ISSN: 0975 -8542

Journal of Global Pharma Technology

Available Online at: www.jgpt.co.in

RESEARCH ARTICLE

In Vitro Dissolution Enhancement of Curcumin by Melt Dispersion and Solvent Casting Technique Aided by Molecular Modelling Approach

Anindya Jana[1], Subrata Kumar Biswal[1], Rudra Narayan Sahoo[2], Partha Niyogi[1,3], Subrata Mallick[1], Rajaram Mohapatra[1]*

1. *School of Pharmaceutical Sciences, Siksha 'O' Anusandhan (Deemed to be University), Bhubaneswar-Khordha, Odisha, India.*
2. *School of Pharmacy and Life Sciences, Centurion University of Technology and Management, Odisha, India.*
3. *School of Pharmacy, The Neotia University, Kolkata, West Bengal, India.*

***Corresponding Author Email: rajaram.liku@gmail.com**

Abstract: Purpose: The oral bioavailability of curcumin is low due to its lipophilic nature. The drug also tends to degrade in alkaline pH. This inherent character of curcumin limits its stability and oral bioavailability. Use of polymeric carriers to alter the physicochemical nature of the drug is one of the favoured techniques of drug formulation. Aim of this study was to improve the *in-vitro* dissolution and solubility of curcumin by using hydrophilic carriers such as polyethylene glycol (PEG) and polyvinylpyrrolidone (PVP) of different grades and to check the effect of the different excipients used in the formulation of curcumin by solid dispersion technique. Methods: Solid dispersions of curcumin have been prepared by the solvent evaporation and melting method by using carriers in suitable ratios. In this experiment, ethanol was used as an organic solvent for solvent evaporation. The presence of different release rate modifiers such as croscacamellose sodium, kollidon CL and sodium and lauryl sulphate (SLS) in the SD formulation were also studied. *In-silico* approach has been applied to quantify the curcumin and carrier interaction. Results: The solubility of the solid dispersion prepared by the solvent evaporation and the melting method was found to be 13.5 and 78.9 fold to that of the pure curcumin respectively. Physical characterization by FTIR and DSC studies advocated that the physical state of crystalline drug has been modified in solid dispersions due to its dispersion in the polymer matrix. Conclusion: Dissolution studies revealed that all the formulations were having better drug release profile compared to the physical mixture. The lowering of binding energy in *in-silico* ducking study indicated towards possible molecular drug carrier interaction.

Keywords: *Curcumin, Solubility, Dissolution, Solid dispersion.*

Article Received: 16 Nov. 2020 **Revised: 08 Jan. 2021** **Accepted: 21 Jan 2021**

Introduction

Curcumin also known as turmeric is a polyphenol extracted from *Curcuma longa* (Zingiberaceae) rhizome [1]. In Indian cuisine it is popularly called as Haldi. The alcoholic extract from *Curcuma longa* comprised of three major components such as curcumin (75-80%), demethoxycurcum (3-5%) in and bis-demethoxycurcumin (15-20%) [2].

Conventionally turmeric has a long history of being used in many diseases as an anti-inflammatory agent. Among the other abundant pharmacological actions it possess antioxidant, antimicrobial, hypoglycemic, anti-rheumatic and anti-carcinogenic activities [3-5]. Though curcumin has been effective in many diseases, still it is not an approved therapeutic drug.

Disadvantages like poor bioavailability, limited tissue distribution, rapid metabolism, and short half-life of curcumin has inhibited its widespread use in the clinical practices.

It has been reported that the plasma concentration of curcumin was found to be 22-41 mg/ml after oral administration of 8 g/day in humans. A pattern of maximum drug excretion in faeces (75%) has been observed in rat model. The stability of the drug is also reported to be poor as it degrades in both neutral and alkaline pH [6].

Different approaches have been made in past to overcome the poor bioavailability of curcumin including the use of adjuvants [7], nanoparticle technology [8], micro emulsion, liposome [9, 10], chelation strategies and bioconjugates [11-13]. Though these novel attempts were promising, implementation and use of these are still at large in case of food products.

Use of polymers such as DMA and MPeG-b-PCL in the above said formulations which are not included in the generally recognised as safe list of USFDA made them less useful. The limited drug loading capacity of these delivery systems also made them unsuitable for curcumin as the dose of curcumin is high. The powder state stability issue (degradation in stomach before reaching site of action) associated with formulations like micro emulsions, liposome, and micelles leads to poor bioavailability of actives [14].

In Indian subcontinent and some other parts of the world curcumin is consumed in large quantities as a spice [3]. Curcumin has been exempted from the provisions of market authorization by USFDA as it has been generally recognized as a safe ingredient in food.

One can find the use curcumin throughout the world in therapy (tablet, capsule and ointment), cosmetics (soap, cream and oil) and beverages [15]. This study is mainly aimed at improving the solubility and dissolution rate of curcumin and to check the effect of different excipients used in the formulation of curcumin by solid dispersion technique.

In this study, ethanol was used as an organic solvent for solvent evaporation PVPK30 & PVPK90 were used as carriers and in melting method PEG4000 & PEG 6000 were used as carriers. Further Physical characterization like FTIR and DSC were carried out to justify the decreased crystallinity of curcumin.

Materials and Methods

Materials

Curcumin powder (C95, 95% curcuminoids) from rhizomes of *Curcuma longa* (Zingiberaceae), was procured from Plant Lipid, India. PVP K30, PVP K90, PEG4000, PEG6000 and Sodium Lauryl Sulphate obtained from the Merck Life Sciences Pvt. Ltd., India, Kollidon CL was obtained from BASF, West Bengal and Croscacamellose Sodium was obtained from the Blanver & Solutab, India as a gift sample.

Methods

Preparation of Standard Curve of Curcumin:

Preparation of standard curve of curcumin was carried out in 3 different organic solvents such as acetone, methanol & ethanol. Separate dilutions were prepared in different organic solvents. The maximum absorbance was determined by using UV Spectrophotometer [16]. The absorbance maxima recorded for these solutions were found to be at 419 nm, 423 nm & 425 nm for acetone methanol & ethanol respectively in Shimadzu UV Spectrophotometer. The graphs were plotted between absorbance versus concentration.

