The Bioscan 19(2): S.I (1), 543-553, 2024 www.thebioscan.com
AN INTERNATIONAL QUARTERLY JOURNAL OF LIFE SCIENCES

ENHANCING SOLUBILITY: INNOVATIVE APPROACHES TO ENHANCE SOLUBILITY OF POORLY WATER-SOLUBLE DRUG

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DOI: https://doi.org/10.63001/tbs.2024.v19.i02.S.I(1).pp543-553

KEYWORDS
Curcumin, Ƃ-CD, Freeze Drying Method, Solubility Enhancement Technique, Dissolution Enhancement, Poloxamer-407.
Received on:
20-07-2024
Accepted on:
10-12-2024

Abstract

This investigation aimed to determine the effectiveness of innovative method by using single or double combinatorial technique approach in preparing a solid matrix to enhance the aqueous solubility and dissolution of poorly water-soluble drugs like *Curcumin* (Cur). In order to use different techniques to improve aqueous solubility of poorly water-soluble drug with beta cyclodextrin (β-CD). The using of different techniques with hydrophilic polymer in differen t ratio and developed a solid matrix. Solid matrixes were characterized for solubility, in-vitro dissolution, Fourier Transform infrared (FTIR), X-ray diffractometry (XRD), Scanning electron microscopy (SEM). Its enhanced solubility is crucial in the selection of suitable methods for double combinatorial methods approach.

INTRODUCTION

Turmeric is a rhizomatous herbaceous perennial plant (Curcuma longa) of the ginger family. The medicinal properties of turmeric, the source of curcumin, have been known for thousands of years, however, the ability to determine the exact mechanism(s) of action and to determine the bioactive components have only recently been investigated.

Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), also called diferuloylmethane. Curcumin is a main natural polyphenol found in the rhizome of Curcuma longa (turmeric). Curcuma longa has been traditionally used in Asian countries as a medicinal herb. Curcumin is well known for its potential therapeutic properties, including antioxidant, anti-inflammatory, antimicrobial, and anticancer properties. (Hewlings, 2017)

Despite its reported benefits via inflammatory and antioxidant mechanisms, one of the major problems with ingesting curcumin by itself, is its poor water solubility. Since the absorption of poorly soluble drugs in the gastrointestinal tract is limited, the bioavailability of oral drug formulations is affected, thereby posing a major challenge to formulation scientists. This is particularly applicable for drugs classified as BCS class II in the US Food and Drug Administration's Biopharmaceutical Classification System; the dissolution rate represents the rate-determining step of the absorption process. (Kim, 2022)

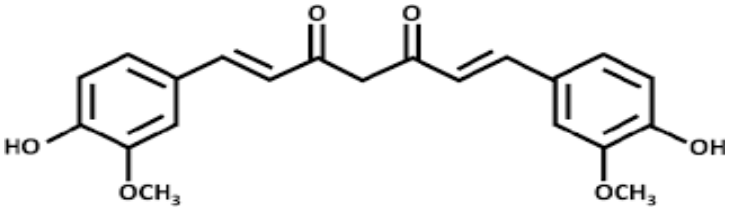
In the case of crystalline compounds, there are some compounds formulated which can be considered for improving the solubility of drugs via a relatively simple methods that involves conversion to amorphous form. In this research article one or more than one technique used alone and in combination to form solid aqueous matrixes. In this article using physical mixture, kneading method, solvent evaporation method and freeze-drying method.

In this study, decided to investigate the effect of method or methods on solubility of poorly aqueous soluble drug like curcumin. Different solid matrixes formulations of curcumin and hydrophilic polymers were formulated by physical mixture, kneading method, solvent evaporation method, microwave irradiation method and freeze-drying method. These methods were selected due to their simplicity, cost effectiveness and ease of scalability. In addition to polymer selection, the polymer ratio is also a significant aspect of solid matrixes that can affect the solubility and stability of the drug. Therefore, the solubility and release behaviour of the solid matrixes were examined in accordance with the different methods and polymers with their different ratios.

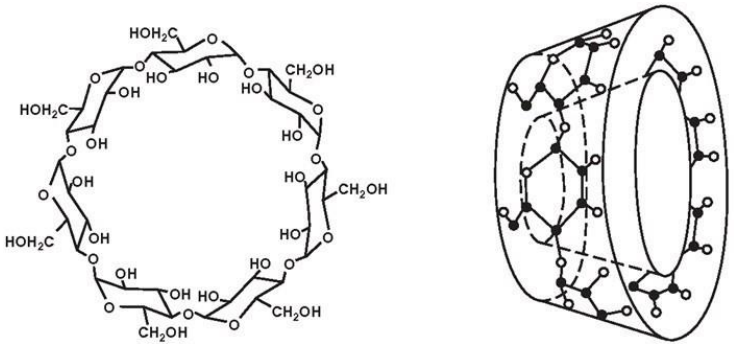
Hence this study was to develop and explore the effect of Ƃ-Cyclodextrin in different ratios-based curcumin solid matrixes in enhancing the solubility and dissolution of poorly aqueous soluble drug curcumin. Depending on the different methods and combination of different methods with same polymer in different ratios and the physicochemical properties of the prepared formulations were evaluated using scanning electron microscopy (SEM), Fourier transform infrared (FTIR) and X-ray powder diffraction (XRD).

Cyclodextrin is used to improve the solubilization of poorly soluble drugs, to achieve higher degrees of drug solubilization, the synergistic effect of an active pharmaceutical ingredient (API), a cyclodextrin with suitable method. The solid matrixes formed by using combinatorial method gives an alternative novel approach for solubilization, especially when a high amount of Ƃ-CD is needed for complexation. The interaction of water-soluble carriers with drug molecules may occur by means of ion–ion, ion-

dipole and dipole–dipole electrostatic bonds, van der Waals force, or 3-center or 2-electron bonds. The water solubility and absence of biological activity are the most important requirements to choose polymers for complexes.



Chemical structure of CURCUMIN



Chemical structure of ß-Cyclodextrin

Figure: 1

2.0 MATERIALS AND METHODS:

2.1 MATERIALS

Curcumin was obtained as a gift sample from Sunpure Extracts Pvt. Ltd., Dilshad Garden, Delhi-110095, India; ß-Cyclodextrin was gifted from Signet Chemical Corporation Pvt. Mumbai, India; Liquid Ammonia was obtained from Rankem, Avantor Performance Material India Ltd. Hiranandani Business Park, Thane, Maharashtra, India and other reagents were used of analytical and HPLC grade.

2.2 INSTRUMENTS:

The instruments being used in this study are analytical balance (Wensar, serial No. 60255, IND/09/08/557), Rotary Flask Shaker and Centrifuge of (Gentek India Pvt. Ltd. Lucknow (U.P.), Hot air oven (AADI Lab Ware, Haryana), Freeze Dryer (Allied Frost Lyophilizer-FD) and UV Visible spectrophotometer (Systronic Double Beam, Spectrophotometer 2203).

