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Development and Evaluation of Hydrophilic Polymer- Integrated Curcuminoid Nanoparticles for Improved Dissolution Rates

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ABSTRACT:
Curcuminoid a natural polyphenol possess anticancer activity but its poor water solubility and degradation of this drug in alkaline medium restricts its application as anticancer drug. The invincible effect of drug can be achieved by reducing the size of drug particles. Fabrication of the drug particles to its corresponding nanoparticles can be one of the best solutions to reveal the excellent properties of drug. Herewith we are reporting the fabrication of curcuminoid nanoparticles and its complex with polymer (PVP) via Evaporative Precipitation of Nanosuspension (EPN) method. Characterization of these drug nanoparticles and its complex with biocompatible polymer PVP have been done by advance characterizing techniques such as FT-IR, , Transmission electron microscopy (TEM), Differential scanning calorimetric (DSC) and dissolution testing followed by UV-Visible spectroscopy. Results of these characterizations have revealed that synthesized nano curcuminoid particles have shown potent dissolution rate and on complexation with PVP crystallinity of drug decrease with tremendous decrease in particle size as much improved dissolution rate and can further be exploited for the anticancer action of the drug.

I. INTRODUCTION:

An extract of curcuma longa, curcuminoid consist of curcumin, demethoxy curcumin and bis-demethoxy curcumin, in which curcumin is an important component which shows physiological properties. The drug curcumin shows antitumor[1,2], anticarcinogenic[3], antioxidant[4.5], antibacterial[6], antiviral[7], anticoagulant[8] etc. properties. It can be consumed 12g/day without any adverse effect [9,10]. As the therapeutic properties, its obscure solubility in aqueous medium and low bioavailability, besides of its safety doesn't make it useful for pharmaceutical applications [11]. Formation of nanoparticles along with dispersion of drug in hydrophilic polymer is a neoteric approach to mend solubility and bioavailability of drug. Top-down and bottom-up are the two approaches to produce nanoparticles. In the first method larger particles are mechanically breakdown into smaller particles whereas in next method we can get nanoparticles from molecular level. High pressure homogenization, wet and jet milling are spaciously used top-down method. Evaporation of solvent, spray drying and precipitation are some generic approaches for bottom-up method [12, 13,14]. Evaporative precipitation of nanosuspension made by adding antisolvent to a true solution of drug is also used as a bottom-up approach [15, 16].

In this method various parameters are responsible for drug size such as formation of supersaturated solution; nucleation and growth after addition of solution to antisolvent determine particle size. Supersaturation drive an external force for precipitation of solute in solution [17, 18].

Where supersaturation is define as

$$S = \frac{Co}{C^*}$$

Where S denotes super saturation, C_0 concentration of solute in solvent and C* solubility of solute in final system (mixture of solvent and antisolvent). For smaller particle size, fast nucleation is required which is achieved by higher value of supersaturation and lower value of surface tension and is related to Gibbs free energy ΔG =

$$\frac{16\pi y\, V2}{3(Kt)2(\ln(l+s))2}$$

Where, γ denotes surface tension and V molecular volume. Further ΔG is related to speed of nucleation R_N as RN= $C0kT/3\pi\lambda 3\eta \exp(\Delta G/k)$

All above three equations clearly indicate that higher concentration of solute in solvent (C0) leads to high value of supersaturation result in lower Gibbs free energy and thus fast rate of

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nucleation leads to lower particle size. Smaller particle size tends to higher surface area. According to Noyes-Witneny's conclusion, dissolution rate of any substance is related to its surface area.

$$\frac{dc}{dt} = \frac{DA(Cs-Cx)}{h}$$

Where dc/dt denotes dissolution velocity, A denotes surface area, D denotes diffusion coefficient and (cs-cx)/h denotes concentration gradient here cs, cx, h are saturation solubility, bulk concentration and diffusional distance respectively. This equation shows that there is inflation in dissolution rate on expanding the surface area. Thus by reducing the size of curcuminoid particles, dissolution rate and hence bioavailability of drug can be improved enormously. Along with reduction of size complexation of hydrophilic polymer as PVP can further improve dissolution rate of drug [19]. In our work, fabrication of pure drug nanoparticles and its complex with PVP was done by evaporation of nano suspension made by adding solution of drug/polymer to antisolvent. Dissolution studies were performed to find effect of polymer on drug as well as drug to polymer ratio on dissolution rate.