Preparation of Curcumin Solid Dispersion by Solvent Evaporation Method:

Solvent evaporation method involved two steps. In the first step a solution containing both the drug and carrier matrix was prepared by co-mixing in magnetic stirrer for 30 minutes. . In the second step a resultant solid mass was obtained after the removal of the solvent by drying the mixture for 48 hours.

The final powder SDs was obtained by grounding and sieving the solid mass. As the nature of the solvent used affects the rate and extent of evaporation and ultimately formation of solid mass, its selection is critical [17]. Ethanol was used as an organic solvent for the preparation of curcumin of solid dispersion. Solid dispersion was prepared by two ratios of drug and carrier (1: 0.5 and 1:1).

Table 1: Cur-cumin solid dispersion prepared by using solvent evaporation method

Batch No.	Composition (gm)						Solvent Used (ml)
	C95	PVPK30	PVPK90	Croscarmellose sodium	Kollidon CL	SLS	Ethanol
T1	3.75	1.875	-	-	-	-	20
T2	3.75	1.875	-	0.38	0.187	0.038	20
T3	3.75	3.75	-	-	-	-	20
T4	3.75	3.75	-	0.38	0.187	0.038	20
T5	3.75	-	3.75	-	-	-	20
T6	3.75	-	3.75	0.38	0.187	0.038	20
T7	3.75	-	1.875	-	-	-	20
T8	3.75	-	1.875	0.38	1.875	0.038	20
T9	3.75	3.75	-	-	-	0.038	20
T10	3.75	-	3.75	-	-	0.038	20

Preparation of Curcumin Solid Dispersion by Melting Method

This method involved melting of the proportional mixture of drug and polymers. The obtained molten mass was solidified rapidly in an ice-bath under continuous mixing in magnetic stirrer until a homogenous product was obtained. The homogenous product was dried for 24 hours. The final solid mass was crushed and sieved [18]. For the preparation of curcumin solid dispersion by melting, PVP K30, PVP K90, PEG4000 & PEG6000 were chosen as the water-soluble carriers. Solid dispersion was prepared in four different ratios i.e. 1:1:4, 1:0.5:4, 1:1:8 and 1:0.5:8 (Drug: Carrier: Carrier) (Table2). The temperature range maintained for PEG 4000 and PEG 6000 was 62-64°C and 55-57°C respectively.

Table 2: Cur-cumin solid dispersion prepared by using melting method

Composition (gm)	Batch No.											
	T11	T12	T13	T14	T15	T16	T17	T18	T19	T20	T21	T22
C95	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75
PVPK30	3.75	3.75	1.875	1.875	-	-	-	-	-	-	-	-
PVPK90	-	-	-	-	3.75	3.75	1.875	1.875	-	-	-	-
Croscarmellose Sodium	-	0.38	-	0.38	-	38	-	0.38		0.38		0.38
SLS	-	0.038	-	0.038	-	0.038	-	0.038	-	0.038	-	0.038
Crospovidone	-	0.187	-	0.187	-	0.187	-	0.187	-	0.187	-	0.187
PEG4000		-		-		-		-	15	15		
PEG6000	-		-		-		-		-		15	15

Table 3: Cur-cumin solid dispersion prepared by using melting Method

Composition (gm)	Batch No.											
	T23	T24	T25	T26	T27	T28	T29	T30	T31	T32	T33	T34
C95	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75
PVPK30	3.75	3.75	1.875	1.875	-	-	-	-	-	-	-	-
PVPK90	-	-	-	-	3.75	3.75	1.875	1.875	-	-	-	-
Croscarmellose Sodium	-	0.38	-	0.38	-	38	-	0.38		0.38		0.38
SLS		0.03	-	0.03	-	0.03	-	0.03	-	0.03	-	0.03

		8		8		8		8		8		8
Crospovidone	-	0.187	-	0.187	-	0.187	-	0.187	-	0.187	-	0.187
PEG4000	15	15		-	15	15		-	30	30		-
PEG6000	-		15	15	-		15	15	-		30	30

Evaluation of Curcumin Solid Dispersion

Solubility Study

The extent of solute dissolves in solvent at a certain investigational condition is known as solubility. The specific amount of SDs (250 mg equivalent of C95) was taken in a conical flask (200 ml water) & kept in sonicator at 37 ± 2ºC & 100 RPM for 6 hours to check the aqueous solubility. After 6 hours solution was filtered through whatman filter paper & absorbance was checked in UV-Vis Spectrophotometer at a fixed wavelength of 419 nm.

Bulk Density

Density of SDs can be affected by a change in the formulation. If the density of pellets varies significantly from batch to batch, the potency of SDs can be measured by using an automated tapping instrument. A weighed amount of SDs was introduced in a 100 ml cylinder. The net volume of the powder before tapping was recorded. The cylinder was tapped for 100 times in bulk density apparatus. After tapping, the final volume was noted. Bulk density was calculated by using following formula:

$$Bulk\ density = \frac{Mass\ of\ SDs}{Bulk\ Vol.}$$

Hausner Ratio

The ratio between tapped density and poured density is related to inter particulate friction and through which powder flow can be predicted. Hausner ratio was calculated by using the formula:

$$Hausner\ Ratio = \frac{Tapped\ Density}{Poured\ Density}$$

Carr's Index

The Hausner ratio and Carr's index are both measures of the flow properties of the powder, calculated that according to the formula:

$$Percentage\ Compressibility = \frac{Tapped\ Density - Poured\ density}{Tapped\ Density} * 100$$

Angle of Repose

The powder flow property can be coined in terms of angle of repose (tan θ). The angle formed between the surface of a heap of powder with its horizontal plane is referred to as angle of repose A higher angle of repose is the sign of greater frictional drag and lesser flow ability and vice versa [19]. It was calculated that the formula:

$$Angle\ of\ repose\ (tan\theta) = \frac{Height\ of\ pile\ (h)}{Radius\ of\ pile\ (r)}$$

Particle Size analysis by Sieving Method

Particle size determination by sieving method has been applied to the free flowing of dry powders, and some prepared slurries. In this technique powdered samples were passed through piled sieves with varying mess aperture size (lowest at bottom and highest at top) trough shaking for a predetermined time span [20]. For this study specific amount of SDs were taken in lab shifter containing standard required different mesh sizes #45, #75, #106, #125, #177 and #420 and the percentage of retention of SDs were calculated.

