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Solubility Enhancement of Sertraline by Solvent Evaporation Co-Crystal Technique

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Abstract

Objective: Sertraline belongs to a class of antidepressant agent known as selective serotonin reuptake inhibitors (SSRIs). It is a class two drug, low solubility and high permeability. The aim of this study is to enhance the aqueous solubility of sertraline by solvent evaporation co-crystal technique. **Methods**: In this research, co-crystals formation between sertraline (drug) and aromatic acids benzoic acid, salicylic acid and oxalic acid (co-formers) in quimolar ratio have been prepared by solvent evaporation method with methanol, acetonitrile and diethyl ether as solvents. Co-crystal formation of sertraline-benzoic acid, and sertraline-salicylic acid sertraline-oxalic acid was characterized by powder x-ray diffraction (PXRD), Fourier transform infrared (FTIR) spectroscopy, fluorescence microscopy, solubility and dissolution methods. **Results:** The XRD patterns of sertraline benzoic acid co-crystals were different from pure components. The solubility test showed the sertraline-benzoic acid co-crystals has 14 folds higher than pure sertraline. The dissolution rate test showed that sertraline-benzoic acid co-crystals has percentage of dissolved after 60 min higher than pure sertraline. **Conclusion:** Sertraline-benzoic acid co-crystals can increase the solubility and dissolution rate of sertraline.

Keywords
benzoic acid, co-crystals, oxalic acid, salicylic acid, sertraline.

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INTRODUCTION:

A solid can exist in two structures, for example, powdered and crystalline. In crystalline shape a co-crystal can exist as polymorph, hydrate, solvate or co-crystals. Scientists in the pharmaceuticals like to convey crystalline types of their dynamic mixes, fundamentally due to the solidness of crystalline materials and the settled effect of crystallization forms on isolation and purification of chemical substances. More than 40 % of advertised drugs today have low solubility and, in the R, and D pipeline, 80–90% of medication hopefuls could come up short as a result of solvency issues. Co-crystals what's more, in pharmaceutically worthy visitor atoms into a crystal cross section alongside the dynamic pharmaceutical (API). In addition, co-crystals frequently offer solids with properties better than those of the free drug. Pharmaceutical co-crystals assume important role in the plan of new solids especially in the pharmaceutical industry as special disintegration profiles can be accomplished through co-crystallization.

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MATERIALS AND METHODS:

Table 1: List of materials

S.NO	CHEMICHAL NAME	CATEGORY	SUPPLIER
1	Sertraline	Anti-depressant (SSRI)	Hetero
2	Salicylic acid	Carboxylic acid	Finar chemicals (LR)
3	Benzoic acid	Carboxylic acid	Finar chemicals (LR)
4	Oxalic acid	Carboxylic acid	Finar chemicals (LR)
5	Methanol	Solvent	Finar chemicals (LR)
6	Acetonitrile	Solvent	Finar chemicals (LR)
7	Diethyl ether	Solvent	Finar chemical (LR)

Table 2: List of instruments:

S.NO	EQUIPMENT NAME	MODEL	MANUFACTURING COMPANY
1	Analytical balance	CPA 225 D	Sartorius, India
2	pH meter	pH system 361	Systronics
3	Micro pipette	-	Pfact
4	Fluorescence microscope	-	-
6	FT-IR(OPUS Software)	-	Alfa-Bruker
7	Milli Q water purifier	-	Millipore (India) Pvt.Ltd
8	PXRD	-	-
9	Rotary shaker	-	-

Method:

Preparation of sertraline co-crystals by solvent evaporation method

drug and co-former were weighed equimolar ratio's

↓

Each compound was dissolved separately in a solvent

↓

These solutions were mixed and stirred for a few minutes

↓

This solution was gently heated at 50°C

↓

Equimoles solution of both components was evaporated

↓

at room temperature for 48 hrs

↓

After the evaporation the obtained co-crystals were collected

Table 3: Co-crystal formulation

FORMULATIONS	SERTRALINE (mg, 1 mmol)	SALICYLIC ACID (mg, 1 mmol)	BENZOIC ACID (mg,1 mmol)	OXALIC ACID (mg,1 mmol)	METHANOL (ml)	ACETONITRILE (ml)	DIETHYL ETHER (ml)
SERT 1	306.23	138.122			8		
SERT 2	306.23	138.122				8	
SERT 3	306.23	138.122					8
SERT 4	306.23		122.12		8		
SERT 5	306.23		122.12			8	
SERT 6	306.23		122.12				8
SERT 7	306.23			90.034	8		
SERT 8	306.23			90.034		8	
SERT 9	306.23			90.034			8

EVALUATIONS OF CO-CRYSTALS:

Solubility Studies:

Drug solubility studies were performed by adding excess amounts of sertraline and prepared co-crystals to water and 0.1 N HCL in separate vials. The vials containing mixtures were shaken at 37.0 ± 0.5 º C for 48 hrs in rotary shaker. After 48 hrs, samples were filtered through a 0.45-µm filter paper and analyzed in UV spectrophotometer at wavelength of 271nm. Solubility studies were performed in triplicate (n=3).

Dissolution Studies

The dissolution of cocrystals were studied using USP Type II dissolution apparatus containing 900ml 0.1N Hcl maintained at 37±0.5°C and stirred at 75 rpm. Dissolution studies have been performed for the formulation of sertraline, and sertraline co-crystals (1:1) ratio in 0.1N HCl. 5 mL of sample was withdrawn after suitable time intervals and replaced each time with 5mL fresh medium. The solutions were immediately filtered, diluted and the concentration of drug was determined with the help of UV spectrophotometer (Schimadzu) at wavelength of 271nm. Percentage of drug dissolved was calculated by plotting time on X-axis against % cumulative drug release on Y-axis**.**

Percentage Practical Yields

Rate down to earth yield of arranged Cocrystals was ascertained to think about percent yield or on the other hand proficiency of strategy. Cocrystals were gathered and weighed to decide percentage yield (PY) from the accompanying condition.

Percentage of practical yield = practical yield / theoretical yield x 100

Fluorescence Microscopy:

A fluorescence magnifying lens is an optical magnifying lens that utilizations fluorescence and brightness rather than, or notwithstanding, reflection and absorption to think about properties of natural or inorganic substances. The fluorescence magnifying lens alludes to any magnifying lens that utilizations fluorescence to produce a picture, whether it is a more straight forward set up like an epifluorescence magnifying lens, or a more convoluted outline, for example, a confocal magnifying instrument, which utilizes optical separating to

show signs of improvement goals of the flurescent picture.