II. MATERIAL

Curcuminoid (95%) was purchased from Polymer Research Lab, Corporate R & D Centre. Hexane was purchased from Avantor Performance Materials India Limited; ethanol was obtained from Chongshu Hongsheng Fine Chemical Co. Ltd. Methanol purchased from Loba Chemie Pvt. Ltd., acetone purchased from Finar Limited. All chemicals were of chemical grade.

III. METHOD

Curcuminoid nanoparticles and its complexes with polyvinyl pyrrolidone (PVP) were formed by making nanosuspension followed by evaporative precipitation. Pure drug was dissolved in solvent (Methanol, Ethanol and Acetone) in various drug to solvent ratio and then quickly added to antisolvent (Water) where solvent to antisolvent ratio vary in different samples. (Table 1) To form complexes of drug with polymer, different drug to polymer composition in different ratios (table 2) were mixed with common solvent (ethanol) and then added to common antisolvent (Hexane). The suspensions thus formed were quickly heated upto boiling point. The obtained dry powder was collected for further investigation. Dissolution enhancement of quercetin through nanofabrication, complexation, and solid dispersion.

Table 1: Different batches of Samples prepared with various solvents at different drug concentration and different solvent to antisolvent ratios.

Sample no	Sample Name	Solvent: Antisolvent	Drug Concentration (mg/ml)	Solvent	Antisolvent
1	C 1N	1:20	10	Methanol	Water
2	C 2N	1:20	15	Methanol	Water
3	C 3N	1:20	5	Methanol	Water
4	C 4N	1:10	10	Methanol	Water
5	C 5N	1:15	10	Methanol	Water
6	C 6N	1:20	10	Acetone	Water
7	C 7N	1:20	15	Acetone	Water
8	C 8N	1:20	5	Acetone	Water
9	C 9N	1:10	10	Acetone	Water
10	C 10N	1:15	10	Acetone	Water
11	C 1E	1:20	10	Ethanol	Water
12	C 2E	1:20	15	Ethanol	Water
13	C 3E	1:20	5	Ethanol	Water
14	C 4E	1:10	10	Ethanol	Water
15	C 5E	1:15	10	Ethanol	Water

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Table: 2 Different batches of Samples prepared with various drug concentration and different drug to polymer ratios

Sample.no	Sample Name	Solvent: Antisolvent	Drug Concentration (mg/ml)	Drug: Polymer	Drug + Polymer Conc. (mg/ml)	Solvent	Anti Solvent
16	C 22N	1:20	5	1:1	10	Ethanol	Hexane
17	C 23N	1:20	3.33	1:2	10	Ethanol	Hexane
18	C 24N	1:20	5	1:2	15	Ethanol	Hexane
19	C 25N	1:20	5	1:3	20	Ethanol	Hexane

CHARACTERIZATION:

Characterization of synthesized curcuminoid particles were done by using various techniques. Surface morphology of curcuminoid particles and their complex with polymer was done by using Transmission electron microscopy (TEM). Differential Scanning Calorimetric (DSC) for thermal properties (melting point and heat of fusion) interaction between curcuminoid and polymer was determined by using FT-IR and UV was done for dissolution test.

Transmission electron microscopy

TEM for surface morphology was carried out by JEOL (JEM 2100) Japan.

Differential Scanning Calorimetric

Thermal analysis was done by Perkin Elmer's Differential Scanning Calorimetric (DSC 4000). The analysis was done between 300 C to 2200C with the rate of 100C per minute with gas flow 19.8 ml in nitrogen atmosphere. To calculate heat of fusion and melting point instrument software was used.

FT-IR

The fourier transform infrared spectroscopy (FT-IR) was carried out by Agilent Technologies, Carry 630 FTIR to explore interaction between drug and polymer.

Dissolution Test

Fabricated drug particles were weighed 20mg and then dissolved in 100ml of 0.1N HCl reference 23. Set up was adjusted at approx 37 degree Celsius with constant stirring of 100 RPM. 5ml of samples were collected at time intervals 15min, 30min, 1hour, 2hours, 3hours with simultaneously addition of dissolution medium. All collected samples were investigated under UV-Visible spectroscopy to find its absorbance at 422 nm.