Dissolution

The dissolution process is the in-vitro simulation of a drug entity getting dissolved in body fluid and becoming available to systemic circulation. Different physicochemical properties of drug product, drug substance and solvent influence the rate of dissolution [21]. Dissolution study was carried out using USP Apparatus I (Electro lab, India) in 500 ml of water and/ HCl buffer pH 1.2, at 37±0.5 ºC and 75 RPM.

A capsule size 0 (equivalent to 25 mg of Curcumin) was placed in the basket of the dissolution apparatus. 5ml sample was withdrawn at regular time intervals (15, 30, 45, 60, 75, 90, 105 and 120 min) and replenished to maintain sink condition. The analysis of withdrawn samples was done in UV-VIS spectrophotometer at a fixed wavelength of 419 nm. All studies were carried out in triplicates.

Kinetic Studies of the Dissolution

Kinetic modeling approach has been applied to the dissolution data of SDs to understand the underlying mechanism. Zero order, first order, Higuchi, Hixson Crowell and Korsmeyer Pappas equation models were tried. Selection of best fit was made on the basis of highest regression coefficient (r^2) value [22].

Drug Content Analysis

Accurately dispensed 5 mg equivalent curcumin SD sample was dissolved in 10 ml Acetone. The solution was kept in sonicator for 20 mins. The absorbance of the filtered solution was recorded at 419 nm using UV visible spectrophotometer. The drug content was determined by using a standard plot of absorbance versus concentration.

Differential Scanning Calorimetry (DSC)

DSC analysis was used to estimate the thermal behavior of prepared SDs like melting temperature, latent het of melting and reaction energy [23]. Nearly about 5 to 10 mg of sample (curcumin, SDs and excipient) were taken aluminum pans and heated at 10 ˚C/min under a nitrogen purge (20 ml/min) from 0 to 250 ˚C in DSC apparatus (Mettler toledo) using STAR^e SW 12.10. The samples were heated at 10 ˚C/min to 250 ˚C.

FT-IR spectroscopy (FTIR)

IR spectroscopy was employed to determine the fingerprint region of the functional groups in the molecule and measure the vibrational atoms [24]. For FTIR purpose, samples (curcumin, SDs and excipient) were triturated with KBr powder to make discs and analyzed over a range 4000-400 cm^{-1} using an FTIR spectrophotometer.

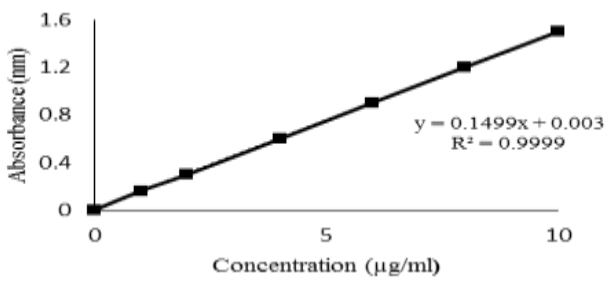
Molecular Docking

Auto Dock Vina 1.1.2 program was used to predict the binding between drug and polymer. The programme helps in pre-calculating the interaction between curcumin -PEG and curcumin - PVP. The 3-D structure of (curcumin, PEG and PVP) was drawn by using Marvin sketch. The PDBQT files of curcumin, PEG and PVP were prepared with the help of Auto Dock tools programme [25]. The curcumin was taken as ligand against the receptors like PEG and PVP. The stability was measured on the basis of interaction energy. The progressive negative score is the sign of better binding.

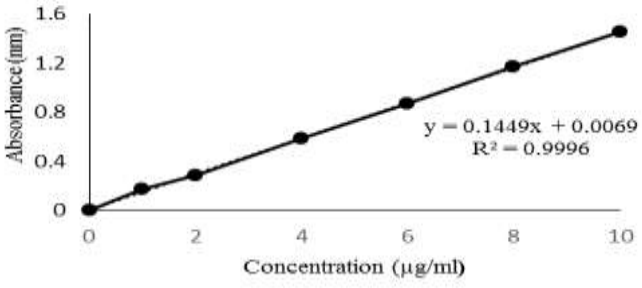
Results & discussion

Standard Curve of Curcumin

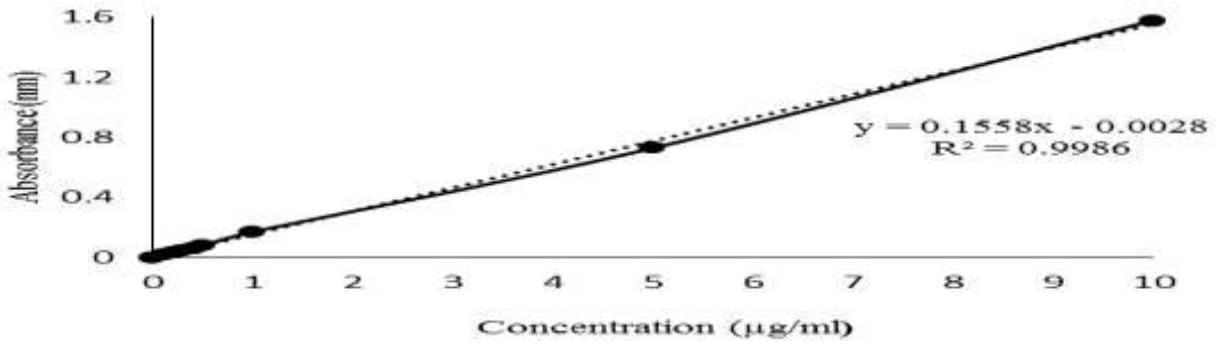
The standard curve was prepared by plotting different concentrations of curcumin versus the corresponding absorbance.