Powder X-ray Diffraction (XRD):

Powder XRD techniques contain the transcendent device utilized for the portrayal of cocrystals. Single-cocrystal XRD is routinely utilized for the structure arrangement of cocrystals, while powder XRD (PXRD) is for the most part utilized for ID purposes, since cocrystals display trademark sharp pinnacles that are not quite the same as the pinnacles of the cocrystal parts. In addition, measurement of cocrystals in the crystallization blend utilizing PXRDhas been announced by Pardela et al. Right now, programming projects such as DIFFRAC.TOPAS (Bruker AXS, Karlsruhe, Germany) permit basic assurance and refinement in light of Rietveld examination. They are additionally routinely used to survey the yield of cocrystallization by having the capacityto measure the level of cocrystals and their segments in a blend. An assortment of warm furthermore, spectroscopic procedures are utilized all the while to describe and measure potential new cocrystals. **Accelerated Stability Studies**: Led according to ICH rules at 40oC±2oC/75%±5% RH for upgraded co-crystal formulation at examining intervals of 0, 30, 60 and 90

days separately. The medication substance, consistency resolved occasionally.

RESULTS AND DISCUSSION:

Table: 4 Physical characterization of API

DESCRIPTION	SERTRALINE
Color	White
Morphology	Amorphous
Taste	Metallic

Table 5: The solubility studies of API

SOLVENT	SOLUBILITY
Water	Poorly soluble
0.1 N Hcl	Soluble
Methanol	Soluble
Acetonitrile	Soluble
DMSO	Soluble
Diethyl ether	Soluble

Sertraline standard graph determination of sertraline λmax:

This spectrum shows maximum absorption at 271 nm

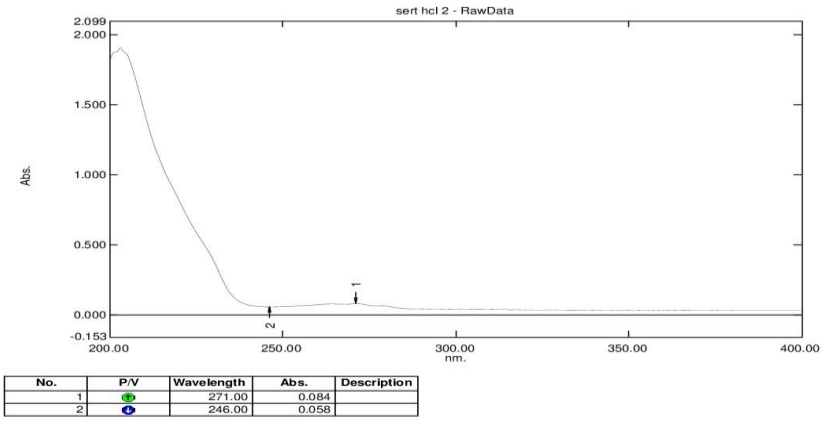
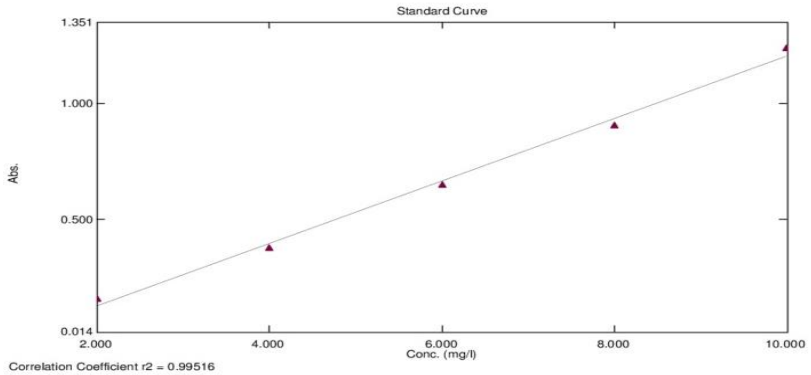


Figure 1: absorption spectrum of sertraline in 0.1N Hcl

Sertraline standard graph in 0.1 N HCL:

Absorption and concentration are plotted to obtain a standard graph with regression Co-efficient of 0.995



Correlation Coefficient r2 = 0.99516

Standard Table

	Sample ID	Type	Ex	Conc	WL400.0_200.0	Wgt.Factor	Comments
1	sert2	Standard		2.000	0.156	1.000	
2	sert4	Standard		4.000	0.376	1.000	
3	sert6	Standard		6.000	0.649	1.000	
4	sert8	Standard		8.000	0.908	1.000	
5	sert10	Standard		10.000	1.240	1.000	
6							

Figure 2: sertraline standard graph in 0.1N HCL

FTIR STUDIES:

The interaction examines between the drug and excipients and additionally enhanced detailing was assessed utilizing IR spectrophotometer. Sertraline has characteristic absorption peaks at 2033.2 cm-1, 1462.9 cm-1, 1328.7 cm-1, 1294.0 cm-1, 1065.5 cm-1, 826.9 cm-1, 671.8 cm-1 separately. Comparable peaks were seen in spectra of various combinations of co-formers and in improved plan, alongside nonappearance of interfering peaks showing there is no undesirable response between sertraline and different co-formers utilized as a part of the investigation.