IV. RESULT AND DISCUSSION:

Particle Morphology

TEM images help to evaluate average particle size of pure curcuminoid, curcuminoid nanoparticles and curcuminoid- polymer (PVP) complex are shown in figure 1 (a), (b), (c). It was found that there is lack of uniform size and distribution of the original curcuminoid particles. TEM image of curcuminoid particles fabricated by taking acetone as solvent and water as antisolvent (C 8N system) it was found that size of particles were reduced upto the range 170 nm to 420 nm with an average size of 230 nm. On analyzing TEM image of curcuminoid PVP complex we found here tremendous drop in particles size. Smallest particles size was about 25 nm to average particles size about 60 nm. From figure it is clearly shown that curcuminoid is totally encapsulated in polymer bed. DSC data also supported this result.

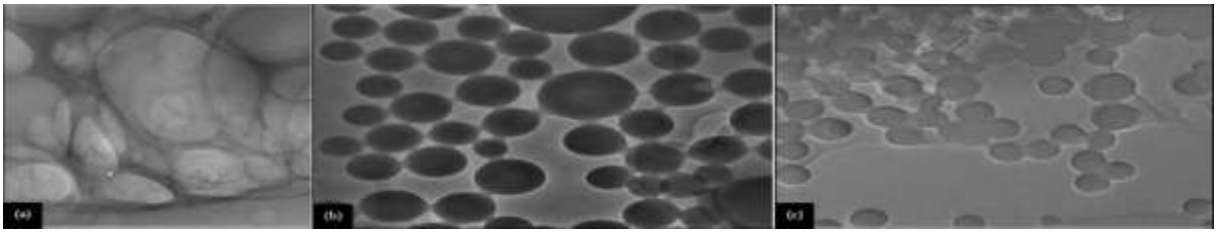

Figure.1 (a) TEM image of Crude Curcuminoid
Figure.1 (b) TEM image of Crude Curcuminoid Nanoparticles
Figure.1 (c) TEM image of Crude Curcuminoid-Polyvinyl Pyrrolidone complex

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DSC

To study thermal behavior of curcuminoid nanoparticles DSC was done. Raw curcuminoid showed a sharp peak at 173.28^{o}C expressing its melting endotherm. On changing solvents and various combinations of drug concentration and solvent to anti solvent ratio melting endotherm varied from 155.88^{o}C to 173.86^{o}C. With different formulations it was found that heat of fusion decreased than raw drug, which indicated that crystallinity of drug was decreased. As PVP absorbs atmospheric water, pure PVP showed a broad peak between 25oC to 125^{o}C. Solid dispersion of curcuminoid and PVP did not show any peak at about 173oC indicated complete encapsulation of drug in polymer bed. And thus curcuminoid particles adopted amorphous behavior of PVP.