(A)



(B)



(C)

Figure 1: (A) The standard curve of curcumin in acetone (B) standard curve of curcumin in methanol (C) The standard curve of curcumin in ethanol

The λmax of curcumin in acetone, methanol and ethanol was found to be 419 nm, 423 nm and 425 nm respectively by spectral analysis. The regression coefficient value (r^2) corresponding to acetone, methanol and ethanol was found to be 0.9999, 0.9996 and 0.9986 respectively.

Solubility Study

The solubility study results of prepared SDs are depicted in Fig. 2.

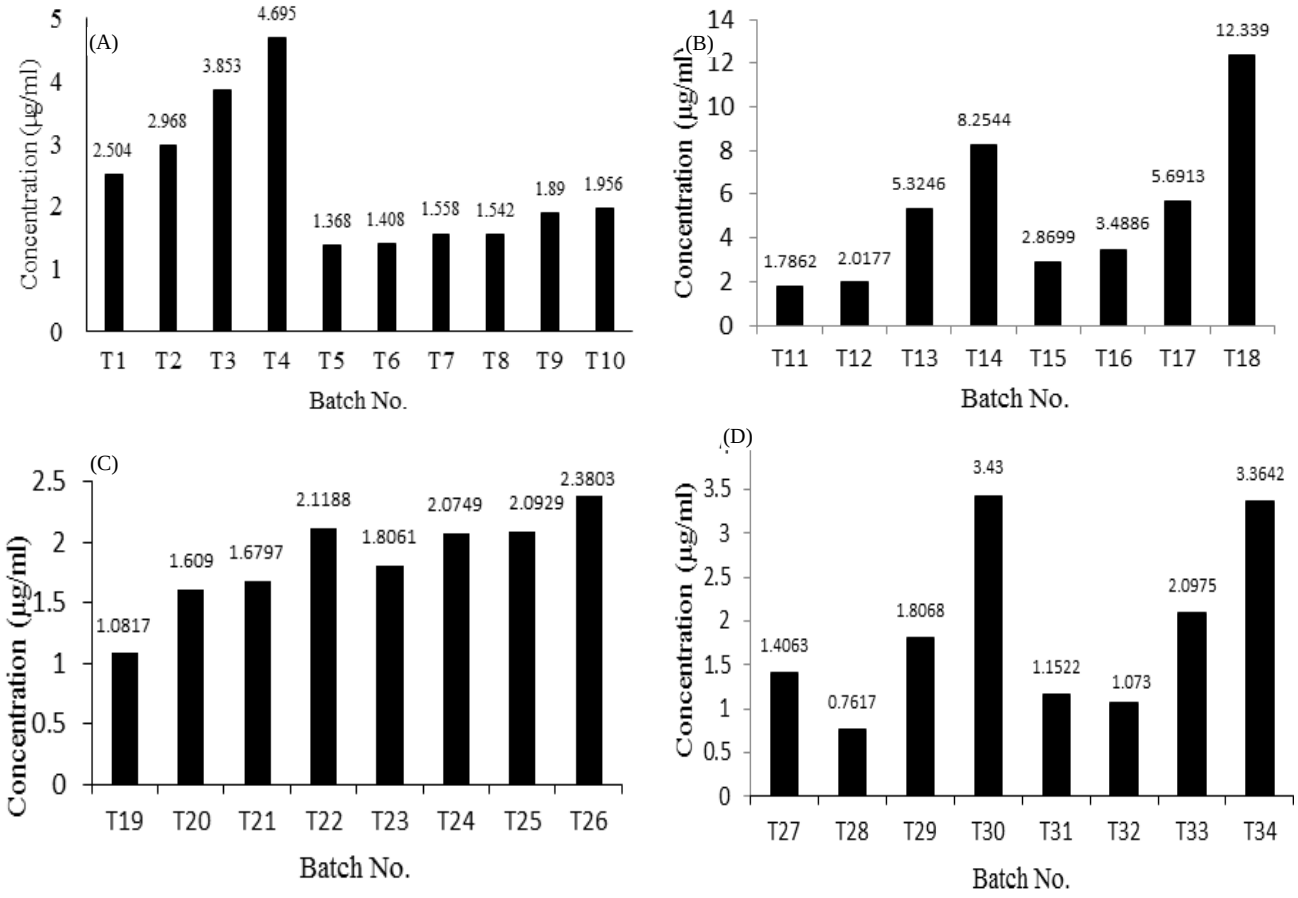


Figure 2: (A) Solubility data of SDs prepared by Solvent evaporation method; (B) T11-T18, (C) T19-T26 and (D) T27-T34, Solubility data of SDs prepared by Melting method

From the solubility data it has been concluded that the SDs prepared by melting method depicted significant improvement in aqueous solubility as compared the SDs prepared by solvent evaporation. T4 showed 13.5 folds increased solubility than pure curcumin powder. T14 & T18 demonstrated 52.8 & 78.9 folds solubility as compared to pure curcumin respectively. For further studies trial 13, 14, 17, 18, 30 & 34 has been chosen.

Powder Flow Properties

Different powder flow properties such as angle of repose, compressibility index and Hausner ratio for selected SDs are listed in Table 4.

Table 4: Powder flow properties of SDs

Batch No.	Parameters		
	Average Angle of Repose	Average Compressibility Index	Average Hausner Ratio
T13	24.37 ± 0.12	23.36 ± 0.3	1.3 ± 0.005
T14	23.31 ± 0.04	18.49 ± 0.75	1.22 ± 0.01
T17	25.82 ± 0.18	21.25 ± 0.54	1.26 ± 0.008
T18	21.09 ± 0.63	14.75 ± 1.01	1.17 ± 0.013
T30	29.83 ± 0.49	24.11 ± 0.83	1.31 ± 0.01
T34	27.92 ± 0.37	25.99 ± 0.87	1.35 ± 0.15

Basing on the data obtained from the powder flow properties data it has been concluded that T14 and T18 were showing excellent flow properties

Particle Size Analysis by Sieving Method

Particles size analysis report of selected SDs passed through different mesh size are reported in Table 5.

