J. Indian Chem. Soc.,
Vol. 96, January 2019, pp. 14-18

# Penetration enhancer accelerated solubilization of curcumin by poly(vinylpyrrolidone)

**Anjitha Satheesh[a], Sreedevi Paramparambath[a], Elango Kandasamy[a]* and Susithra Selvam[b]***

[a]Department of Sciences, Amrita Vishwa Vidyapeetham, Coimbatore-641 112, Tamilnadu, India

*E-mail:* k_elango@cb.amrita.edu *Fax:* 91-422-2656274

[b]Department of Chemistry, PSG Institute of Technology, Peelamedu, Coimbatore-641 004, Tamilnadu, India

*E-mail:* susithra.selvam@yahoo.com *Fax:* 91-422- 2592277

*Manuscript received online 28 August 2018, accepted 09 October 2018*

Curcumin (CUR), a well-known Indian cooking ingredient is now an established pharmaceutical agent. The medicinal qualities of CUR vary from being a simple anti-inflammatory agent to anti-cancer and anti-HIV agent. Recently, CUR is also tried as a photosensitizer in photodynamic therapy for the treatment of cancer. For the effective administration of a PS molecule, transdermal route of drug administration has profound advantage and to have a better penetration of the drug molecule, it is possible to use a penetration enhancer. CUR is fluorescent in nature and owing to its hydrophobicity, dissolution studies with various drug delivery systems are carried out using fluorescence spectroscopic techniques. The solubilization of CUR is achieved by using poly(vinylpyrrolidone) (PVP) as the drug delivery media. To accelerate the solubilization and transdermal penetration, myristic acid (MA), a fatty acid is used as a penetration enhancer. The pre-formulation studies of ternary system of CUR-PVP-MA show that it is a feasible system.

Keywords: Curcumin, poly(vinylpyrrolidone), myristic acid, penetration enhancer.

## Introduction

Among the various routes of drug administration, the transdermal route has been both beneficial and potential in cancer therapy, especially photodynamic therapy (PDT). In PDT, the drug used is termed as photosensitizer (PS) and these molecules are fluorescent in nature[1,2]. Most of the PSs are bulky, hydrophobic and poorly water soluble. Numerous research works has been carried out to identify ideal PS and scientist have tried a variety of formulation techniques for the better administration of PS[1,2]. In the current work, curcumin (CUR), which is the major constituent of turmeric, imparting bright yellow colour is used as a model PS system. CUR is widely studied by various researchers for its medicinal properties[3–6]. Studies indicate that CUR can be used in variety of diseases such as Alzheimer, AIDS and cancer. Although studies on CUR reveal their anti-cancer property, there are few instances where it has been used as a PS in PDT and PDD. CUR is a fluorescent molecule and literature indicates its usage as fluorophore to understand biological systems.

For the solubilization of CUR, poly(vinylpyrrolidone) (PVP) is chosen as the polymer. It is used extensively in pharmaceutical technology as a drug carrier and mostly used for solid dispersion preparations. PVP has strong hydrophilicity, through which molecular adducts with many compounds can be formed. The presence of carboxyl group in the repeat unit of the polymer tends to increase the water solubility and stability of drug and also PVP can improve the bioavailability of drug[7]. PVP K12 to K30 (MW 2500–50000) has been widely used for solid dispersions. It is an amorphous polymer and possesses high glass transition temperature ($T_g$) due to the presence of the rigid pyrrolidone moiety.

The fatty acid, myristic acid (MA) is a unique penetration enhancer for transdermal administration of a particular drug[8]. MA is used here to enhance the transdermal delivery of CUR.

In the first step of present work, a pre-formulation study of CUR is to be presented with the polymer PVP K25 as the drug delivery system. In the second step, ternary systems were prepared by adding, MA to the previously prepared CUR-PVP system. Since CUR is fluorescent in nature, the photophysical properties of CUR are used as indicative parameters of the solubilization of CUR.