2.3 PREPARATION OF SOLID MATRIXES:

The preparation of solid matrixes of curcumin and ß-CD were prepared in the following molar ratios of 1:0.5, 1:1 and 1:1.5. there were overall five techniques were employed like, Physical Mixture (PM); Kneading Method (KM); Solvent Evaporation (SE); Microwave Irradiation (MW) and Freez Drying (FD) methods were used in single and double combinatorial technique approach.

Table 1: Double Combinatorial Method Approach Design with different techniques:

Methods	PM	KM	SE	MW	FD
PM	**PM:PM**	PM:KM	PM:SE	PM:MW	PM:FD
KM	KM:PM	**KM:KM**	KM:SE	KM:MW	KM:FD
SE	SE:PM	SE:KM	**SE:SE**	SE:MW	SE:FD
MW	MW:PM	MW:KM	MW:SE	**MW: MW**	MW:FD
FD	FD:PM	FD:KM	FD:SE	FD:MW	**FD: FD**

Note: PM (Physical Mixture); KM (Kneading Method); SE (Solvent Evaporation); MW (Microwave Irradiation); FD (Freez Drying)

Table 2. Formulation Design of Curcumin and ß-CD in Different Ratios by Using Single and Double Combinatorial Technique Approach Design:

S. No.	Method	Drug: Polymer (Cur:ß-CD)	Single and Double Combinatorial Technique	Formulation Code
1	Physical Method	1:0.5	PM1	P1
2		1:1		P2
3		1:1.5		P3
4		1:0.5	PM:KM	PK1
5		1:1		PK2
6		1:1.5		PK3
7		1:05	PM:SE	PS1
8		1:1		PS2
9		1:1.5		PS3
10		1:0.5	PM:MW	PM1
11		1:1		PM2
12		1:1.5		PM3
13		1:0.5	PM: FD	PF1
14		1:1		PF2
15		1:1.5		PF3
16	Kneaded	1:05	KM	K1

17		1:1		K2
18		1:1.5		K3
19		1:0.5	KM:PM	KP1
20		1:1		KP2
21		1:1.5		KP3
22		1:05	KM:SE	KS1
23		1:1		KS2
24		1:1.5		KS3
25		1:0.5	KM:MW	KM1
26		1:1		KM2
27		1:1.5		KM3
28		1:0.5	KM:FD	KF1
29		1:1		KF2
30		1:1.5		KF3
31	Solvent Evaporation Method	1:0.5	SE	S1
32		1:1		S2
33		1:1.5		S3
34		1:0.5	SE:PM	SP1
35		1:1		SP2
36		1:1.5		SP3
37		1:0.5	SE:KM	SK1
38		1:1		SK2
39		1:1.5		SK3
40		1:0.5	SE:MW	SM1
41		1:1		SM2
42		1:1.5		SM3
43		1:0.5	SE:FD	SF1
44		1:1		SF2
45		1:1.5		SF3
46	Microwave Irradiation Method	1:0.5	MW	M1
47		1:1		M2
48		1:1.5		M3
49		1:0.5	MW:PM	MP1
50		1:1		MP2
51		1:1.5		MP3
52		1:0.5	MW:KM	MK1
53		1:1		MK2
54		1:1.5		MK3
55		1:0.5	MW:SE	MS1
56		1:1		MS2
57		1:1.5		MS3
58		1:0.5	MW:FD	MF1
59		1:1		MF2
60		1:1.5		MF3
61	Freez Drying Method	1:0.5	FD	F1
62		1:1		F2
63		1:1.5		F3
64		1:0.5	FD:PM	FP1
65		1:1		FP2
66		1:1.5		FP3
67		1:0.5	FD:KM	FK1
68		1:1		FK2
69		1:1.5		FK3
70		1:0.5	FD:SE	FS1
71		1:1		FS2
72		1:1.5		FS3
73		1:0.5	FD:MW	FM1
74		1:1		FM2
75		1:1.5		FM3

2.3.1 PHYSICAL METHOD: Physical mixtures of curcumin were prepared by using ß-Cyclodextrin, in ratios of 1:05, 1:1 and 1:1.5. Drug Cur and ß-CD were mixing accurately weighed amount in a mortar by simple trituration. The mixtures obtained were passed through sieve no. 100 µm mesh. These physical mixtures were preserved in polyethylene bag in desiccators at normal temperature until future use. (Hassan, *et.al.*2019, Muthu et.al. 2019)

2.3.2 KNEADING METHOD: In the kneading method, ß-Cyclodextrin, dissolve with little amount of water or ethanol to convert into paste. The pure drug, Cur, is then added into the above paste of ß-CD and kneaded for a specified time. The kneaded mixture is kept into hot air oven at 60°C for 25 minutes. The dried mass passed through sieve no. 100 and store in desiccators at normal temperature until further use. (Pawar *et.al.* 2019; Yadav *et.al.* 2012)

2.3.3 SOLVENT EVAPORATION METHOD: Solvent evaporation method involves dissolving of the pure drug, Cur, and ß-CD separately in to two mutually miscible solvents (ß-CD dissolve in water and Curcumin dissolve in Ammonia solution), mixing of both solutions to get molecular dispersion of drug and complexing agents and finally evaporating the solvent under vacuum at 45°C to obtain solid powdered inclusion compound. The dried mass was pulverized and passed through a 100-mesh sieve. This method is quite simple and economic both on laboratory and large-scale production and is considered alternative to the spray drying technique. (Jin *et.al*. 2021; Yusuf *et.al*. 2020)

2.3.4 MICROWAVE IRRADIATION METHOD:

In this method drug and carrier ß-CD take in a flask and minimum amount of acetone: water (1:1 v/v) mixture. The solid mass kept in microwave oven for 2 minutes at 60°C, dried it again in vacuum oven then passed through sieve no. 100 mesh size. (Alshehri *et.al*. 2021; Raina *et.al*. 2020)

2.3.5 FREEZE DRYING: In this technique the solvents from the solution is removed through a primary freezing and subsequent drying of the solution containing both drug and excipients at reduced pressure. Thermolabile substances can be successfully made into complex form by this method. Lyophilisation has been thought of a molecular mixing technique where the Cur and excipients are co-dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion. (Mahapatra *et.al*. 2020; Kumar *et.al*.2022)