Table 5: Particle size analysis by sieving method

Batch No.	% Passed Through40 Mesh(420 Microns)	% Passed Through80 Mesh(177 Microns)	% Passed Through120 Mesh(125 Microns)	% Passed Through140 Mesh(106 Microns)	% Passed Through200 Mesh(75 Microns)	% Passed Through325 Mesh(45 Microns)
T13	100	43	30.59	18.52	4.89	0
T14	100	40.18	30.05	18.24	4.25	0
T17	100	47.68	33.92	19.86	5.6	0
T18	100	45.29	32.05	19.48	5.32	0
T30	100	42.01	35.45	22.62	6.1	0
T34	100	43.4	35.82	23.55	5.98	0

It was found from the above table that the particle sizes of the prepared SDs batches ranges within 45 to 420 microns in size

Dissolution Study:

Dissolution study of selected SD capsules and physical mixture in water and HCl (pH.1.2) are portrayed in Figure 3.

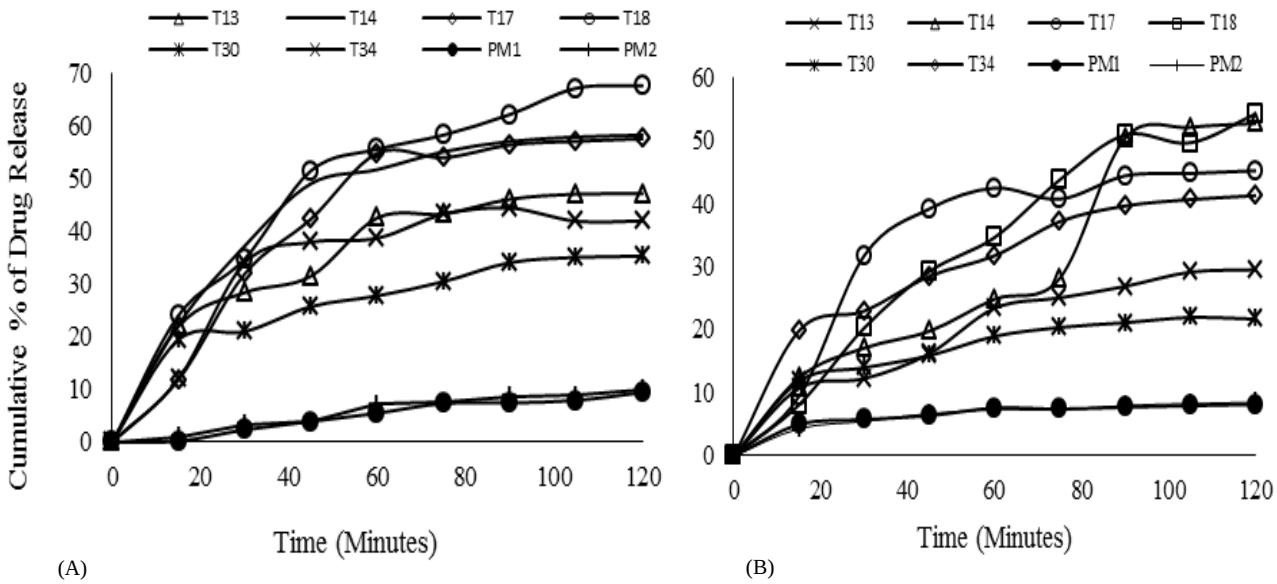


Figure 3: (A) In-vitro dissolution study of selected SD capsules and physical mixture in water; (B) In-vitro dissolution study of selected SD capsules and physical mixture in HCl pH.1.2.

It has been found that all the prepared curcumin SD had better release profile compared to prepared physical mixture. In the dissolution study for 120 mins, an initial burst was abundant in all the SDs followed by a steady pattern of release. The

hydrophobicity of pure curcumin resulted in slow release. Further the release seemed to be affected by the pH of the dissolution medium. In pH 1.2 batch no. T14 (52.71%) and T18 (54.24 %) were showing a better result than others. This improvement in solubility and dissolution rate of SDs was contributed by several factors such as improved wettability and ready dispersion in dissolving medium due to the hydrophilic carrier.

Kinetic Studies of the Dissolution

Kinetic modeling approach has been applied to the release profile of the SD formulations and physical mixture.

The dissolution kinetic studies were conducted and drug release profiles from all these SDs formulations were best expressed by Zero order model. Higher correlation evident from r^2 (0.9728 to 0.9909 in water and 0.9721 to 0.9819 in HCL) was observed for Zero order release kinetics in all formulations, suggested the dependency of drug release rate on its concentration.

Drug Content Analysis

From the drug content analysis it was found that the assay value of all the formulations was found within the range of 98.5 to 99.2 %.

Differential Scanning calorimetry (DSC)

