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CHITOSAN CO-CRYSTAL FOR ENHANCING THE SOLUBITY AND DISSOLUTION RATE OF DICLOFENAC SODIUM

Sunita Devi [*1], Kavita Bahmani [1] and Rinkle [2]

Departmental of Pharmaceutical Sciences [1], Guru Jambheshwar University of Science and Technology, Hisar - 125001, Haryana, India
Departmental of Pharmaceutical Sciences [2], Manav Institute of Pharmacy, Hisar - 125121, Haryana, India.

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Diclofenac sodium, Cocrystal, Dissolution rate and solubility study

Correspondence to Author:
Sunita Devi

Departmental of Pharmaceutical Sciences, Guru Jambheshwar University of Science and Technology, Hisar - 125001, Haryana, India.

E-mail: sunitamechu1504@gmail.com

ABSTRACT: The present study is designed to enhance the aqueous solubility of diclofenac sodium. For the said purpose co-crystal employing chitosan with diclofenac sodium is prepared by solvent exchange. The prepared co-crystal was characterized by FTIR, DSC, XRD and TGA studies. Further, solubility, anti-inflammatory activity and *in-vitro* release study was determined for different batches of the formulation. The solubility of different bathes of co-crystal was found to be between 34.6 to 46.6µg/ml as compared to the pure drug having a solubility of 18.6 and a physical mixture of 30.9µg/ml. The *in-vitro* release is found to be 72.5 to 84.8%, whereas PM shows 58.7 % release and pure drug shows 27.8 % release. The *in-vitro* release data of the optimized batch followed fickian diffusion mechanism. The % inhibition of formulation co-crystal is much more than the model drug (diclofenac sodium). Thus, the diclofenac-loaded co-crystal would be useful for delivering poorly water-soluble drugs with enhanced dissolution, solubility and improved anti-inflammatory activity of the drug.

INTRODUCTION: One of the interesting tasks in the pharmaceutical industry is to discover ways of improving the physicochemical properties of active pharmaceutical ingredients (APIs). More than 40 % of newly developed drugs candidates are poorly water-soluble [1]. APIs that permeate easily through mucous membranes but are poorly soluble (BCS class II) have poor bioavailability and are consequently associated with difficulties in dosage form design and manufacturing.

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In such scenarios, to improve the solubility and thereby the dissolution rate, formulation scientists often turned to various basic approaches such as salt formation, changes in the solid state structure, complexation [2], encapsulation, drug micronization into amorphous form [3], prodrug formation [4], solid dispersion [5, 6], salt formation [7], solubilization of drug in solvents, nanoparticles technology [8], physical modification, nanosuspension [9], modification of crystal habits such as polymorphous, pseudo polymorphous, self-emulsifying drug delivery systems (SEDDS) [10], liposomes [11], co-crystal [12-15], liquisolid [16-18] and use of surfactant "micellization" [19] *etc*. Out of numerous techniques explored so far, co-crystals have been proven to be the most capable approach to developing the solubility of poorly soluble drugs.

Co-crystals are defined as "solids that are crystalline single phase materials composed of two or more different molecular and/or ionic compounds generally in a stoichiometric ratio which are neither solvates nor simple salts" [20]. Noncovalent interactions such as hydrogen bonds (the main interaction), π-π interactions, halogen bonding and van der Waals forces are responsible for the formation of co-crystals [21]. When components of a co-crystal are a drug and a pharmaceutically acceptable excipient (coformer) the resultant molecular complex is called a pharmaceutical co-crystal. The conformers usually are water-soluble molecules such as saccharin, caffeine, nicotinamide, and carboxylic acids [22]. The availability of numerous coformers makes it possible to prepare several co-crystals for each drug and select the most appropriate one [23]. Example of pharmaceutical co-crystals chitosan co-crystal with acelofenac [24], Chitosan-telmisartan polymeric co-crystals [25], Acetazolamide co-crystal with theophylline and piperazine [26]. Co-crystals can modify properties of drugs without any impact on the intrinsic pharmacological activity of the molecule. Co-crystallization has been studied to optimize physicochemical properties of drugs such as mechanical properties, stability, solubility, permeability and bioavailability.