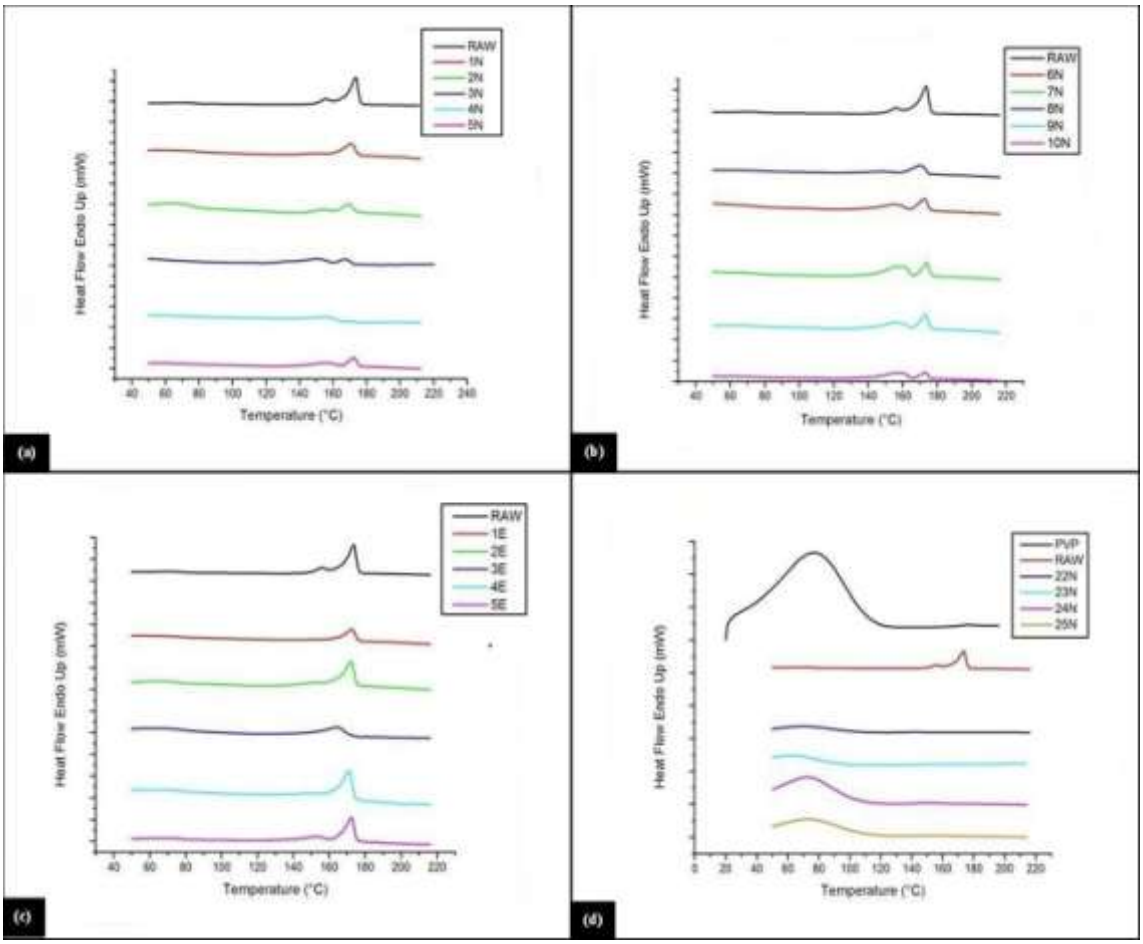

Figure.2 (a) DSC graph of Curcuminoid nanoparticles using methanol as a solvent Figure.2 (b) DSC graph of Curcuminoid nanoparticles using acetone as a solvent Figure.2 (c) DSC graph of Curcuminoid nanoparticles using ethanol as a solvent Figure.2 (d) DSC graph of Curcuminoid-Polyvinyl pyrolidone complex

FT-IR:

FT-IR graph of raw drug showed a peak at 3510 cm-1 due to –OH stretching of curcuminoid. In the FT-IR spectrum of PVP a broad peak at 3410 cm-1 was found due to absorption of water molecule by PVP which was also confirmed by DSC result of it. In the resultant dispersion of curcuminoid into PVP showed complete absence of –OH peak of curcuminoid which indicates the interaction of –OH group of curcuminoid with PVP which further confirmed by shifting of C=O peak of PVP from 1660 cm^{-1} to 1640 cm^{-1}. This shifting clearly reveals interaction of PVP with curcuminoid through hydrogen bonding.

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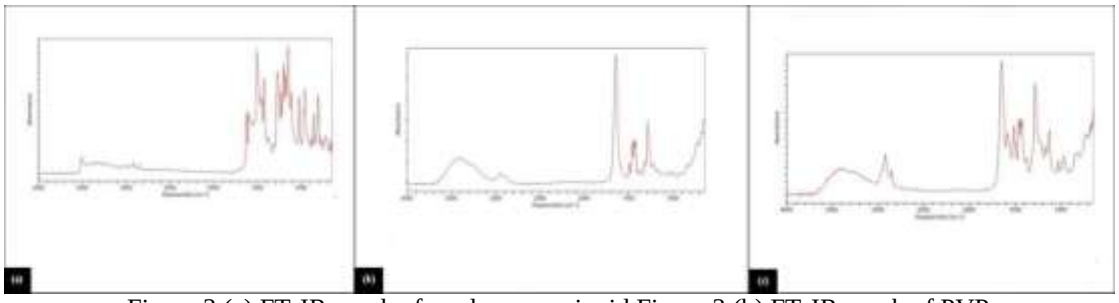

Figure.3 (a) FT-IR graph of crude curcuminoid Figure.3 (b) FT-IR graph of PVP
Figure.3 (c) FT-IR graph of curcuminoid-PVP complex