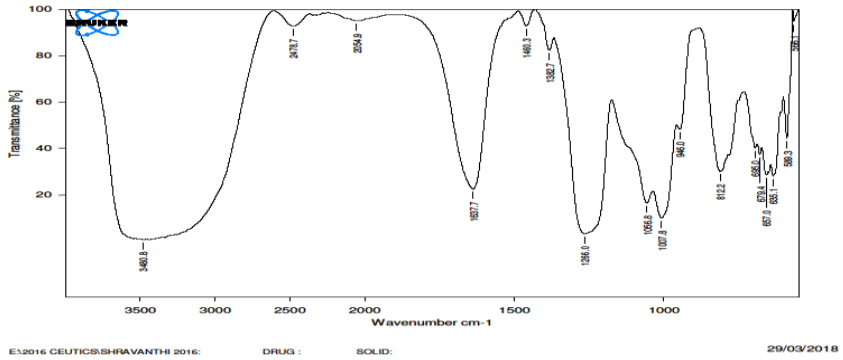


Figure 3: sertraline FTIR spectrum

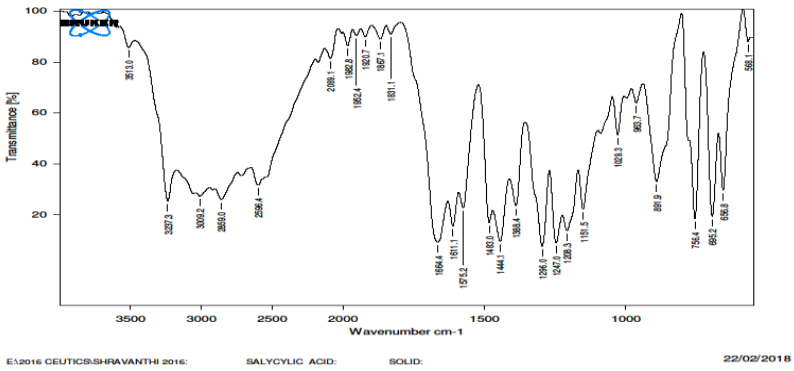


Figure 4: salicylic acid FTIR spectrum

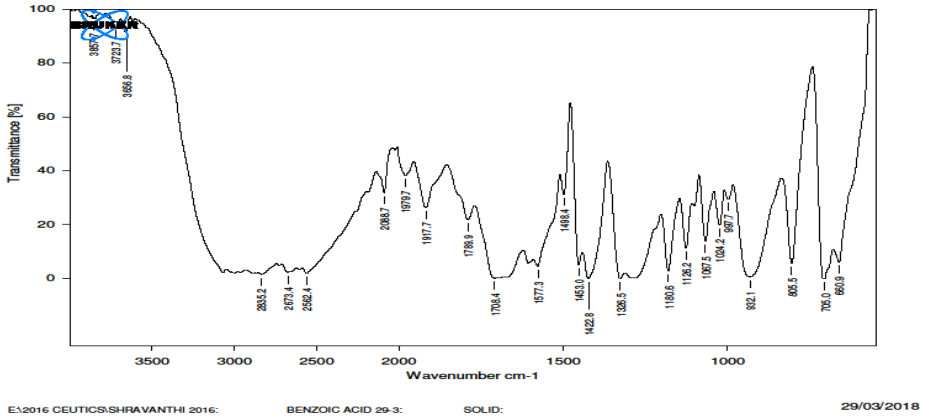


Figure 5: benzoic acid FTIR spectrum

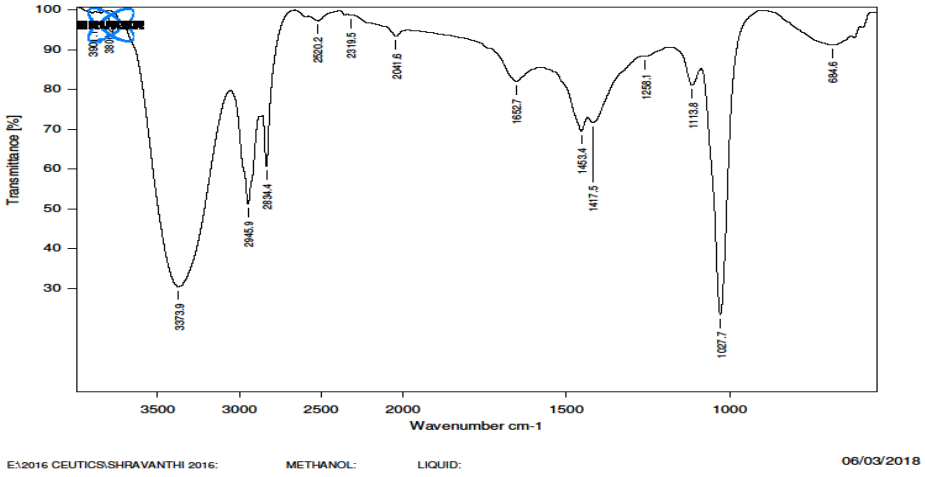


Figure 6: methanol FTIR spectrum

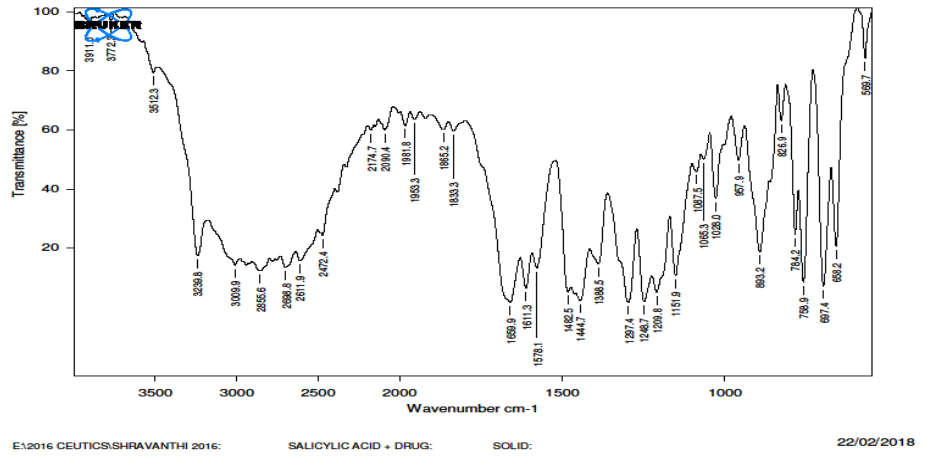


Figure 7: salicylic acid +drug FTIR spectrum

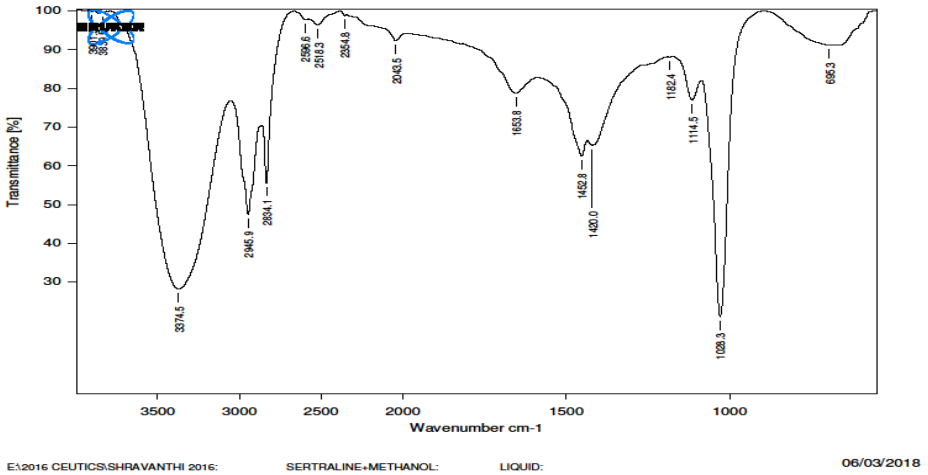


Figure 8: Methanol +drug FTIR spectrum

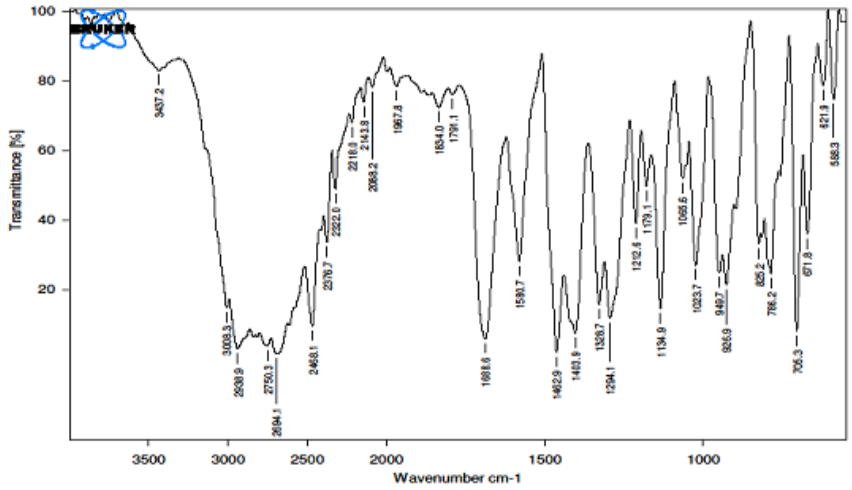