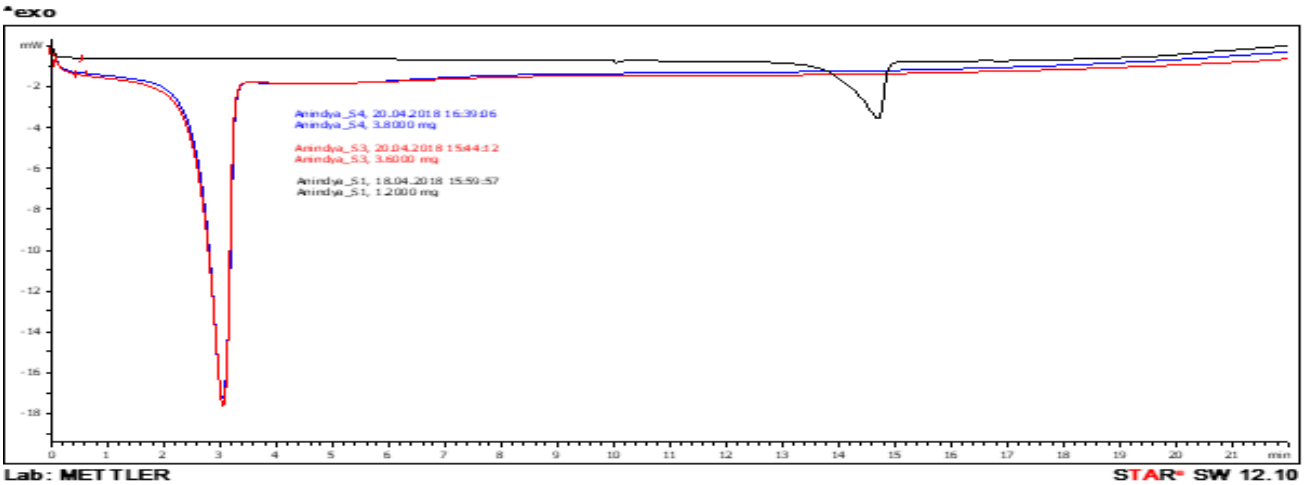
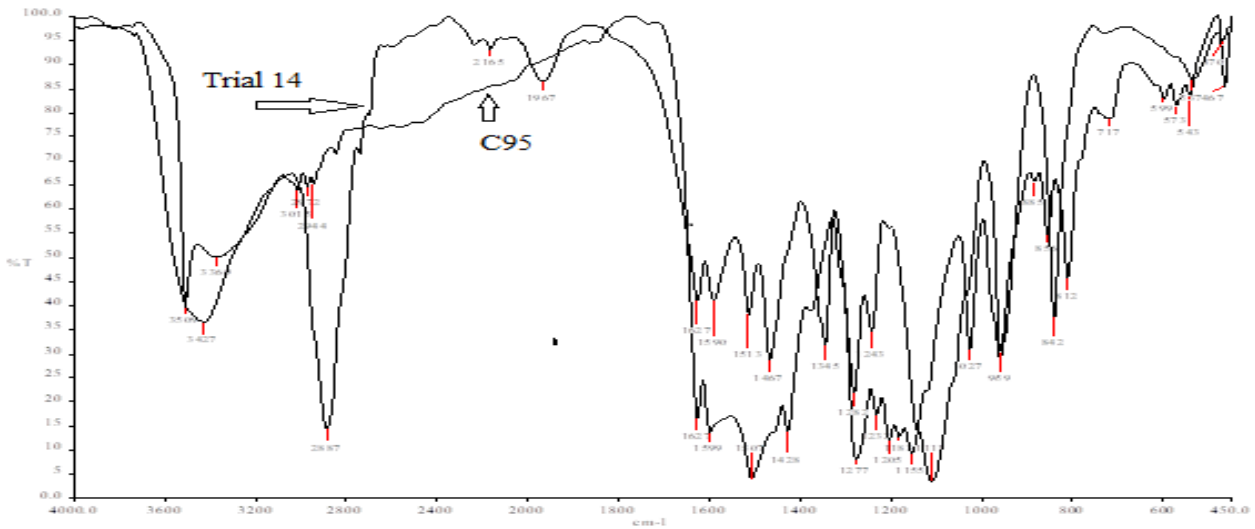


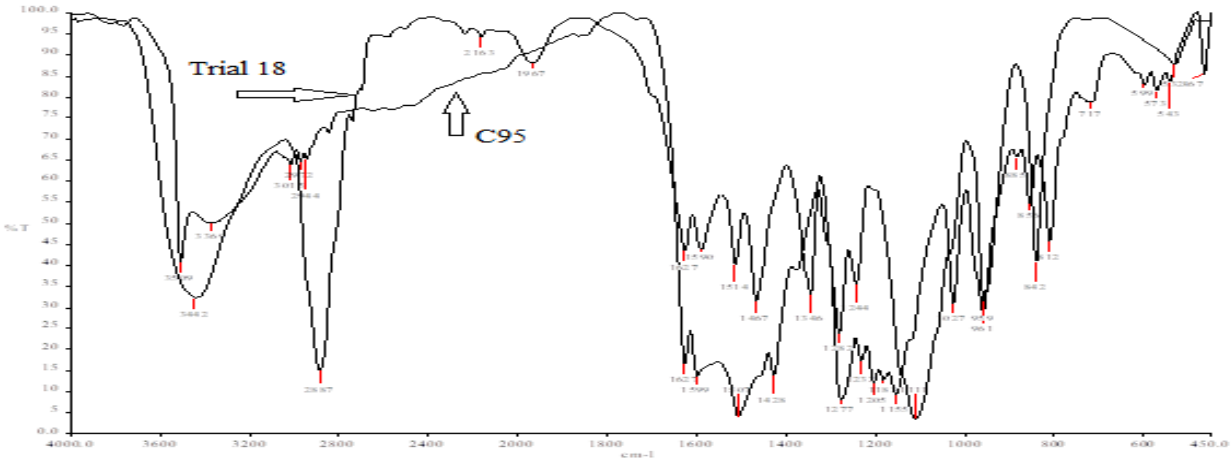
Figure 4: Differential scanning calorimetry of pure curcumin, SDs and excipients

DSC study (Fig.4) was carried out to verify the crystalinity of the drug in the formulation. A sharp endothermic peak was observed at 176.83°C with a fusion enthalpy of 93.23 J/g indicating the melting of pure drug. Meanwhile the carriers depicted no such peak. T14 & T18 demonstrated characteristic endothermic peak at 59.96°C & 59.80°C respectively. Both the formulation peaks were broad and has been shifted to a lower temperature. This broadening and shifting of peaks could have been the result of uniform mixing and dispersion of pure curcumin in the polymer matrix.

FT-IR spectroscopy (FTIR)



(A)



(B)

Figure 5: Comparative FTIR spectra (A) C95 & T14 and (B) C95 & T18

Drug polymer interaction within the formulation was studied in FTIR. The spectra of C95 and SDs are portrayed in figure 5A & B. The sharp peak at 3502 cm^{-1} and the broad band at 3369 cm^{-1} in the pure drug spectra are due to OH stretching vibration.