## Experimental

*Materials:*

CUR is obtained from Lobachemie, India. PVP K25 is purchased from BASF, Germany. Analytical grade ethanol is obtained from Merck, USA. The stock solutions of CUR for the homogeneous media study are prepared by dissolving it in ethanol. The polymer samples are prepared by dissolving them in water. Triply distilled water is used in all the experiments.

*Measurements:*

The fluorescence spectra are measured using Horiba Jobin Yvon Fluoromax-4 spectrofluorometer. The excitation and emission slits are set to a bandwidth of 5 nm. For steady-state fluorescence anisotropy measurements polacoat grating polarisers and Glan-Thompson polarisers are used. The steady state fluorescence anisotropy is defined as[9],

$$r_{ss} = \frac{I_{VV} - GI_{VH}}{I_{VV} + 2GI_{VH}}$$

where, $I_{VV}$ and $I_{VH}$ are the fluorescence intensities and the subscript indicates the vertical (*V*) and horizontal (*H*) orientations of the excitation and emission polarizer. *G* is the instrumental correction factor,

$$G = I_{HV} / I_{HH}$$

*Preparation of CUR-PVP solutions:*

CUR is first dissolved in ethanol and further diluted with PVP K25 solutions to prepare the test sample solutions. In these solutions, the final CUR concentration is maintained constant at 10 μM. Varying PVP K25 concentrations are prepared by appropriate addition of PVP solution and the ethanol contamination is kept at 2%. The range of concentration used for both the PVP solution is from 0% to 1.0%.

*Preparation of CUR-PVP-MA solutions:*

CUR–PVP K25 solutions are prepared as stated earlier. Stock solutions of MA are prepared by dissolving MA in ethanol initially and then diluted with water. Varying concentrations of MA are added to the pre-formed CUR-PVP K25 system.

## Results and discussion

*Interaction between curcumin and PVP K25:*

Fig. 1 shows the fluorescence emission spectra of CUR with PVP K25 ($\lambda_{ex}$ @ 430 nm). The figure shows a gradual increase in the fluorescence intensity of CUR with increasing composition of PVP K25, along with a minimal blue shift in the emission wavelength. $\lambda_{ex}$ of CUR in homogeneous medium is obtained at 430 nm and emission peak at 590 nm. When CUR is added with the polymeric environment (i.e. PVP K25), emission spectra of CUR suffers a hypsochromic shift to 540 nm, collaborating with the emission peak of CUR in polar aprotic solvents like dimethyl sulphoxide (DMSO) and dimethyl formamide (DMF)[3–6]. The data obtained indicates a probable association of CUR with PVP K25 and a solubilization of CUR by PVP K25 is observed from the increase in fluorescence intensity. Steady state fluorescence anisotropy ($r_{ss}$) measurements were carried out for the samples and it is observed that there is a gradual increase in the $r_{ss}$ values with increasing composition of PVP K25 from 0.30 to 0.35. The higher value of CUR in the absence of PVP is indicative of CUR experiencing a restricted molecular rotation around its environment within polymer, due to its rod-like structure CUR, similar to other molecular probes