Diclofenac (DFA) is used to treat mild to moderate pain or signs and symptoms of osteoarthritis or rheumatoid arthritis. DFA structure, shown in **Fig. 1**, belongs to BCS class II thus it behaves as a low soluble and a high permeable drug so once it is available in the form of a solution, it rapidly gets absorbed. Diclofenac (pKa = 4.18) is a weak acid that is mainly available in its salt form. Its sodium, potassium [27] and alkyl-hydroxyl amine salts are the most common.

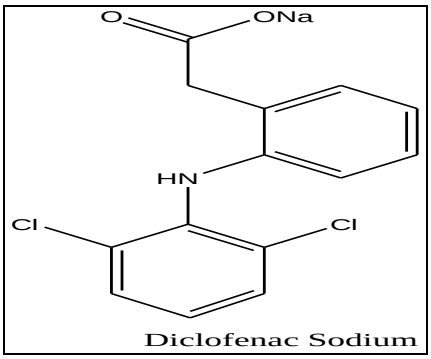

FIG. 1: CHEMICAL STRUCTURE OF DICLOFENAC SODIUM

Numbers of efforts have been made to incorporate DFA into co-crystal using l-proline [28], ranitidine hydrochloride [29], and theophylline [30] are known. Still, there is no report on the crystal structure of any of the chitosan co-crystals.

A detailed scan of scouring the literature shows that chitosan (CS) is the most popularly used polymer to prepare co-crystals. CS given in **Fig. 2**. is the best biodegradable conformer that can increase the solubility of poorly soluble drugs, as stated earlier [31-34]. This has prompted us to explore the possibility of developing DFA-CS co-crystals by a one-step process using a citrate ion without any toxic cross-linking agents and to study their potential for improving dissolution rate and physicochemical properties. Our objective is to develop a DFA co-crystal using chitosan to increase the solubility and dissolution rate of DFA by preparing its co-crystals using citrate-ion cross linking and to carry out the physicochemical characterization of the optimal formulation by using infrared spectroscopy, XRD, DSC, and TGA, as well as an in vitro drug release study.

METHODOLOGY:

MATERIALS: DFA was obtained as a gift sample from Arbro Pharmaceuticals Pvt. Ltd (New Delhi, India). Chitosan (low molecular weight, > 85% deacetylated, poly (d-glucosamine) was supplied by Sisco Research Laboratories Pvt. Ltd. Mumbai, India. CS structure is shown in **Fig. 2**. All other reagents and chemicals used in the study were of analytical grade and used as received.

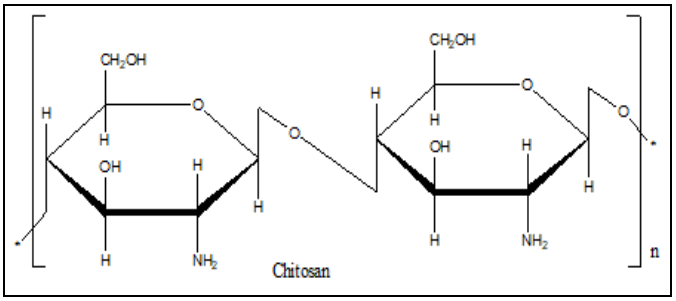

FIG. 2: CHEMICAL STRUCTURE OF CHITOSAN

Preparation of Cocrystal: DFA, chitosan co-crystal were prepared by solvent exchange method. An accurately weighed chitosan was dissolved in 1% aceticacid (20ml). Then an accurately weighed quantity of drug (DFA) was added into the above solution and the resulting solution was added drop wise into 1% sodium citrate solution with

continuous stirring. Here, sodium citrate was used as a salting-out agent to precipitate chitosan as chitosan citrate on DFA crystals. DFA chitosan co-crystal was filtered through Whatman filter paper No.1, and crystals were dried at 45 ºC for 24 h and passed through sieve no#40. **Table 1** depicts the various co-crystals formulation using chitosan at different concentrations.

Physical mixtures (PM) was prepared by thoroughly mixing presieved equal weight ratio of drug (DFA) and CS using pestle and mortar until a homogeneous mixture was obtained.

Entrapment Efficiency (EE): The amount of drug entrapped in co-crystals was calculated by separating the free drug by centrifuging co-crystals at 15000rpm for 40 min. by cooling centrifuge (C-24 BL, Remi Instruments, and Mumbai, India). The clear supernatant was analyzed for the contents of unentrapped drug i.e. diclofenac sodium by measuring the absorbance at 276 nm in a UV-VIS spectrophotometer (Varian cary 5000, Australia) [35]. The entrapment efficiency (%) was calculated as follows:

$$EE\ (\%) = (DFA\ t\text{-}DFAs) / (DFA\ t) \times 100$$

Here, DFAt= is the total amount of drug used in the preparation of co-crystals and

DFAs = is the unentrapped drug (DFA) present in the supernatant.