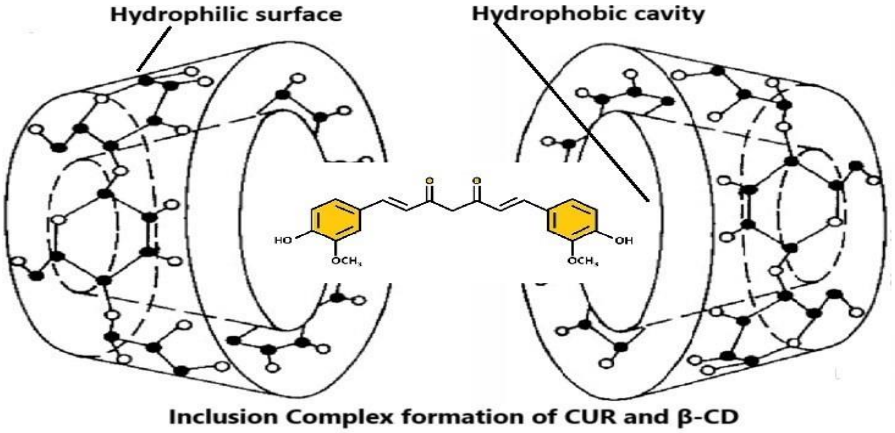
2.4 DETERMINATION OF λ_{max} OF CURCUMIN IN METHANOL:

CUR was scanned using the ultraviolet−visible (UV−vis) spectrophotometer range of wavelengths 200 to 800 nm (Systronic Double Beam, Specrophotometer 2203). Each sample was diluted with methanol before being maintained in a quartz cell. The double-beam UV−vis spectrophotometer sample was used for the UV scan of CUR, which covered wavelengths from 200 to 800 nm. The spectrometer was calibrated for around 20 min before the cuvette was filled with samples and positioned in the right orientation. A cover was used to keep out any light or scattering so that the absorbance could be maximized. The equipment was allowed to scan through various wavelengths, and the absorbance spectrum was obtained by comparing it to the blank sample and its absorbance graph. (Rahman *et.al*. 2022)

2.5 INCLUSION COMPLEX FORMATION OF CURCUMIN WITH ß-CD:

The most notable and successive feature of cyclodextrin is their ability to form solid inclusion complexes (host-guest complexes or cup and ball) with a very wide range of solid, liquid and gaseous compounds by a phenomenon of molecular inclusion complexation. In these complexes, a guest molecule is held within the cavity of the cyclodextrin host molecule. Complex formation is a dimensional fit between host cavity and guest molecule. The lipophilic cavity of cyclodextrin molecules provides a microenvironment into which an appropriately fit sized non-polar moiety can enter into form inclusion complex.

The main driving force of complex formation is the release of enthalpy-rich water molecules from the cavity. Water molecules are displaced by more hydrophobic guest molecules present in the solution to attain an apolar-apolar association and decrease of cyclodextrin ring strain resulting in a more stable lower energy state. (Yadav *et.al*. 2012)



Inclusion Complex formation of CUR and β-CD

Figure 2

2.6 SOLUBILITY STUDY OF PREPARED SOLID MATRIXES:

To check solubilities of solid matrixes, a sufficient amount of the drug and solid matrix was added to the distilled water, 10 ml, and mixed for approximately 3 min using a vortex mixture. After that, all samples were placed in a rotatory shaking machine at 25ºC ± 5ºC and 150 rotation per minute for 24 hours. The obtained mixture supernatant was filtered by using a whatman filter paper and analysed through UV Visible spectrophotometrically (Systronic Double Beam, Specrophotometer 2203) and record the results.

2.7 SOLUBILITY ENHANCEMENT BY DOUBLE COMBINATORIAL TECHNIQUES APPROACH:

Techniques used for solubility enhancement of Cur were Physical Mixture (PM), Kneading Method (KM), Solvent Evaporation method (SE), Microwave Irradiation Method (MW) and Freeze Drying (FD) with hydrophilic carrier, ß-Cyclodextrin (ß-CD), in different ratios. The double combinatorial method approach was applied on selected formulations of single method formulation, to enhance aqueous solubility of Cur.

Table 3: Double Combinatorial Approach by Using Different Methods

S. No.	Techniques	PM	KM	SE	MW	FD
	Formulation Code	P	K	S	M	F
1	PM	P:P	P: K	P: S	P: M	P: F
2	KM	K: P	K: K	K: S	K: M	K: F
3	SE	S: P	S: K	S: S	S: M	S: F
4	MW	M: P	M: K	M: S	M: M	M: F
5	FD	F: P	F: K	F: S	F: M	F: F

(Physical Mixture (PM) code (P), Kneading Method (KM) code (K), Solvent Evaporation (SE) code S, Microwave Irradiation (MW) code (M), Freez Drying (FD) code (F)

2.8 *IN-VITRO* DISSOLUTION STUDIES:

Dissolution studies done by using a USP apparatus II or paddle method (Microprocessor Tablet Dissolution Test Apparatus), was employed with dissolution media consisting of distilled water and a paddle rotation is 100 rotation per minute. The temperature of the dissolution medium was maintained at 37.0 ± 0.5 °C. Each

vessel contained an equal amount of the drug (10 mg) and was sampled (5 mL) at intervals of 5, 10, 20, 30, 40, 50, and 60 minute. Then each sample was filtered and analysed by using a UV Visible Spectrophotometer (Systronic Double Beam, Specrophotometer 2203) at wavelength of curcumin, 421.6 nm. To maintain the sink

conditions, each sample taken was and then substituted with an equal amount of the dissolution medium.

The cyclodextrin complex formation is usually enthalpy driven. In an aqueous solution the cyclodextrin cavity contains polar water molecules that are readily exchanged for non-polar hydrophobic guest molecules. The water molecules situated inside the non-polar environment of the cyclodextrin cavity do not have a full complement of hydrogen bonds and are higher in energy than the water molecules outside the cyclodextrin. Liberating the water molecules that are enthalpy-rich, high in energy, is a driving force for the complexation.

2.9 SCANNING ELECTRON MICROSCOPY (SEM):

The surface morphology of both the pure drug and solid matrixes was examined by using Scanning Electron Microscopy (Zeiss EVO® 50, UK). In this study the samples were fixed on a brass stub using double-sided tape and then gold coated in vacuum by a sputter coater. The pictures were then taken at an excitation voltage of 15 kV.

2.10 FOURIER TRANSFORMS INFRARED SPECTROSCOPY SYSTEM (FTIR)

Fourier transform Infrared Spectroscopy (FTIR) spectra of the pure drug Cur, ß-CD, PVP K-30, PXM-407, physical mixture and prepared complexes were previously ground and thoroughly mixed with KBr, and formed an infrared transparent solid disk by means of hydraulic pellet press. The 3 scans were executed at a resolution of 1 cm^{-1} (from 4000-400 cm^{-1}). Sampe was scabbed using Jasco Model FT-761 spectrometer (Tokyo, Japan).