Figure 9: Acetonitrile FTIR spectrum

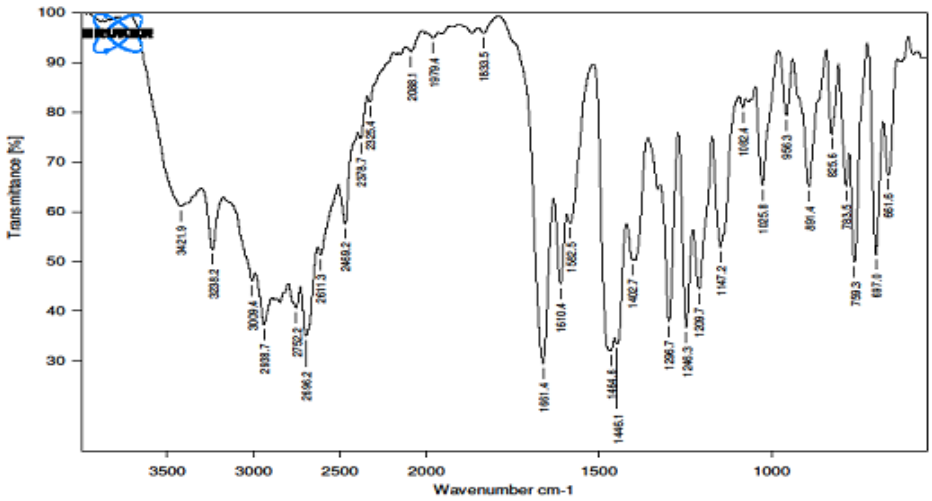


Figure 10: Acetonitrile +drug FT-IR specrum

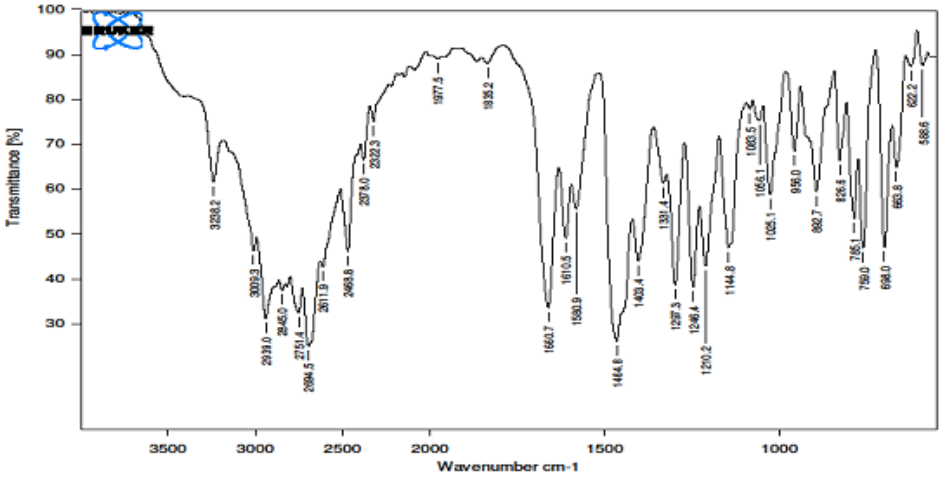


Figure 11: Diethyl ether FTIR spectrum

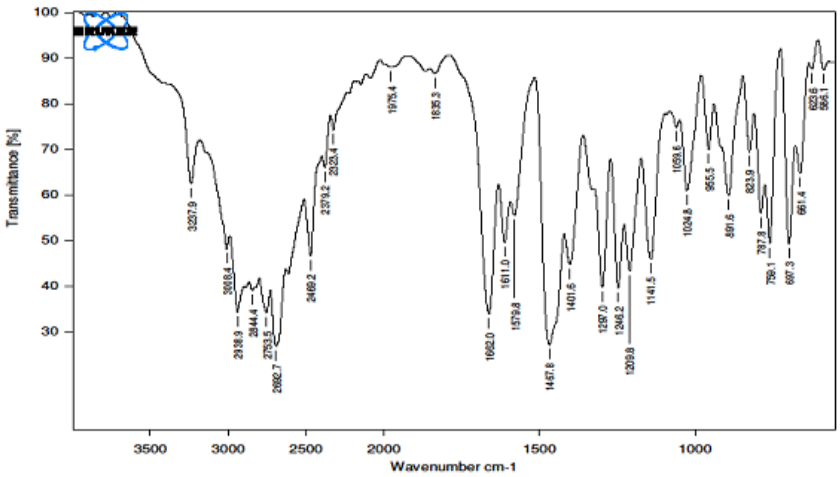


Figure 12: Diethyl ether +drug FTIR spectrum

Co-crystals Dissolution studies:
dissolution studies were conducted for various formulations in 0.1 N HCL. various formulation codes along with cumulative drug release values are given table and fig below in table