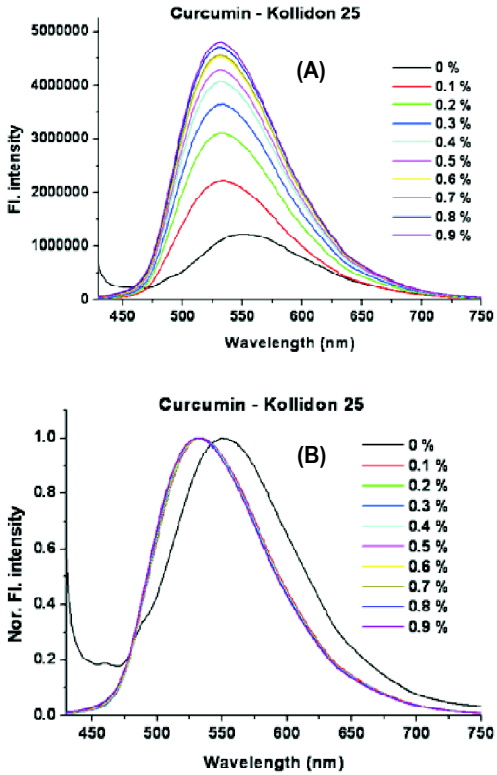


**Fig. 1.** (A) Emission spectra and (B) normalized emission spectra of CUR ($\lambda_{ex}$ 430 nm, $\lambda_{em}$ 590 nm) at different concentrations of PVP K25. T = 25°C.

such as diphenyl-1,6-hexatriene (DPH). Fluorescence anisotropy measurements of curcuminoid-loaded solid lipid nanoparticles also show a decreased mobility of curcuminoids within the nanoparticles[10].

This is further verified with the analysis of fluorescence intensity and emission wavelength along with $r_{ss}$ against the concentration of PVP K25 (Fig. 2). At a concentration of about 0.5% w/v of PVP K25, the fluorescence intensity and fluorescence anisotropy values attain a saturation level, indicating the complete solubilization of CUR in PVP K25. In the neutral form, CUR is found to be undergo tautomerism and available as an *enol*, which increases the rigidity of the molecule. This observation in collaboration with the fluorescence multi-parametric data obtained here shows a possibility of CUR associating with the hydrophobic moiety of the polymer.

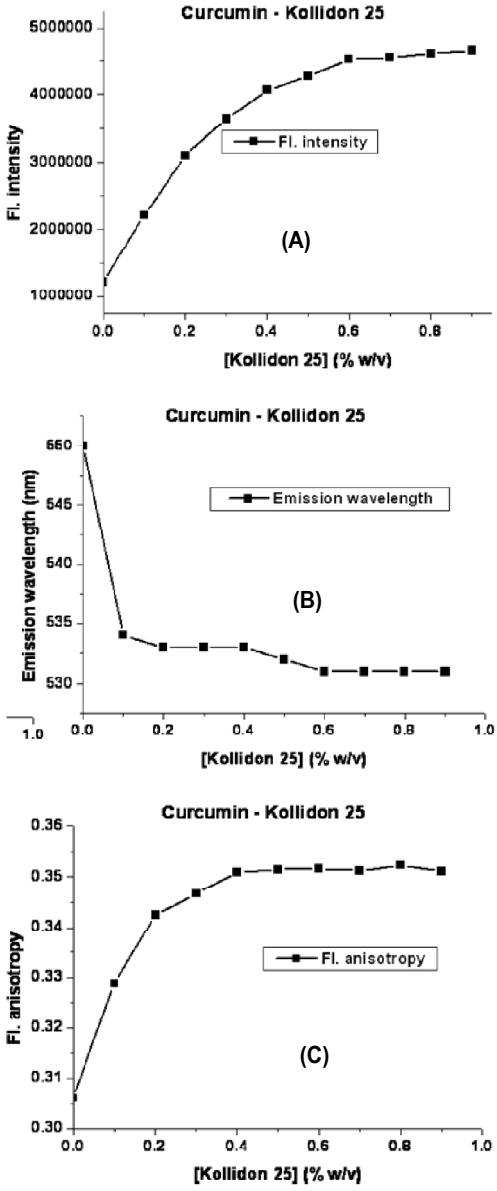


**Fig. 2.** Plot of variation of (A) fluorescence intensity, (B) emission wavelength and (C) fluorescence anisotropy of CUR-PVP K25. T = 25°C.

PVP molecules being a versatile pharmaceutical excipients, have been used in many drug formulations including the formualtion of PSs[1]. CUR already has been explored for its photosensitizing property to be used in PDD and PDT in the detection and treatment of cancer.