2.11 POWDER X-RAY DIFFRACTION STUDY (XRD)

To access the structural information of the solid matrixes, an X-ray diffractometer (Bruker D-8 Advance, Germany) equipped with a graphite monochromator and Cu-Kα radiation was used. Each sample was scanned over an array of 5 to 80° at a rate of 5°/min followed by additions of 0.05° at 40 KV and a 30-mA current.

3.0 RESULT AND DISCUSSION

3.1 SOLUBILITY STUDIES

The solubility studies of CUR and its solid matrixes are shown in Table 4. The incorporation of the hydrophilic polymer like ß-cyclodextrin resulted in a substantial increase in the solubilization. the molecular structure of curcumin contains two benzene rings and a carbon chain, which makes the molecular polarity of curcumin low and hydrophobic, while ß-cyclodextrins is an external hydrophilic and internal hydrophobic cavity structure. Thus, curcumin molecules could migrate into the cavity of the ß-cyclodextrins through hydrophobic interaction. It could avoid the direct contact of curcumin with the surrounding environment, so improved its stability to light, heat and oxygen, and facilitated the dispersion of curcumin-ß-cyclodextrin in the aqueous phase. Overall, the addition of the ß-cyclodextrin resulted in superior solubility with different ratio. These findings confirm the selection of method with drug and carrier molar ratio.

Consequently, only SE5 and FD4 were selected for further investigation.

These findings confirm the selection of method and novel approach to be a key element in enhancing the solubility of poorly water-soluble drugs. Consequently, only SE5 and FD4 were selected for further investigation. Typically, an increase in the proportion of a hydrophilic polymer and double combinatorial method approach of methods is capable of enhancing the solubility of a solid matrixes of curcumin and ß-cyclodextrin; however, in this investigation, the degree of solubility increases by the use of double combinatorial methods and drug and carrier ratio of 1:1.5. (zhang, *et.al.* 2023; Guo, *et.al.* 2019)

Table No. 4 Solubility Analysis After Single Method Used With ß-CD in Different Ratios

S.No.	Method	Codes	Curcumin and ß-CD (Molar Ratio)	Solubility
1	Physical Mixture (PM)	PM1	1:0.5	Poor soluble
2		PM2	1:1	
3		PM3	1:1.5	
4	Kneading Method (KM)	KM1	1:0.5	
5		KM2	1:1	
6		KM3	1:1.5	
7	Solvent Evaporation (SE)	SE1	1:0.5	Slightly soluble
8		SE2	1:1	
9		SE3	1:1.5	
10	Microwave Irradiation (MW)	MW1	1:0.5	
11		MW2	1:1	
12		MW3	1:1.5	
13	Freeze Drying (FD)	FD1	1:0.5	Sparingly soluble
14		FD2	1:1	
15		FD3	1:1.5	

Result: On the basis of solubility analysis of Cur with ß-cyclodextrin by using various techniques and formulation FD3 with 1:1.5 molar ratio given the best solubility in aqueous µ medium.

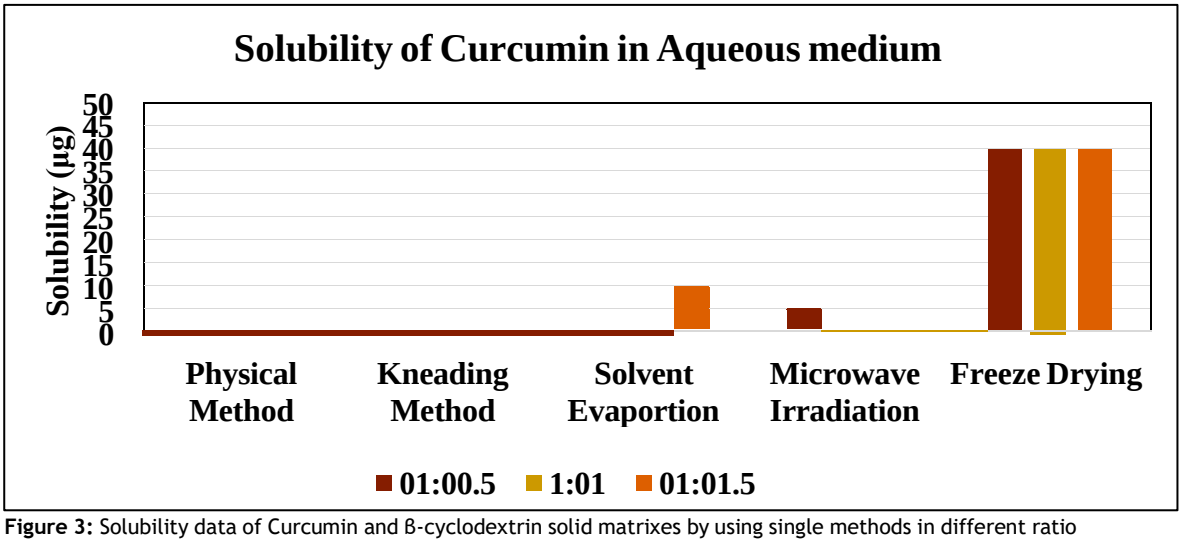
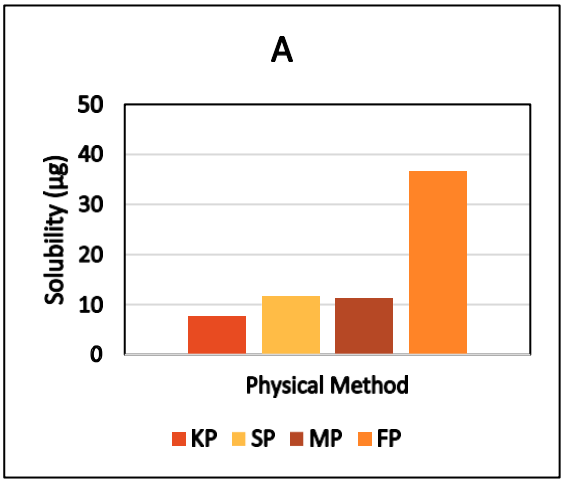
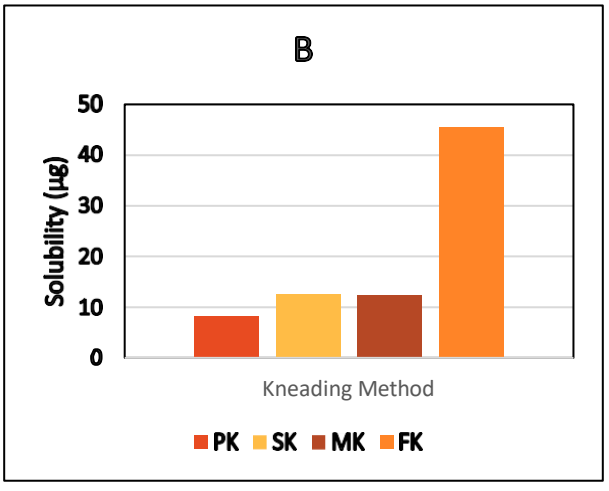