Table 6: cumulative % drug release of different formulations

Time in (hrs)	Cumulative % drug release								
	SERT 1	SERT 2	SERT 3	SERT 4	SERT 5	SERT 6	SERT 7	SERT 8	SERT 9
0	0	0	0	0	0	0	0	0	0
5	23 ± 0.5	21 ± 0.9	15 ± 0.6	27 ±0.4	13 ± 0.4	10 ± 0.5	15 ±0.4	12 ±0.7	16 ±0.4
10	26 ± 0.4	24 ± 0.8	25 ± 0.4	30 ± 0.2	15 ± 0.2	17 ± 0.2	21 ±0.2	14 ±0.5	20 ±0.2
15	29 ± 0.1	26 ± 0.5	28 ± 0.8	36 ± 0.3	25 ± 0.3	22 ± 0.7	33 ±0.8	29 ±0.2	31 ±0.2
20	34 ± 0.6	31 ± 0.4	29 ± 0.3	41 ± 0.7	27 ± 0.1	25 4± 0.8	42 ±0.3	37 ±0.3	40 ±0.3
30	55 ± 0.2	35 ± 0.6	31 ± 0.7	59 ± 0.5	31 ± 0.9	29 ± 0.4	66 ±0.8	58 ±0.6	57 ±0.6
40	76 ± 0.3	48 ± 0.3	50 ± 0.9	79 ± 0.6	37 ± 0.8	33 ± 0.3	79 ±0.9	65 ±0.8	62 ±0.8
50	85 ± 0.6	69 ± 0.1	71 ± 0.4	86 ± 0.7	67 ± 0.4	58 ± 0.1	86 ±0.5	78 ±0.4	79 ±0.4
60	91 ± 0.9	78 ± 0.4	87 ± 0.1	98 ± 0.1	81 ± 0.5	79 ± 0.8	92 ±0.1	84 ±0.5	88 ±0.7

Values in mean of cumulative % drug release ± standard deviation (n=3)

Figure 13: Cumulative % drug release of sertraline different formulations

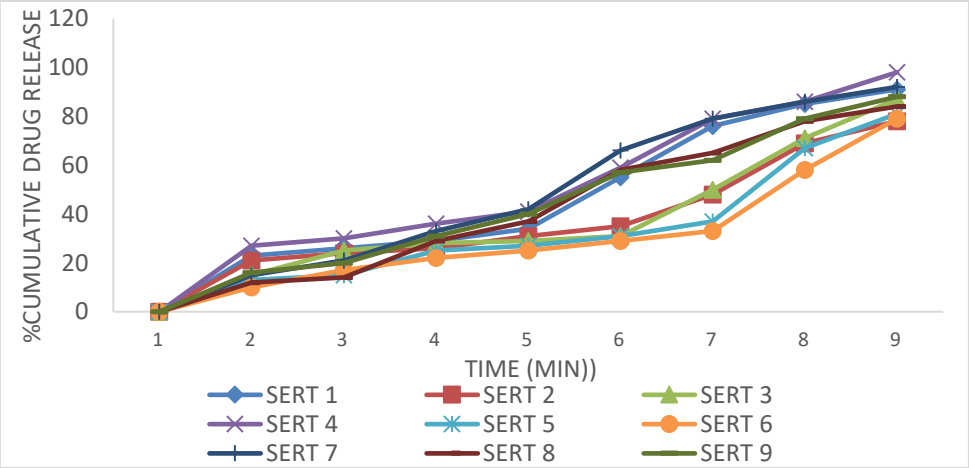
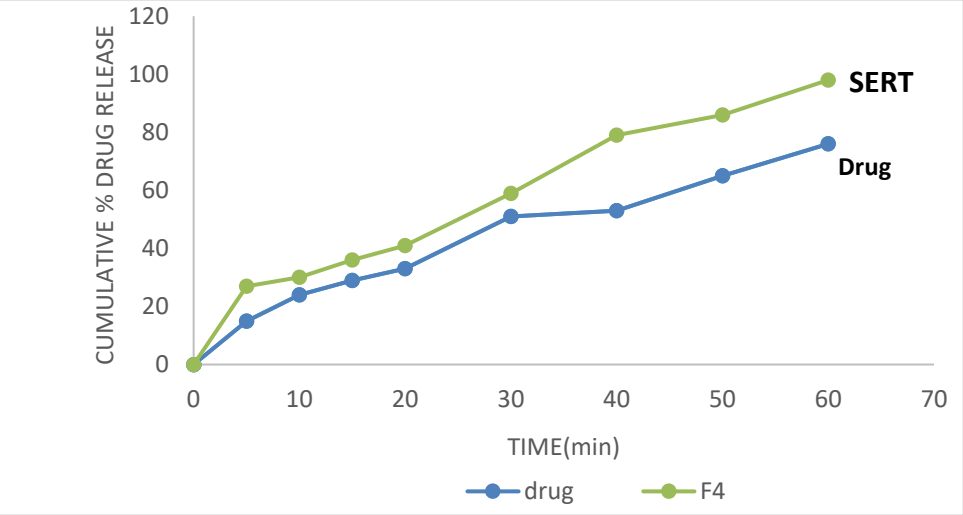


Table 7: % cumulative drug release of pure drug and optimized form SERT

TIME (min)	SERTRALINE (drug)	SERT 4 (optimized form)
0	0	0
5	15 ± 0.6	27 ± 0.4
10	24 ± 0.2	30 ± 0.2
15	29 ± 0.8	36 ± 0.3
20	33 ± 0.4	41 ± 0.7
30	51 ± 0.5	59 ± 0.5
40	53 ± 0.1	79 ± 0.6
50	65 ± 0.2	86 ± 0.7
60	76 ± 0.3	98 ± 0.1

All values Expressed as Mean ±SD (n=3)

Figure 14: % cumulative drug release of sertraline (Pure Drug) and optimized form (SERT 4)



Solubility Studies:

The solubility studies of pure drug and prepared Co-crystals were performed in 0.1 N HCL and water. The solubility of Co-crystals in water is 14 folds more than the pure drug and solubility of Co-crystals in 0.1 N HCL is 5.24 folds more than the pure drug.

Table 8: solubility studies

	Solubility (mg/ml)	
Formulations	**Water**	**0.1N Hcl**
Sertraline	0.035±0.2	0.132±0.4
SERT 1	0.422±0.5	0.608±0.2
SERT 2	0.291±0.8	0.364±0.4
SERT 3	0.383±0.4	0.432±0.9
SERT 4	0.492±0.7	0.692±0.1
SERT 5	0.398±0.2	0.428±0.6
SERT 6	0.297±0.3	0.487±0.8
SERT 7	0.432±0.2	0.611±0.7
SERT 8	0.300±0.8	0.537±0.5
SERT 9	0.279±0.4	0.469±0.1