Characterization of Co-crystal:

Fourier Transform Infrared Spectroscopy (FT-IR): FT-IR spectral analysis of DFA and various drug-chitosan co-crystal formulations were recorded using a Thermo Scientific Nicolet IR 200 spectrometer by KBR pressed-pellet technique. The KBr pellets were made by mixing required quantities of pure drug (DFA), chitosan and various formulations with 100 mg of dried KBr and pressed into pellets using a KBr pellet press [36]. Then each pellet was scanned 40 times at 4 cm^{-1} resolution over the wave number range of 4000–400 cm^{-1}.

Powder X-ray Diffraction (PXRD): Changes in the crystalline structure of DFA before and after formulation were studied using Powder X-ray diffraction. The required quantity of drug and formulations were placed in the XRD sample holder then scanned using Rigaku Miniflex X-ray diffractometer with Cu Kα radiation and operated at 40 kV and 30 mA (l = 1.54 (Å); a 2θ range of 5–45º with a 0.02º step size and a 1 s step time was fixed as the parameter for retrieving the XRD [37, 38].

Differential scanning Calorimetry (DSC): To study the changes in the crystal structure during the co-crystal formulation, DSC analysis was done [39]. A Scinco DSC N 650 differential scanning calorimeter was used to record the DSC traces of the DFA pure and co-crystals. The samples were loaded into the aluminum pan of the DSC instrument and scanned at a heating rate of 10ºC/min under a helium environment by purging helium at 40 ml/min.

Thermogravimetric Analysis (TGA): Pure drug and co-crystal samples were loaded (ca. 10 mg) into the platinum sample pan of the Scinco N-1000 thermogravimeter unit, and the temperature was programmed to reach 600ºC at a heating rate of 10ºC /min in a nitrogen atmosphere.

Solubility Studies: DFA pure drug and co-crystals formulation containing DFA equivalent to 10 mg was dispersed in 10 ml of distilled water and kept on shake for 48hrs at room temperature (25°C) to determine the solubility of the drug. The obtained solution was filtered by 0.45µm millipore filter paper, and the drug content was determined by taking absorbance at 276nm using UV-Visible Spectrophotometer. The amount of drug was calculated using the calibration curve in water.

***In-vitro* Drug Release:** *In-vitro* dissolution studies were performed using the USP type II dissolution apparatus. Dissolution studies of the pure drug (DFA) and a co-crystals formulation containing DFA equivalent to 10mg were conducted in 300ml phosphate buffer (pH 7.4) at 37±0.5°C with a constant stirring rate of 50 rpm. The powders were dispersed over the dissolution medium. Aliquots of the sample (5ml) were withdrawn at different time intervals and replaced with an equal amount of the dissolution medium to maintain a constant volume. Samples were filtered through 0.45µm millipore filters and analyzed by UV-visible spectro-photometer at 276nm. The mechanism of drug release from the solid dispersion was determined by fitting the release data to several models like

zero order, first- order, Higuchi and Korsmeyer–Peppas model.

Anti-inflammatory Activity: The anti-inflammatory activity of model drug DFA and co-crystals were estimated by using the egg albumin denaturation method, reported [40] by Chavan & Hosamani, (2018) with slight modifications. The mixture was composed of 0.2ml of fresh hen's egg albumin, 2.8ml of pH 6.4 PBS (Phosphate buffered saline), and 2ml of different concentrations (125, 250, 500 & 1000µg/ml) of co-crystals (containing DFA drug equivalent to 5mg) which was made in Dimethyl sulfoxide (DMSO). The obtained mixtures were placed in an incubator (Caltan, NSW, India) at a temperature of 37±2 ^{o}C for 15 min incubation followed by heating at 70^{o}C. Further, the mixtures were allowed to cool at room temp & absorbance was measured at a wavelength of 276nm. A similar experiment was performed for the DFA model drug with the same concentrations as taken for the formulation as a reference or control. The following formula was employed to calculate the % inhibition of protein denaturation.