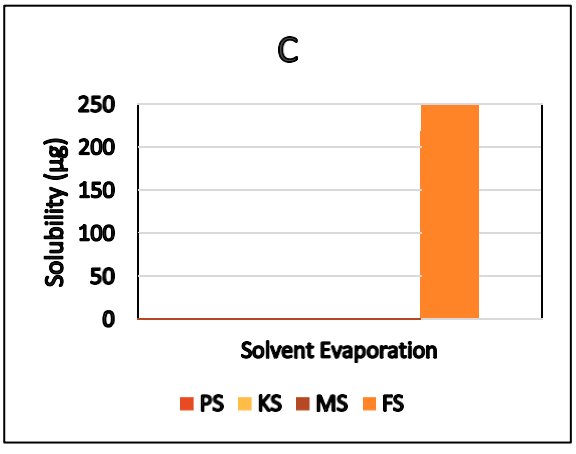
Figure 3: Solubility data of Curcumin and ß-cyclodextrin solid matrixes by using single methods in different ratio

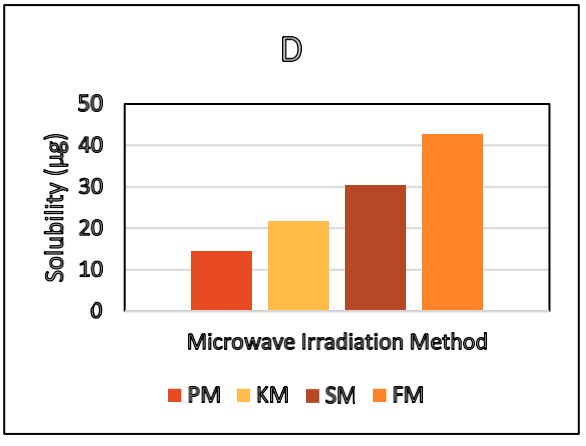
3.2 Combinatorial Design a novel approach to enhance solubility of Curcumin in aqueous medium
Table: 5 Solubility Analysis After Double Combinatorial Method Approach with β-CD in Different Ratios

S. No.	Double Combinatorial Methods approach	Formulation Code	Drug: Carrier Ratio (Cu: β-CD)	Solubility (µg/ml)
1	Physical Method (P)	KP	1:1.5	7.644
2		SP	1:1.5	11.732
3		MP	1:1.5	11.280
4		FP	1:1.5	36.640
5	Kneading Method (K)	PK	1:1.5	8.176
6		SK	1:1.5	12.540
7		MK	1:1.5	12.288
8		FK	1:1.5	45.424
9	Solvent Evaporation Method (S)	PS	1:1.5	10.776
10		KS	1:1.5	12.288
11		MS	1:1.5	15.896
12		FS	1:1.5	218.816
13	Microwave Irradiation Method (M)	PM	1:1.5	14.46
14		KM	1:1.5	21.552
15		SM	1:1.5	30.272
16		FM	1:1.5	42.592
17	Freeze Drying Method (F)	PF	1:1.5	46.320
18		KF	1:1.5	48.048
19		SF	1:1.5	245.254
20		MF	1:1.5	98.242









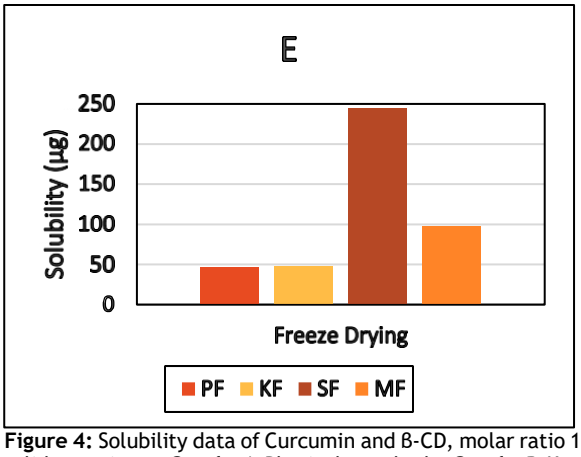


Figure 4: Solubility data of Curcumin and ß-CD, molar ratio 1:1.5, solid matrixes, **Graph A**-Physical method; **Graph B**-Kneading method: **Graph C**-Solvent evaporation method; **Graph D**-Microwave Irradiation Method; **Graph E**-Freeze Drying method with other method in combinatorial approach in Aqueous medium

3.3 *IN-VITRO* DISSOLUTION STUDY:

The in vitro dissolution studies of both the pure drug curcumin and prepared solid matrixes of drug and ß-CD are shown in Figure 2. In comparison to the pure drug, the rate of the dissolution of curcumin with ß-CD indicated a prominent increase in the dissolution up to approximately 80% in 40 min. This was attributed to make complexation by inclusion complexation to the improved wettability as well as the dispersibility potential of the CUR in the solid matrixes which is prepared by the hydrophilic polymer ß-CD by using double combinatorial method approach. The hydrophilic carrier ß-CD which form inclusion complex with drug which is incorporated into the apolar cavity of ß-CD. Furthermore, since an increase in the hydrophilic polymer resulted in an increase in the dissolution, the drug/polymer ratio of 1:1.5 were chosen for subsequent study. Similarly, the method used for the preparation of the solid matrixes also affected the dissolution rate that is double combinatorial technique approach. In this regard, the dissolution rate of the CUR dispersed in the ß-CD matrix by Freeze drying on solvent evaporation techniques was found to be higher in case of double combinatorial technique approach.