FTIR Spectrums of drug and optimized form

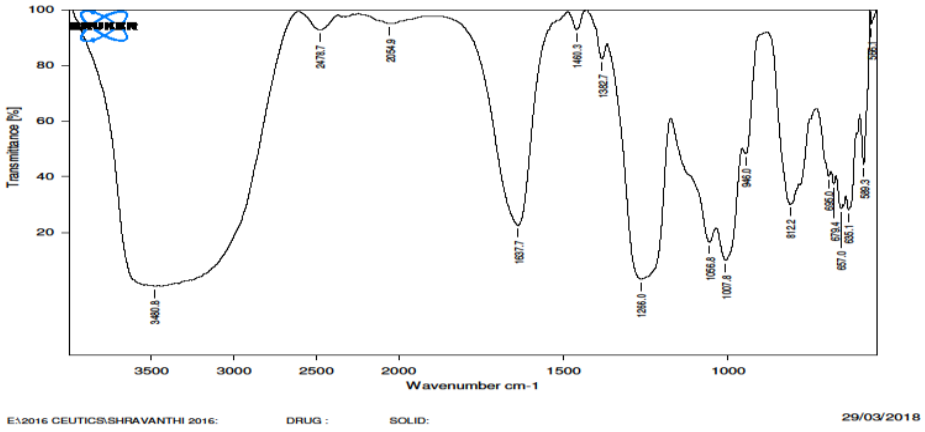


Figure 15: Sertraline FTIR spectrum

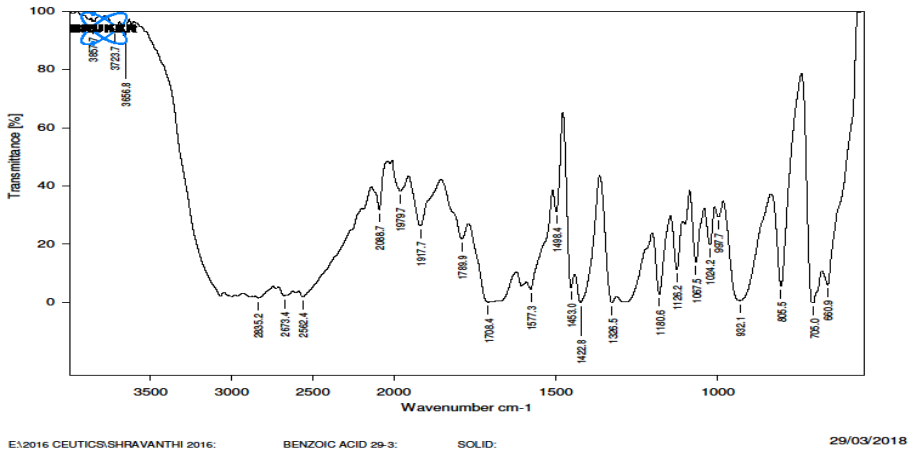


Figure 16: Benzoic acid FTIR spectrum

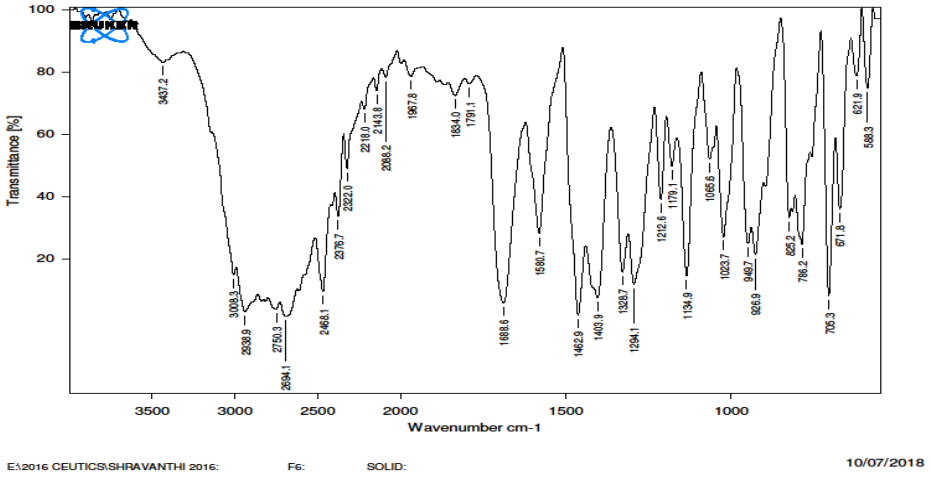


Figure 17: SERT 4 FTIR Spectrum

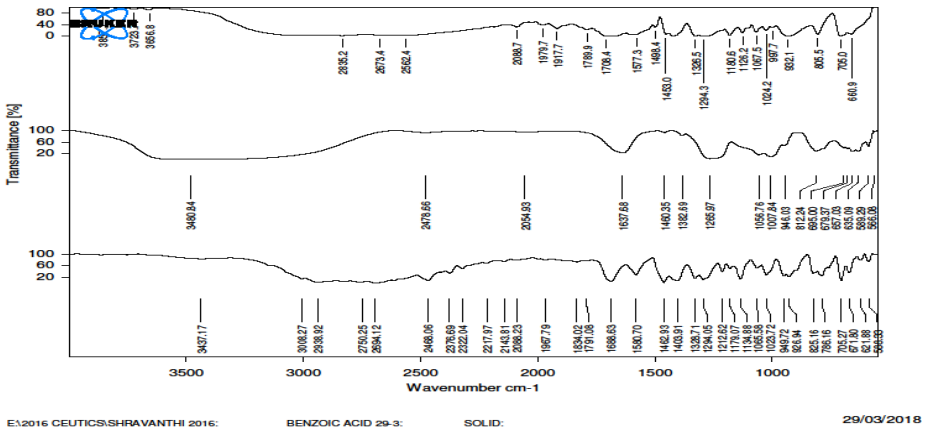


Figure 18: FTIR overlay of 1) sertraline 2) benzoic acid 3) sertraline-benzoic acid co-crystals

Table 9: Functional Group Detection:

SERTRALINE	BENZOIC ACID	SERTRALINE BENZOIC ACID CO-CRYSTALS	FUNCTIONAL GROUP
617.8	679.3	660.9	Alkyl halide
826.9	812.2	805.5	alkenes
1065.5	1007.8	1067.5	Alcohol
1294	1266.9	1294.3	Alkyl halide
1328.7	1382.6	1336.5	Alkane
1462.9	1480.3	1453.0	Alkane

Fluorescence Electron Microscopy:

At a magnification of up to 100X, co-crystals are clearly visible. Both pure drug and Optimized formulation were observed. Needle like structures was observed in optimized formulation.