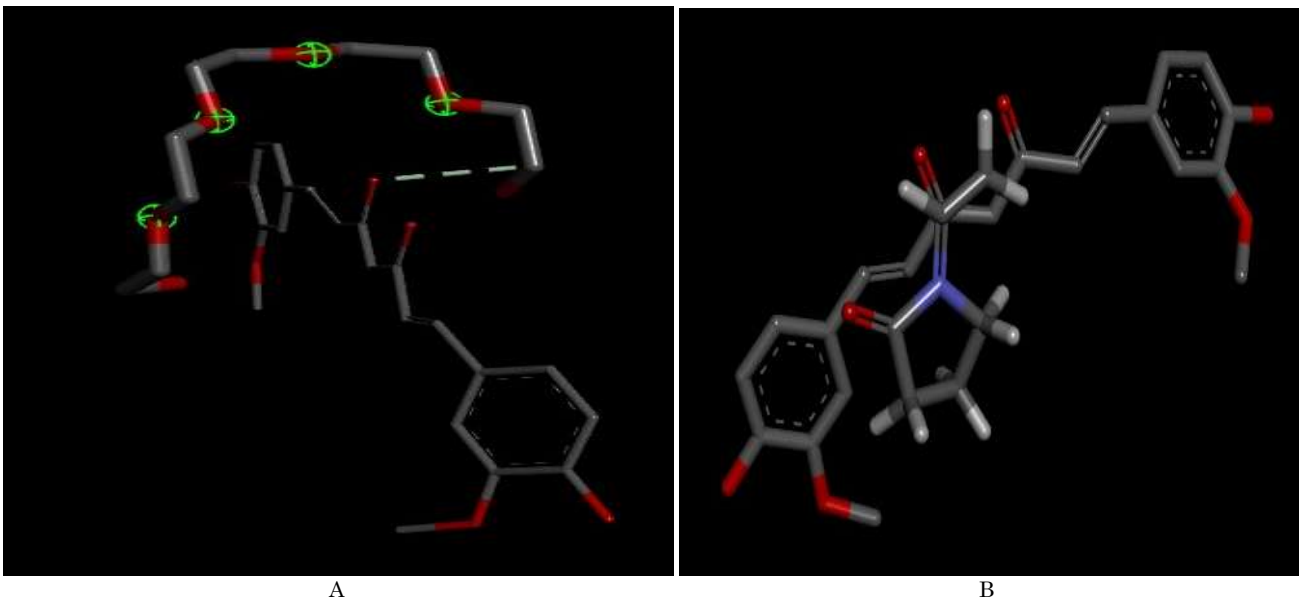
In SDs the peaks has been broadened significantly around 3427 & 3442 cm^{-1} and the disappearance of shoulder peak suggested a possible amorphisation. In both SDs, sharp peak at 2887 cm^{-1} referred to the presence of alkane group with CH Stretch which was absent in pure curcumin. In both solid dispersions, sharp peak at 2887 cm^{-1} confirmed the presence of alkane group CH stretch which was absent in pure curcumin. The peak due to the carboxyl group (C=O) was observed in both curcumin and SDs at around 1627cm^{-1}. Two characteristic peaks in the range of 1520 – 1400 cm^{-1} confirms the aromatic unsaturation (C=C).

Molecular Docking

The docking scores have been cited in Table 6. *In-silico* molecular modeling confirmed the drug-polymer interaction. The binding energy values for curcumin-PEG and curcumin-PVP were -2.4 and -2.3 kcal/mol respectively. This lowered value suggested that the curcumin may have been molecularly embedded in the carrier matrix through hydrogen bonding.

Table 6: Molecular docking energy table

Formulation	Docking score (Affinity) (kcal/mol)
Curumin-PEG	-2.4
Curcumin- PVP	-2.3



A B

Figure 6: Molecular docking (A) Curcumin-PEG, (B) Curcumin-PVP

Conclusion

Since Curcumin comes under the BCS Class IV drug, solubility and permeability are very low. This study was undertaken with an aim to increase the solubility and dissolution of curcumin by solid dispersion method by using inert carriers.

The preformulation study gave a detailed drug-specific review. Dissolution value for batch T14 (58.34%) & T18 (67.75%) in water and T14 (52.71%) & T18 (54.24%) in pH 1.2 demonstrated maximum dissolution in comparison with pure curcumin. Instrumental analysis such as FTIR and DSC suggested possible amorphization and dispersion of drug in polymer matrix.

Cur-cumin solid dispersions were also tested for physical and chemical parameters and results were found satisfactory. Finally the molecular ducking study (lowering of binding energy) supported the findings of other physicochemical characterizations.This made a way of a feasible formulation technique with the better therapeutic ability.

Acknowledgment

The authors are grateful to Prof. Manoj Ranjan Nayak president, Siksha 'O' Anusandhan (Deemed to be University) for the support and facilities.

- Solid dispersions of curcumin have been prepared by the solvent evaporation and melting method by using hydrophilic carriers such as polyethylene glycol (PEG) and polyvinylpyrrolidone (PVP) of different grades in suitable ratios.
- The effect of different release rate modifiers such as croscacamellose sodium, kollidon CL and sodium and lauryl sulphate (SLS) on the solubility and drug release were also studied.
- The solubility of the solid dispersion prepared by the solvent evaporation and the melting method was found to be 13.5 and 78.9 fold to that of the pure curcumin respectively.
- Dissolution value for batch T14 (58.34%) & T18 (67.75%) in water and T14 (52.71%) & T18 (54.24%) in pH 1.2 demonstrated maximum dissolution in comparison with pure curcumin.
- FTIR and DSC studies advocated that the physical state of crystalline drug has been modified in solid dispersions due to its dispersion in the polymer matrix.
- The lowering of binding energy (-2.4 and -2.3 kcal/mol for PEG and PVP respectively) in *in-silico* ducking study indicated towards possible molecular drug carrier interaction.