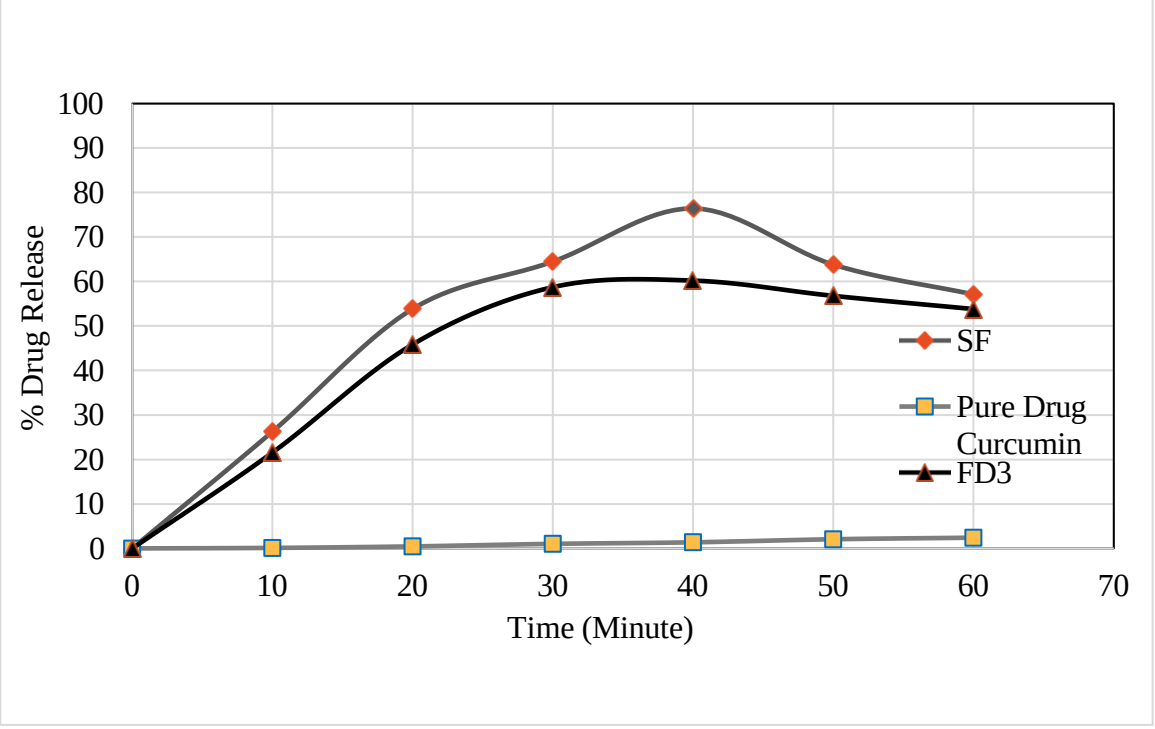


Figure: 5 Dissolution studies of selected solid complexes

3.4 Scanning Electron Microscopy (SEM)

SEM images of pure curcumin powder and its solid matrixes by single method and combinatorial method approach, with ß-CD are presented in Figure 5. SEM is used to study the microscopic aspects of the pure drug, ß-CD and solid matrixes. The Curcumin exhibited flat broken needle particles with irregular shape and smooth surface Figure 5(A), while the pure ß-CD appeared as crystalline particles with different sizes without a characteristic shape, Figure 5(B). the particle shapes and morphologies of the corresponding single method, Figure 5(C) were similar to pure ß-CD. As illustrated in Figure 5(D), the Curcumin and ß-CD inclusion complex has good uniformity in its crystal and regularity in its shapes that were also confirmed by the other characterization results. Curcumin and ß-CD inclusion complex by using double combinatorial method approach shown by Figure 5(E) and (F) like FS and SF solid matrixes shown great uniformity result. Moreover, the possibility of the disappearance of the original structure of the CUR in these matrixes also confirmed the change in structure. In addition, the smoother surface of the original structure of the CUR in these matrixes also confirmed the change in structure. In addition, the smoother surface of the ß-CD solid matrix with double combinatorial method approach in comparison to the single method.

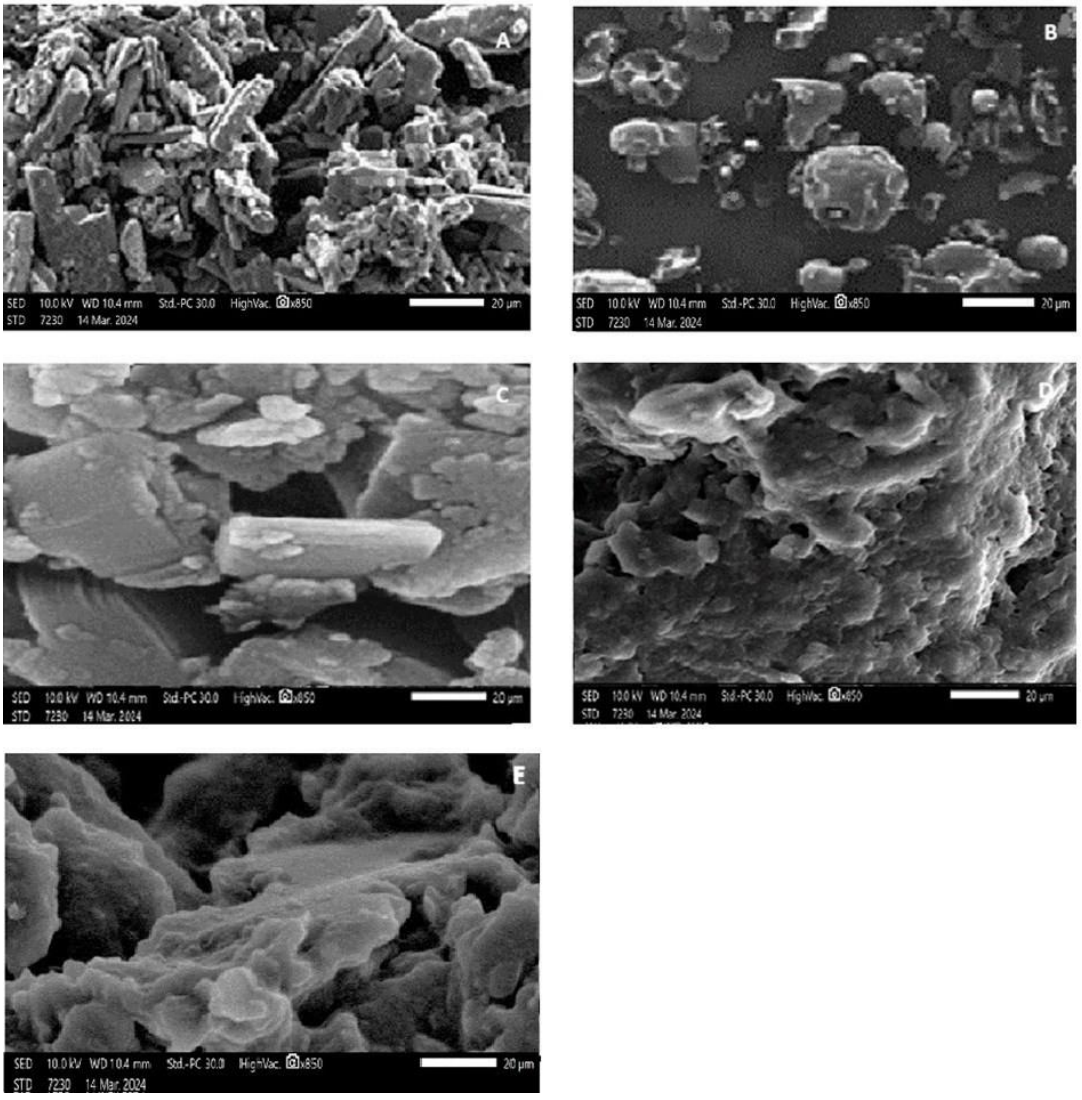


Figure 5: Pure Curcumin **(A),** ß-Cyclodextrin **(B),** PM3 **(C),** FD3 **(D),** Double Combinatorial Method matrix SF 1:1.5 ratio **(E)**