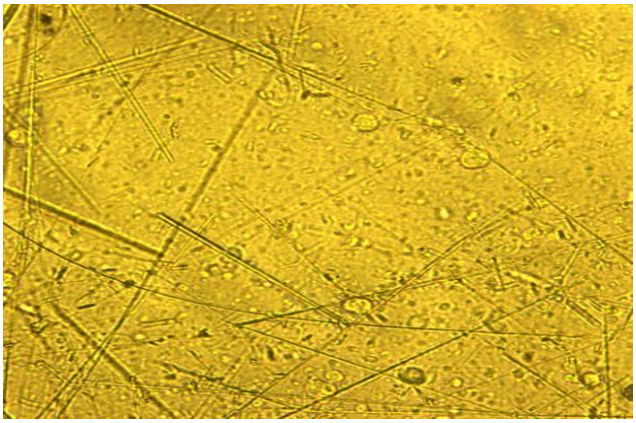
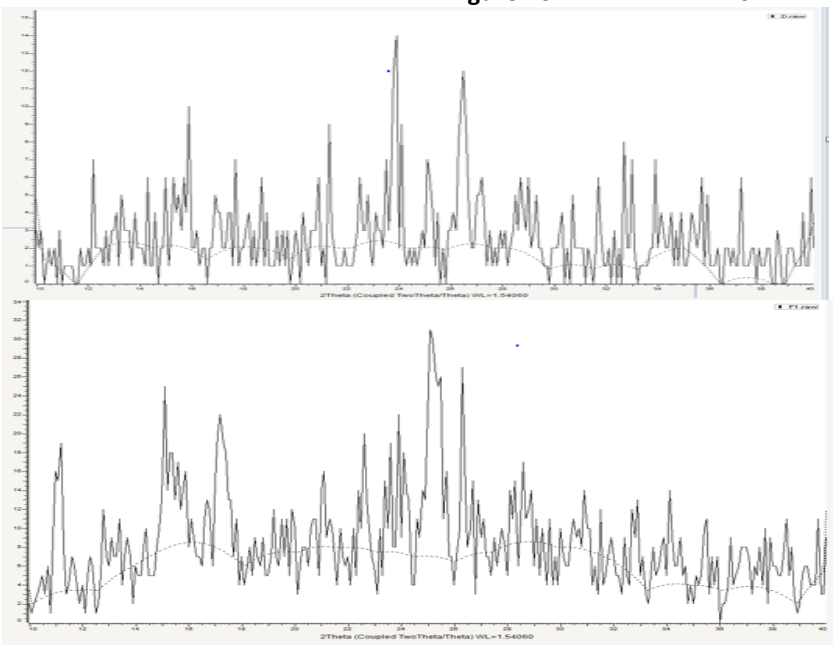


Figure 19: Needle shape co-crystals

Figure 20: PXRD PATTERNS:



SERTRALINE (PURE DRUG)

SERT 4 (optimized form)

Table 10: THETA (°) POSITIONS

Sertraline (PURE DRUG)	Sertraline benzoic acid co-crystals (SERT 4)
11.0	11.1
12.1	14.5
13.3	21.0
15.8	22.5
17.9	23.8
18.4	24.1
21.4	25.2
23.8	26.1
26.3	29.4

KINETICS OF DRUG RELEASE:

Mathematical modelling of % drug release in-vitro dissolution for optimized formulation

Table 11: kinetics of drug release

Time (min)	Cumulative % Drug Release	% Drug Remaining	Square Root Time	Log Cumulative % Drug Remaining	Log Time	Log Cumulative % Drug Released	Cube Root Of % Drug Remaining (Wt)	Wo-Wt
0	0	100	0	2	0	0	4.642	0
5	27	73	2.236	1.863	0.698	0.301	4.179	0.463
10	30	70	3.1622	1.845	1	1.477	4.122	0.520
15	36	69	3.8729	1.838	1.176	1.556	4.102	0.540
20	41	59	4.472	1.770	1.301	1.612	3.892	0.750
30	59	41	5.477	1.612	1.477	1.770	3.449	1.193
40	979	21	6.324	1.322	1.602	1.897	2.759	1.883
50	86	14	7.071	1.146	1.698	1.934	2.411	2.231
60	98	2	7.745	0.301	1.778	1.991	1.259	3.383