Since the best route of administration for a PS drug molecule is by topical administration, the study is extended to analyse the influence of a penetration enhancer on the CUR-PVP K25 system. Myristic acid, a fatty acid is chosen as the penetration enhancer[8,11].

Permeation studies on CUR-loaded myristic acid microemulsions have been carried out earlier and the proposed microemulsions were found to be effective in the topical delivery of CUR[11].

*Association of CUR-PVP system with MA:*

Fig. 3 illustrates the fluorescence data changes when MA is added to the pre-formed CUR-PVP K25 system.

Fluroscence intensity of CUR increases slightly with small shift in emission wavelength with the addition of MA. Formation of ternary system of CUR-PVP K25-MA is observed[12,13]. A possible association of CUR is suggested by two modes of interaction, i.e. (i) CUR is incorporated into the hydrophobic pockets of PVP K25 polymer, which in-turn is associates with

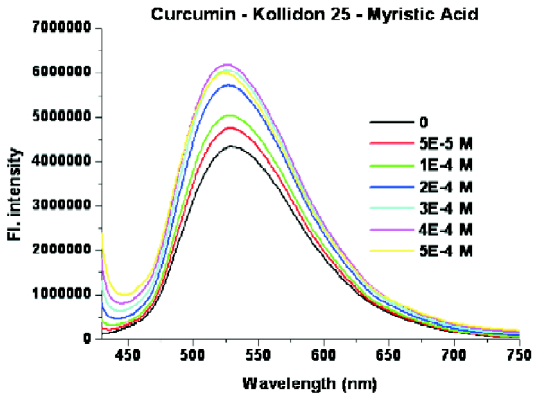


**Fig. 3.** Emission spectra of CUR-PVP K25 at different concentrations of MA. T = 25°C.

the fatty acid, MA. (ii) The molecular complex of CUR-PVP K25 intercalates with the alkyl chains of fatty acid, MA. Further to analyse the mode of association, fluorescence anisotropy measurement of CUR-PVP K25-MA system is carried out. CUR-PVP K25 system suffers a decrease in fluorescence anisotropy with increase in the concentration of MA (Fig. 4).

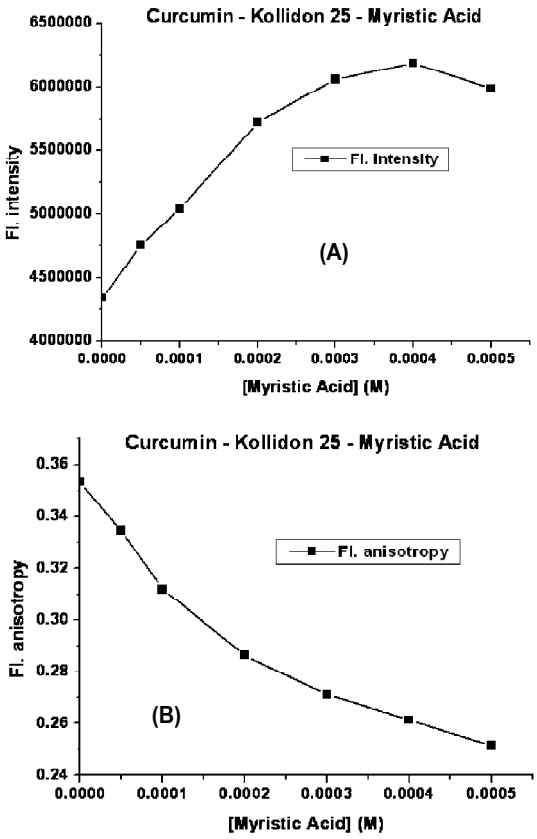


**Fig. 4.** Plot of variation of (A) fluorescence intensity and (B) fluorescence anisotropy of CUR-PVP K25-MA. T = 25°C.

The trend in fluorescence anisotropy follows the assertion that there is a certain interaction of PVP K25 with MA and the CUR-PVP K25 system is slightly disturbed. This leads to that CUR exhibits a better freedom of rotation, increasing fluidity of the environment, surrounding CUR-PVP K25 and thereby a decrease in fluorescence anisotropy is observed. A schematic representation of formation and probable association of CUR-PVP K25-MA is depicted in Fig. 5.