3.5 Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra of the curcumin and its prepared solid matrixes of single method and double combinatorial method, with ß-CD is illustrates in Figure 6. The IR spectroscopy has also been used to assess the interaction between cyclodextrin cavity and guest molecules in the solid state, since upon the complexation, shifts or changes in the absorption spectrum occur. The IR spectrum of the pure drug curcumin had sharp peak at 3435 cm-1 indicates the presence of phenolic OH stretching vibration. A sharp absorption bands at 1605 cm-1 due to stretching vibration of benzene ring of Cur was observed. Spectrum of, ß-CD showed a characteristic peak at 3300-3400 cm-1 due to the O-H group stretching. A sharp peak at 2854 cm^{-1} showed due to C-H as-symetric or symmetric stretching was also seen. There is also one additional peak at 1650 cm-1 showed H-O-H deformation bands of water in ß-CD. Peaks ate 1153 cm^{-1} and 1029 cm-1 indicated C-H overtone stretching and that at 1029 cm^{-1} C-H, C-O stretching. Absorption of the C-O-C vibration was seen at 1153 cm^{-1}. All the FTIR spectra of the inclusion complexes were identical with the ß-CD spectrum. All the sharp peaks of ß-CD were observed and characteristic peaks of Cur disappeared (especially the absorption band at 1,597 cm^{-1} corresponding to the benzene ring of Cur and aromatic C – O stretching at 1,276 cm^{-1}). Based on these results, we inferred that the benzene rings of Cur were contained within the cavity of ß-CD with van der Waals forces and hydrophobic interactions. In addition, Cur could form hydrogen bonds within the ß-CD cavity because of its electron donor groups. Since CUR was included into the ß-CD, all the related ß-CD peaks were shifted to higher or lower wave numbers, i.e., 3,343 – 3,328, 1,650 – 1,643, 1,538 – 1,511, 1,458 – 1,454, 1,153 – 1,157 and 1,029 – 1,041 cm − 1. This confirmed the presence of Cur in the inclusion complex. All these data indicated the successful formation of inclusion complexes of ß-CD and Cur.

Shifting of the O-H stretching peak, indicating the hydrogen bonding between curcumin and ß-CD. Shifting or reducing of intensity of the C=O in stretching peak of curcumin at 1627 cm^{-1}, indicating the interaction or encapsulation of curcumin into ß-CD cavity. Shifting or reducing intensity of other characteristic curcumin peaks, such as those related to C=C stretching and C-H bending, can indicating the formation of an inclusion complex with cyclodextrin, which enhanced the solubility and stability of water insoluble drug curcumin.

Thus, there was no new functional group observed, which indicated no chemical interaction occurred between the curcumin and ß-CD in the solid matrixes with all molar ratios. This result was anticipated, since the preparation of the solid matrix was not to produce a new substance, but also it modifies the physicochemical properties.

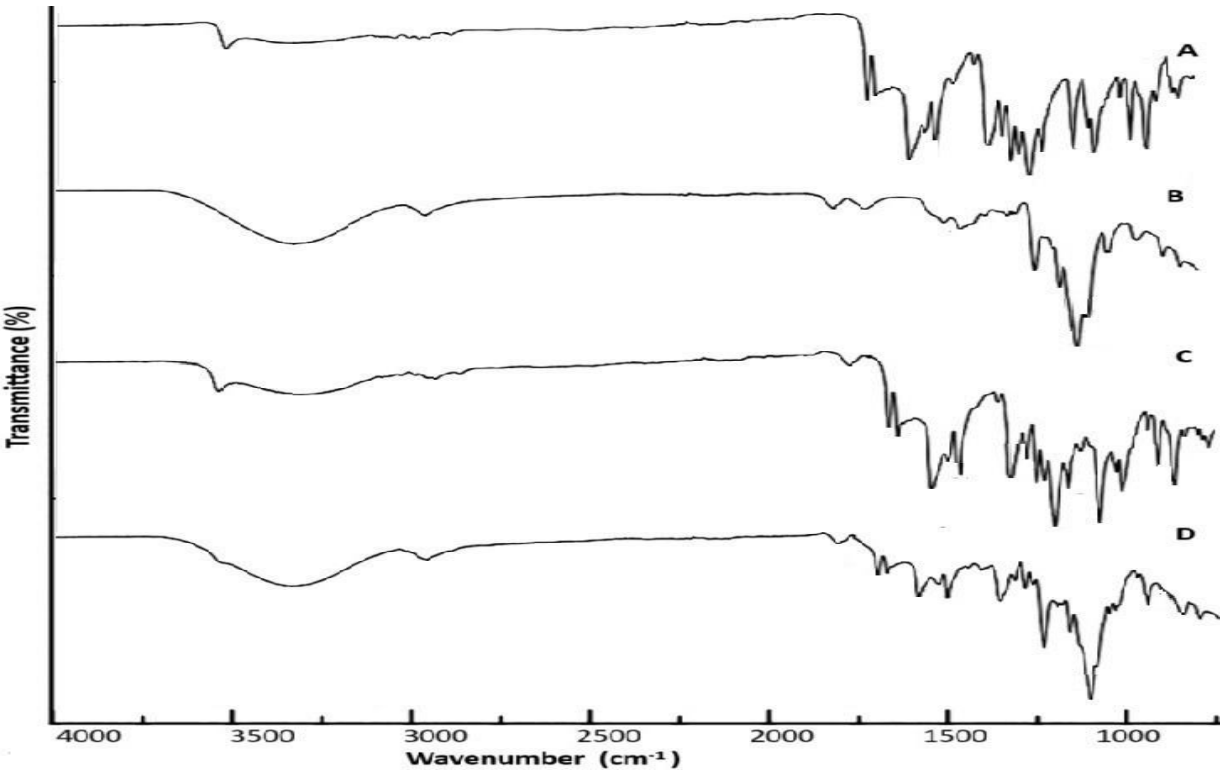


Figure 6: FTIR spectra of Curcumin (A), β-CD (B), inclusion solid matrix of Cur and β-CD by using single method FD3 (C), and Double Combinatorial Method, SF, (D)

3.6 X-ray Diffraction (XRD)

The X-ray diffraction patterns of CUR, β-CD, inclusion solid matrix of Cur and β-CD by using single method FD3, and Double Combinatorial Method, SF are shown in Figure 7. CUR showed the characteristic crystalline peaks of 2θ=8.80°, 14.46°, 17.24°, 17.78°, 18.00°, 21.06°, 23.30°, 24.58°, 27.38° and 29.20°, shows the cha whereas β-CD, displayed peaks of 2θ=12.66°, 15.96°, 16.12°, 18.24°, 19.00°, 21.14°, 23.00°, 24.22°, 25.7° and 27.10°. The Cur crystalline peaks disappeared in the patterns of Cur-β-CD-, especially the peak of 2θ=8.80°, whereas the CUR peak of 2θ=17.78° still but was less sharp appeared, than that in the diffraction pattern of Cur. The results confirmed the successful formation of the inclusion complex.

