique using natural polymers such as albumin and chitosan individually in different ratios. Formulations containing higherproportionofpolymerstakeprolongedtimeforbreakingdownanemulsiontoformtinymicrospheresfromexterna lphase volume.

Figure8: Formulated Curcumin magnetic microspheres with Albumin

Figure 9: Formulated Curcumin magnetic microspheres with Chitosan

Thepreparednaturalpolymer-basedcurcuminmagneticspherewerefurthersubjectedcharacterization of percentage yield, drug content estimation, swelling index determination a and in vitro drug release(dissolution)studies.

Evaluation of curcumin magnetic microspheres:

Determination of percent yield of magnetic microspheres:

The percent yield (% PY) of prepared magnetic microspheres was calculated based on mass of curcumin and excipients) added and values ranges between 81.25 %and 85.43% as shownintable6

Determination of drug loading and entrapment efficiency:

Drugloadingandentrapmentefficiencyofpreparedmagneticmicrospheres was determined and values ranges between 21.60 % and 38.17, 71.69 and 81.27respectively, as shown in table 6.

Table 6: Evaluation parameters of curcumin magnetic microspheres

Determination of in-vitro swelling index:

Formulation code	Percentage yield	%Drug loading	%Entrapment efficiency	%Swelling index
AMMS1	82.36	38.17	71.69	82.56
AMMS2	81.25	26.02	79.23	91.40
CMMS1	83.64	21.60	75.45	79.74
CMMS2	85.43	24.41	81.27	88.50

Swellingpropertyofpreparedmagneticmicrospheres wasdeterminedandvalues ranges between 79.74 % and 91.40 as shown in table 6. studies indicated increase in swelling index with increase in concentration of polymers due to more uptake phosphate buffer(pH7.4) by polymers.

In-vitro dissolution studies:

The in vitro drug release profile performed using phosphate buffer (pH 7.4) solution to evaluate drug release (sustained release). The *in vitro* performance of curcumin magnetic microspheres showed prolonged and sustained release of Curcumin over 12 hours. It was observed that different magnetic spheres containing different ratios of polymers (albumin, chitosan) showed drug release 77.43 % to 93.56% within 12 hrs. The results of the *in vitro* dissolution studies of various formulations (AMMS1 to CMMS2) are shown in Table12 and Fig. 23. The formulation containing chitosan of lower concentration showed a maximum drug release of 93.56% and formulation containing albumin of higher concentration showed a minimum of 77.43 % cumulative drug release. The study indicated that the amount of drug release decreases with an increase in the polymer concentration. It reveals that polymer concentration prominent factor responsible for the release of drug. The optimized formulation AMMS2 showed diffusion controlled sustained drug release mechanism.

Table 7: In vitro cumulative % drug release of curcumin magnetic microspheres (AMMS1TOCMMS2)

Time (hrs)	FORMULATIONCODE			
	AMMS1	AMMS2	CMMS1	CMMS2
0	**0**	**0**	**0**	**0**
1	**8.12**	**6.24**	**11.87**	**9.14**
2	**18.34**	**12.32**	**21.03**	**15.47**
3	**26.42**	**13.24**	**28.17**	**21.35**
4	**36.25**	**17.84**	**38.02**	**32.41**
5	**43.74**	**27.85**	**45.65**	**41.25**
6	**49.35**	**36.74**	**52.24**	**46.62**
8	**61.24**	**39.81**	**65.45**	**52.54**
10	**65.32**	**48.24**	**72.14**	**55.32**
11	**78.97**	**65.47**	**83.32**	**68.53**
12	**88.23**	**77.43**	**93.56**	**82.34**

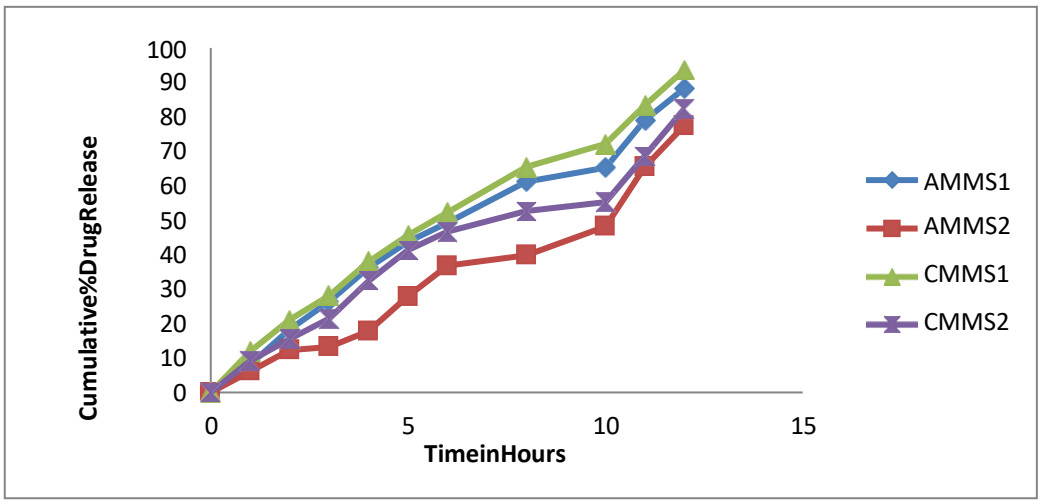

Figure 23: Plot of Cumulative % drug release of curcumin magnetic microspheres (AMMS1TOCMMS2)

Thereleaseofthedrugfromits**curcuminmagneticmicrospheres**formulations can be ranked in the following descending order:

CMMS1>AMMS1>CMMS2>AMMS2

CONCLUSION:

In the early days of the 20th century, Paul Ehrlich envisioned his magic bullet concept-the idea that drugs reach the right site in the body, at the right time, at right concentration. Magnetically triggered microspheres attract considerable attention of researchers due to their enhanced efficacy along with reduced side effects due to targeted release properties. A part from these, the regular objective of targeted controlled drug delivery is aptly achieved with magnetic microspheres.

The present thesis entitled "Formulation and Evaluation of Natural Polymer Based Curcumin Magnetic Microspheres", describes the formulation and evaluation of natural drug (Curcumin) and polymers (Albumin & Chitosan) based magnetic microspheres. The formulations were prepared by using emulsion solvent diffusion evaporation technique.

The FT-IRstudiesshowedsignificantcompatibilitybetweenthedrugandthepolymer.Evaluationstudiesofswellingindicateanincreaseinswellingindexwithincreaseinconcentration of polymers due to more uptake of solvent. The in vitro studies indicated that the rate of Curcumin release from magnetic microsphere decreased with increase in the amount of polymer. The study results proved that curcumin magnetic microspheres can be used for controlled drug delivery due to sustained drug release characteristic of polymers that used. The optimized formulation AMMS2 showed diffusion controlled sustained drug release mechanism and therefore can have benefits such as reduction in total dose and frequency of administration. In future, magnetic studies and in-vivo studies are essential to prove the site-specific delivery and magnetic targeting effect of microsphere.

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