Abbreviations

PEG: Polyethylene glycol, PVP: Polyvinylpyrrolidone, FTIR: Fourier-transform infrared spectroscopy, DSC: Differential Scanning Calorimetry.

References

1. Kumavat SD, Chaudhari YS, Borole P, Mishra P, Shenghani K, Duvvuri P. Degradation studies of curcumin. Int J Pharm Rev Res. 2013; 3(2):50-55.
2. Massimino LC, Faria HA, Yoshioka SA. Curcumin bioactive nanosizing: Increase of bioavailability. Industrial crops and products. 2017: 15(109):493-97.
3. Mulla SI, Shah RR, Mohite SA, Patel NR. Antibacterial activity of some traditional plants. Res J Pharm Technol. 2018; 11(2):766-68.
4. Fadus MC, Lau C, Bikhchandani J, Lynch HT. Curcumin: An age-old anti-inflammatory and anti-neoplastic agent. Journal of traditional and complementary medicine. 2017; 1: 7(3):339-46.
5. Jayandran M, Haneefa MM, Balasubramanian V. Synthesis, Characterization and antimicrobial activities of turmeric curcumin and curcumin stabilized zinc nanoparticles-A green approach. Res J Pharm Technol. 2015; 8(4):445-51.
6. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: problems and promises. Molecular pharmaceutics. 2007; 3: 4(6):807-18.
7. Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas PS. Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. Planta medica. 1998; 64(04):353-56.

8. Bisht S, Maitra A. Systemic delivery of curcumin: 21st century solutions for an ancient conundrum. Curr Drug Discovery Technol. 2009; 1: 6(3):192-99.
9. Tiyaboonchai W, Tungpradit W, Plianbangchang P. Formulation and characterization of curcuminoids loaded solid lipid nanoparticles. International Journal of Pharmaceutics. 2007; 7: 337(1-2):299-306.
10. Kunwar A, Barik A, Pandey R, Priyadarsini KI. Transport of liposomal and albumin loaded curcumin to living cells: an absorption and fluorescence spectroscopic study. Biochimica et Biophysica Acta (BBA)-General Subjects. 2006: 1: 1760(10):1513-20.
11. Maiti K, Mukherjee K, Gantait A, Saha BP, Mukherjee PK. Curcumin-phospholipid complex: preparation, therapeutic evaluation and pharmacokinetic study in rats. International Journal of Pharmaceutics. 2007; 7: 330(1-2):155-63.
12. John VD, Kuttan G, Krishnankutty K. Anti-tumour studies of metal chelates of synthetic curcuminoids. J Exp Clin Cancer Res. CR. 2002; 21(2):219-24.
13. Sui Z, Salto R, Li J, Craik C, de Montellano PR. Inhibition of the HIV-1 and HIV-2 proteases by curcumin and curcumin boron complexes. Bio org Med Chem. 1993; 1; 1(6):415-22.
14. Chuah AM, Jacob B, Jie Z, Ramesh S, Mandal S, Puthan JK, Deshpande P, Vaidyanathan VV, Gelling RW, Patel G, Das T. Enhanced bioavailability and bio efficacy of an amorphous solid dispersion of curcumin. Food chemistry. 2014; 1(156): 227-33.
15. Huang YS, Hsieh TJ, Lu CY. Simple analytical strategy for Maldi-Tof-MS and nano UPLC-MS/MS: Quantitating curcumin in food condiments and dietary supplements and screening of acrylamide-induced ROS protein indicators reduced by curcumin. Food chemistry. 2015; 1(174):571-76.
16. Bijithra C, Ragan G, Shanmugasundaram P. Analytical method development and validation of modafinil in pure and tablet dosage form by Uv spectroscopy. Res J Pharm Technol. 2016; 9(8):1303-8.
17. Yadav P, Patel P, Das P, Deshmukh N, Pillai S. Formulation and evaluation of pioglitazone hcl fast dissolving tablet using solid dispersion. Res J Pharm Technol. 2018; 11(12):5313-18.
18. Mishra R, Gautam SS, Prasad RK, Patel AK, Sahu AK. Solubility enhancement of clarithromycin using solid dispersion and effervescence assisted fusion technique. Res J Pharm Technol. 2016; 9(6):677-86.
19. Akelesh T, Rajagopal V, Chander J, Manavalan R, Venkatanarayanan R. Formulation and evaluation of floating effervescent domperidone tablets. Res J Pharm Technol. 2016; 9(12):2169-79.
20. Karthika C, Sureshkumar R, Upadhyay D, Janani SK, Vasanthi C, Raja M, Upathyayula SS. Formulation development and in-vitro characterization of solid self nano emulsifying drug delivery system for curcumin to target colon adenocarcinoma. Res J Pharm Technol. 2019; 12(7):3338-46.
21. Karki D, Kulkarni GS, Swamy S, Sheeba FR. Formulation and evaluation of mucoadhesive buccal tablets of curcumin and its bioavailability study. Res J Pharm Technol. 2017; 10(12):4121-28.
22. Bhattacharjee S, Guha N, Dutta G, Chakraborty M, Jana M, Pau S. Formulation and Evaluation of Sustained Release Matrix Tablet of Anti-Amoebic Drug by Natural Polymers. Res J Pharm Technol. 2017; 10(7):2041-46.
23. Fadilah F, Widodo VA, Priawan RP, Joyo EO, Abdurrohman H, Paramita RI, Azizah NN. Synthesis nanoparticle extract of clove (Syzygiumaromaticum L.) and characterization by differential scanning colorimetry profiling and its activities as inhibitor of hela cell lines. Res J Pharm Technol. 2019; 12(7):3355-58.
24. Hemashree T, Prasunna SG, Saktiselvan P. Synthesis of keratin and characterization using FTIR. Res J Pharm Technol. 2019; 12(6):2664-68.
25. Sahoo RN, Nanda A, Pramanik A, Nandi S, Swain R, Pradhan SK, Mallick S. Interactions between Ibuprofen and silicified-mcc: Characterization, drug release and modeling approaches. Acta Chimica Slovenica. 2019; 18:66(4):923-33.