X-Ray diffraction only allows the differentiation between crystalline data and amorphous material. Result in reduction in intensity of Cur and β-CD compared to pure and PM endothermic peaks indicted that the complex may have been converted from the crystalline into the amorphous form.

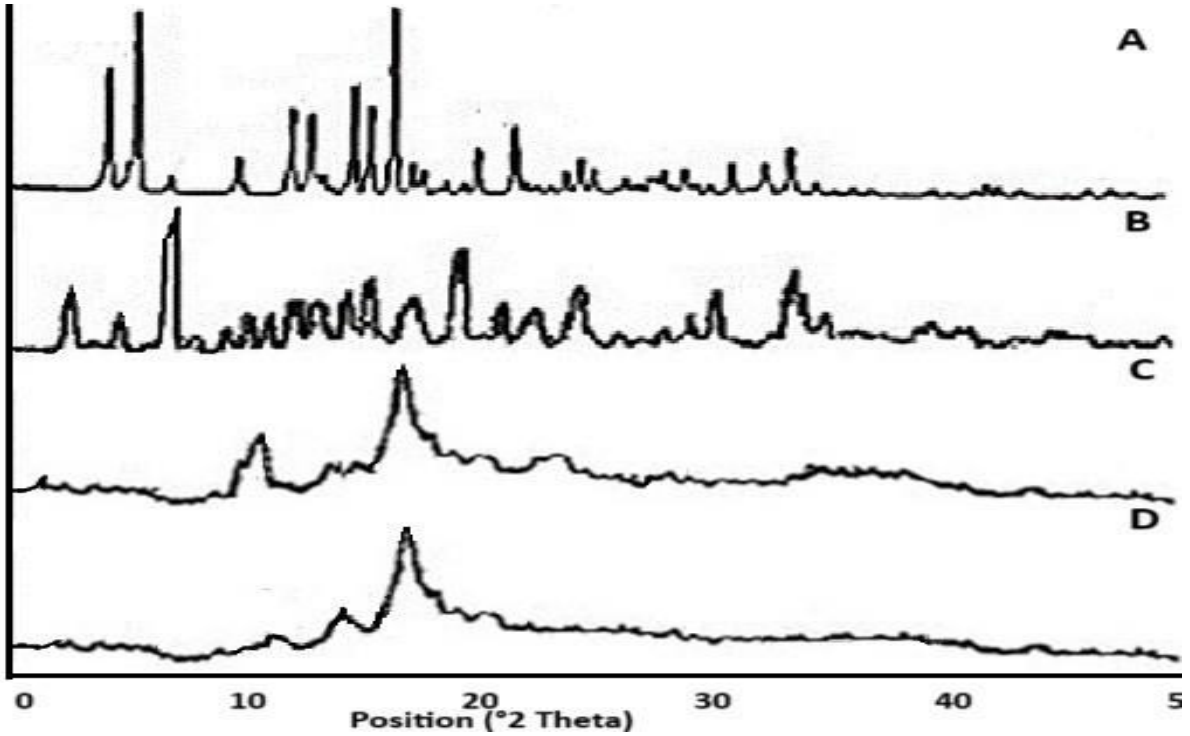


Figure 7: X-ray diffractograms of Pure Curcumin (A), β-CD (B), inclusion solid matrix of Cur and β-CD by using single method FD3 (C), and Double Combinatorial Method, SF, (D)

DISCUSSION

Solubility studies has been done with different molar ratio of ß-CD by using single and double combinatorial method. Solubility studies of Cur were performed in the presence of ß-CD in the concentration range of 0.5 to 1.5 with molar ratio of Cur. Solubility of Cur increased with increasing the concentration of drug and carrier ratio with double combinatorial method.

The solid matrixes of Cur prepared with ß-CD by using single method like physical mixture, kneading method, solvent evaporation method, microwave irradiation method and freeze-drying method. All the batches of the above mixtures were subjected to saturation solubility studies at room temperature in double distilled water. Amount of drug dissolved was analysed by the UV-Visible Spectroscopy. Evaluation of solubility enhancement potential was done by comparing change in solubility by using single method and double combinatorial method.

Enhancement of aqueous solubility of Cur by using single method is recorded in table 4 and Figure 3. Freeze dried solid complex with ß-CD in molar ratio of 1:1.5, showed increased solubility of Cur. Highest solubility of Cur in water was seen in case of FD2 and FD3, which were found with freeze drying method (1:1 and 1:1.5 molar ratios of Cur and ß-CD). The freeze-drying method was found to be most efficient method among in other applied methods in single. To enhance the solubility of Cur in aqueous medium by using a new approach double combinatorial methods which is recorded in table 5 and Figure 4. Freeze dried method and solvent evaporation method in combination to prepared solid matrixes with ß-CD in molar ratio of 1:1.5, showed increased and great solubility of Cur in comparison to single use method. Highest solubility of Cur in water was seen in case of FS and SF, which were found with freeze drying method and solvent evaporation method (1:1.5 molar ratios of Cur and ß-CD). The freeze drying with solvent evaporation method in combination was found to be most efficient methods in combinatorial approach, among in other applied methods in double combinatorial methods.

CONCLUSION

Aqueous solubility enhancement of pure drug Curcumin, was achieved by using ß-CD polymer in different molar ratio by using single method and a new approach double combinatorial method on the best solid matrix of single method results. this article considerably helps to improve the solubility and dissolution of pure drug curcumin, which will the utilization of its significant medicinal potential originating from its activity for key molecular purposes. Prepared solid matrixes by using single and double combinatorial method were characterized for the drug and polymer interaction using SEM, FTIR and X-Ray diffraction, which showed no interaction of Curcumin with ß-CD and there is change in nature of the drug from crystalline to amorphous form. Solubility enhancement of Cur was significantly improved by using double combinatorial method approach. Among these complexes, 1:1.5 ratio of Curcumin and ß-CD in double combinatorial method of solvent evaporation and freeze-drying method, was found to be most efficient method among in other applied methods in combination.

Author Contributions:

Funding: This research received no external funding.

Data Availability Statement: Data is contained within the article.

Conflicts of Interest: The authors declare no conflict of interest.

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