Dissolution test

The dissolution test was done for selected samples, results for raw curcuminoid, its fabricated nanoparticles and its complex with PVP is shown in figure (4). The dissolution of raw drug is insignificant in comparison to curcuminoid nano particles as well as curcuminoid- PVP complex. Dissolution percent of crude curcuminoid was reached upto 8.2%, pure nano curcuminoid upto 52% and that of curcuminoid-PVP complex was upto 92% within 4 hour figure (4)[20,21]. On increasing the PVP to curcuminoid ratio it was observed that dissolution of curcuminoid also get modify as shown in figure (5). Pure nano curcuminoid manifest approx six fold dissolution in four hour, in comparison to raw curcuminoid. Whereas curcuminoid-PVP complex display tremendous dissolution (61%) within 15 minutes. As already mentioned fast supersaturation required higher concentration of solute to solvent. As the amount of curcuminoid and polymer increase dissolution rate increases, here it is noticeable that only solute to solvent ratio is not the only factor along with this with same solute to solvent ratio, lower drug polymer ratio also affect dissolution rate. From Noyes- Witney conclusion it was established that dissolution rate is directly related to surface area of particles. Smaller the size of particles more would be the surface area and higher will be dissolution rate. TEM results also revealed that size of pure curcuminoid nano particles reached upto 175 nm and that of in curcuminoid-PVP complex size of particles reduced upto 25 nm. Thus there was a significant upgradation in dissolution as particles size decrease. Amorphous nature of curcuminoid which is clear from DSC also enhance dissolution efficiency.

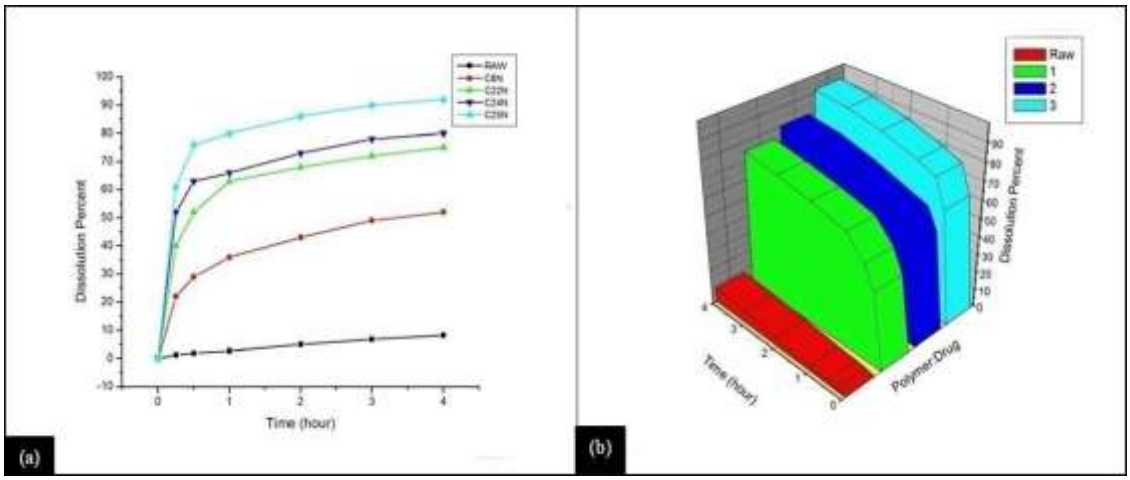

Figure.4 (a) Dissolution profile of crude curcuminoid, pure curcuminoid nanoparticles and its complexation with PVP
Figure.4 (b) 3D dissolution profile with different drug to polymer ratios

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V. CONCLUSION:

Here we resume curcuminoid nanoparticles which are formed by evaporation of nanosuspension in pure and curcuminoid-polymer (PVP) complex that are in high dissolution rate. The dissolution rate shown by PVP-curcuminoid complex is much dignify than that of pure curcuminoid nanoparticles which is directly related to size of curcuminoid as proved by TEM results, smaller the size more is the dissolution rate and DSC reflects the conclusion for the crystalline and amorphous nature of curcuminoid which shows markedly decrease in the heat of fusion that is indication of amorphous behavior for nano drug particles and the crystalline behavior of curcuminoid in curcuminoid-PVP complex is totally extinguished by encapsulating in PVP further interaction between curcuminoid and PVP was confirmed by FT-IR. It was found that there is hydrogen bonding between curcuminoid and PVP. Thus low particle size and high dissolution rate of curcuminoid can make it useful for pharmaceutical applications.

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