Thus the present study details the interaction of CUR with PVP K25 and pre-formed CUR-PVP K25 with MA. The fluorescence parameters evaluated here, indicate a hydrophobic association of CUR with the polymer. Whereas in CUR-PVP K25-MA, the measurements observed indicate the possibility of polymer associating with the fatty acid initially and a slight dis-orientation of CUR-PVP K25. Hence it results in the possible permeation enhancement of CUR by the formation of a ternary system, CUR-PVP K25-MA.

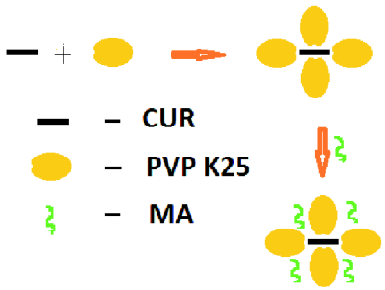


**Fig. 5.** Schematic representation of the hydrophobic association of CUR alone with PVP K25 and CUR-PVP K25 system with MA.

## Conclusions

The hydrophobic molecule, CUR possesses a challenge to be widely used as a drug due to its solubility in physiological conditions. Among the various solubilizers tried for CUR, biocompatibile polymers are found to be more advantageous and also they increase bioavailability of the drug. PVP K25 is a good drug delivery media for CUR, as observed with the changes in the fluorescence parameters such as fluorescence intensity, shift in emission wavelength and fluorescence anisotropy. To increase the permeability of CUR-PVP K25 system, MA is added as the penetration enhancer. MA is found to enhance the solubility of CUR in the PVP K25 polymeric environment.

## Acknowledgements

Authors thank DST-SERB, New Delhi (SR/FT/CS-32/2012) for financial support.

### References

1. S. Paul, S. Selvam, P. Wan Sia Heng and C. Lai Wah, *J. Fluoresc.*, 2013, **23**, 1065.
2. S. B. Brown, E. A. Brown and I. Walker, *Lancet Oncol*, 2004, **5**, 497.
3. K. Indira Priyadarsini, *J. Photochem. Photobiol. C: Photochem. Rev.*, 2009, **10**, 81.
4. C. Banerjee, S. Maiti, M. Mustafi, J. Kuchlyan, D. Banik, N. Kundu, D. Dhara and N. Sarkar, *Langmuir*, 2014, **30(36)**, 10834.
5. T. S. Saranya, V. K. Rajan, R. Biswas, R. Jayakumar and S.

Sathianarayanan, *Int. J. Biol. Macromol.,* 2017, **110**, 227.

6. T. R. Arunraj, N. S. Rejinold, S. Mangalathillam, S. Saroj, R. Biswas, R. Jayakumar and M. Sabitha, *J. Biomed. Nanotechnol.*, 2014, **10(2)**, 238.
7. M. Sun, Y. He, W. Yang and M. Yin, *Soft Matter*, 2014, **10**, 3426.
8. A. Mittal, U. V. S. Sara, A. Ali and M. Aqil, *Curr. Drug Delivery*, 2009, **6**, 274.
9. J. R. Lakowicz, in "Principles of fluorescence spectroscopy", 3rd ed., Springer Publisher Co., New York, 2006.
10. A. Noack, Gerd Hause and K. Mäder, *Intl. J. Pharm.*, 2012, **423**, 440.
11. C. Liu and H. Huang, *Chem. Pharm. Bull.*, 2012, **60(9)**, 1118.
12. D. Patra and B. Christelle, *Spectrochim Acta A: Mol. Biomol. Spectrosc.*, 2011, **79**, 1034.
13. D. Patra, *Biosens. Bioelectron.*, 2010, **25**, 1149.