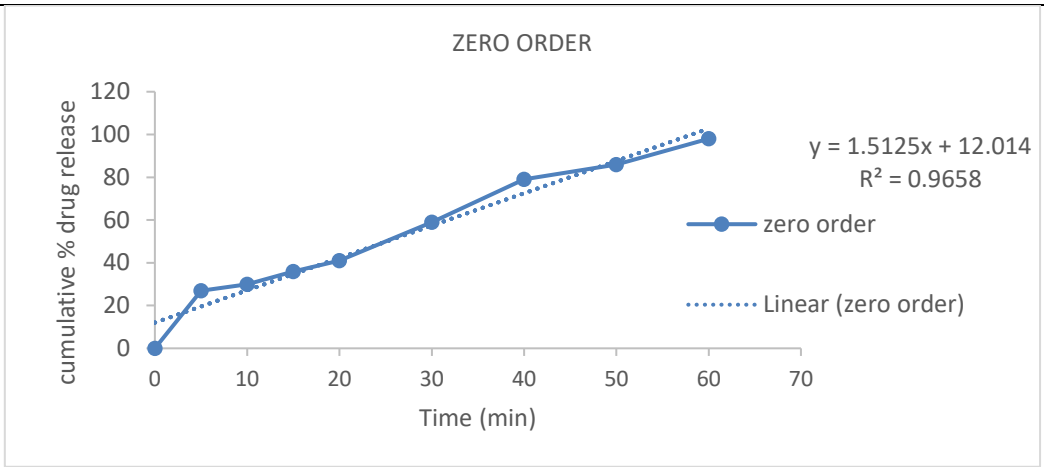


Figure 21: zero order kinetics

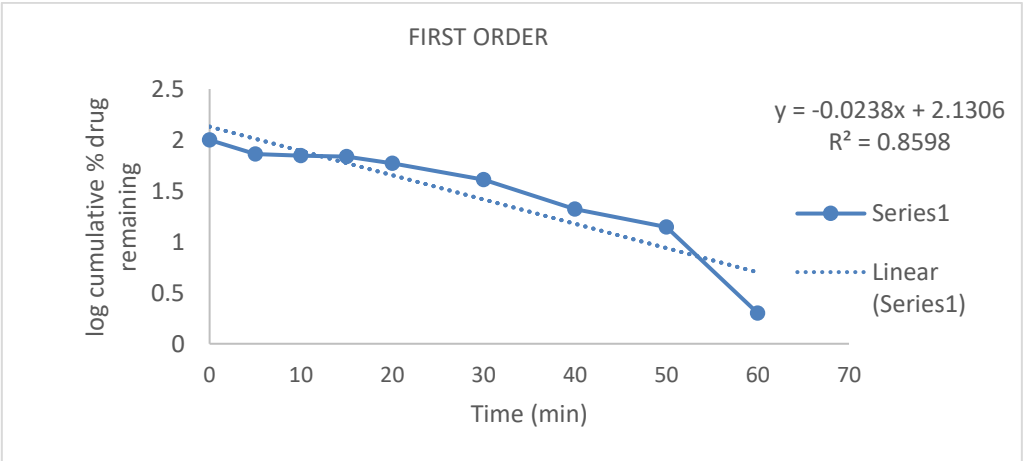


Figure 22: first order kinetics

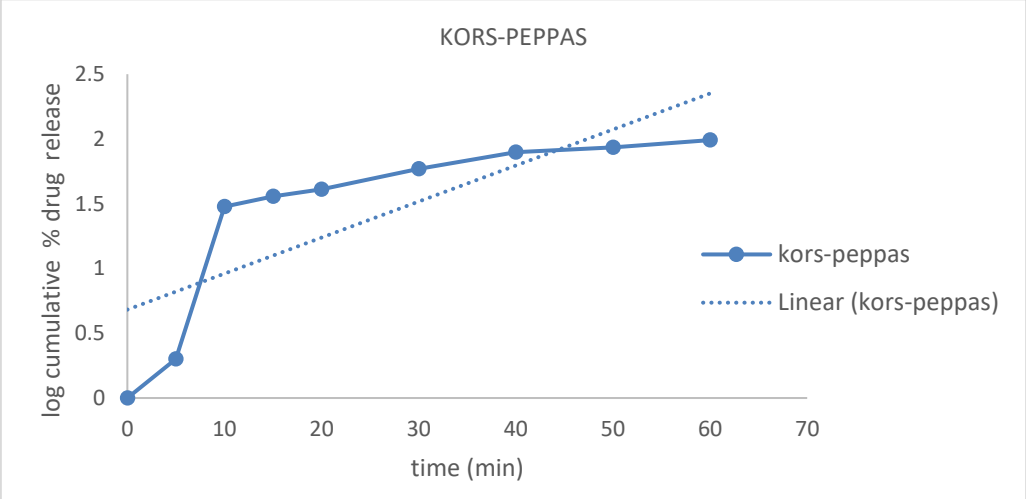


Figure 23: kors-peppas model kinetics

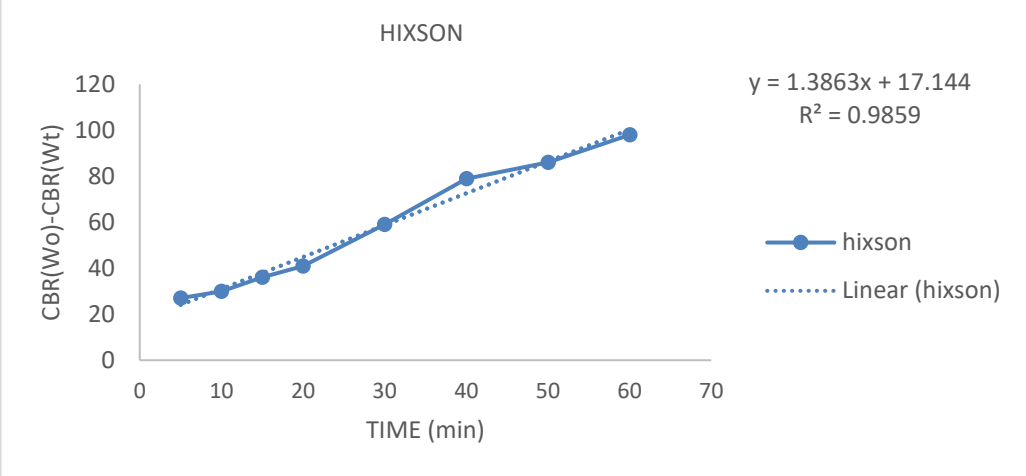


Figure 24: Hixon crowel model kinetics

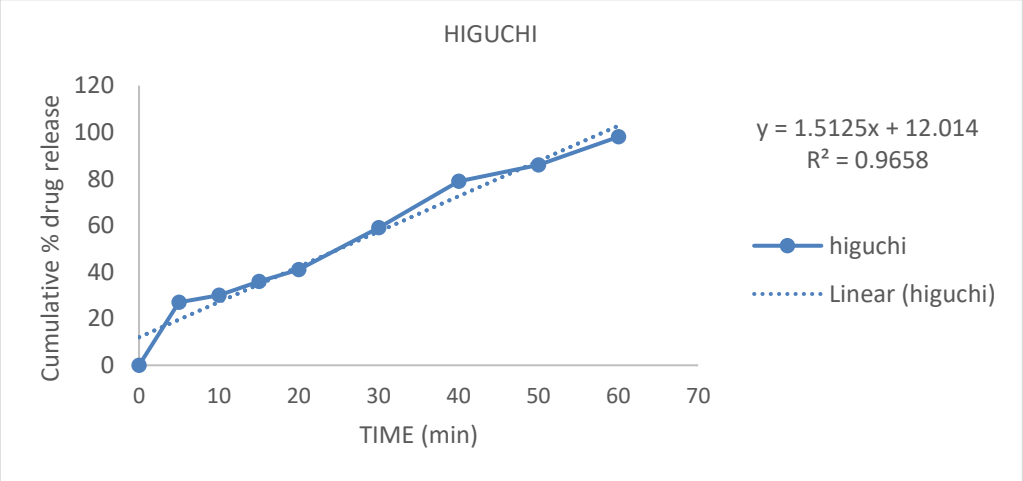


Figure 25: Higuchi model kinetics

Table 12: Results of standard deviation kinetic models:

kinetic model	r^2 values

ZERO ORDER	0.965
FIRST ORDER	0.859
KORSMAEYER- PEPPAS	0.630
HIXSON CROWEL	0.985
HIGUCHI	0.965

Stability Studies:

Table 13: stability studies of optimized formulation SERT 4

% drug release	Time in days			
	1	30	60	90
SERT 4	96.2±0.5	95.8±0.7	95.6±0.1	94.9±0.4

Values in mean of cumulative % drug release ± standard deviation (n=3)

Minor changes in parameters are observed conforming the stability of selected optimized formulation.

SUMMERY AND CONCLUSION:

Pharmaceutical co-crystals speak to an advantageous class of crystal form in the unique situation of pharmaceuticals. Co-crystals of medications and medication competitors speak to another kind of material for pharmaceutical advancement. Co-crystals are generally new to pharmaceutical industry and, pharmaceutical co-crystals have given another heading to manage issues of inadequately solvent medications. Co-crystals can possibly be significantly more helpful in pharmaceutical products than solvates or hydrates.

The relevance of co-crystals in API formulation incorporates the capacity to adjust physical properties, characterization of API, distinguish and grow new, restrictive types of recommended drugs and the chance to produce licensed innovation. Co-crystals development among sertraline and benzoic acid was characterized by PXRD and FTIR.

A novel sertraline benzoic acid co-crystal was prepared by Co-crystallization technique and has demonstrated most extreme % medicate discharge. At long last it was reasoned that the solubility of sertraline was 14 folds expanded by utilizing solvent evaporation co-crystal technique.

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