% Inhibition = 100 × (Abs. of control - Abs. of the sample) / (Abs. of control)

RESULTS AND DISCUSSION:

Entrapment Efficiency (EE): The EE of the co-crystal formulations was 81.5 to 91.7 whereas the EE of PM was 80.4. High values of EE revealed the non-significant losses that occurred during the processes of preparing co-crystal by solvent exchange method.

Fourier Transform Infrared Spectroscopy (FT-IR): Fig. 3. Exhibits the FT-IR spectra of DFA and co-crystal formulation in the frequency range of 4000-400cm^{-1}. The literature of CS shows a broad absorption band 3422.04cm^{-1} which may be attributed to -OH stretching of alcohols. The peak appearing at 2874.61cm^{-1} can be ascribed to a –CH stretch of alkane, while the peak appearing at 2145.70cm^{-1} is due to–C≡C– stretch of alkynes, whereas the peak appear at 1602.93cm^{-1} is due to –NH bending while the peak at 1420.62cm^{-1} and 1384.11cm^{-1} are due to –CH bending of alkanes [25]. The spectra of DFA exhibits a broad absorption band at 3233.10 cm^{-1} is due to –OH stretching of alcohols. The peak appearing at 1398.03 cm^{-1} are due to –CH bending of alkanes [29], while the peaks are appearing at 952.54 cm^{-1} , 869.80 cm^{-1}, 840.47cm^{-1} and 747.98 cm^{-1}. The CS-DFA co-crystal spectra displayed a characteristic drug peak at 3325cm^{-1}that is attributed to –OH structure in the co-crystal, and the peak appearing at 1067.17 cm^{-1} may be ascribed to –CN stretch of amine. The peak appearing at 922.28 cm^{-1} and 612.07 cm^{-1} are due to ≡ C-H bending of alkane that appeared in co-crystals. The spectra of the CS-DFA co-crystal demonstrated a slight shift of peak at 3325cm^{-1} due to the interaction between drug DFA and carrier that confirms the formation of co-crystals.

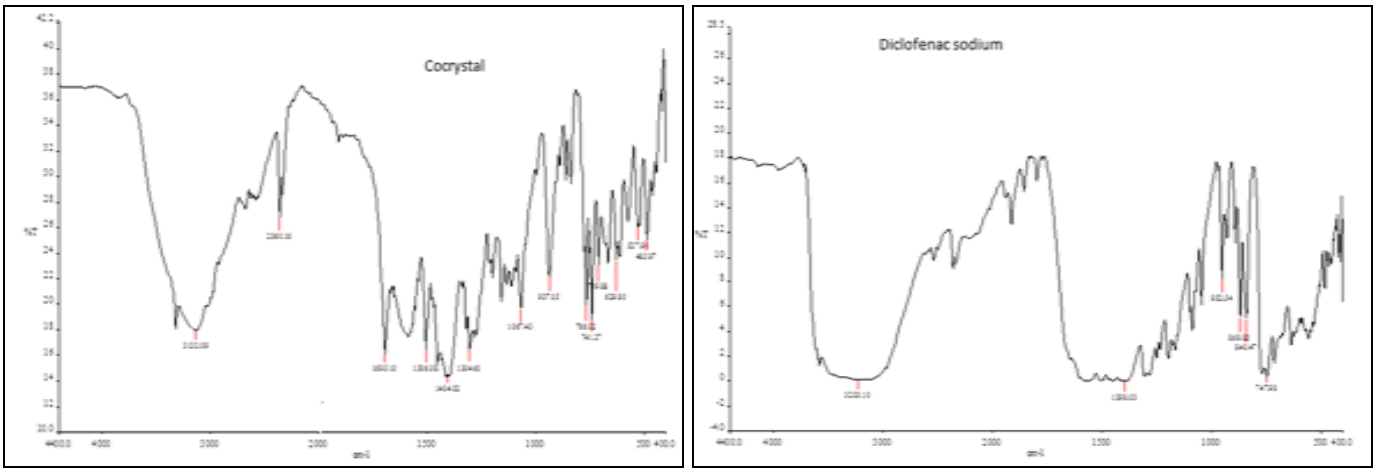

FIG. 3: FTIR SPECTRA OF DRUG (DFA) AND ITS CO-CRYSTAL

Powder X-ray Diffraction (PXRD): The XRD result of the drug and its co-crystal formulation are shown in **Fig. 4**. The major characteristic diffraction peaks for DFA were observed at 2θ of 5.29°, 9.73°, 10.54°, 12.18°, and 13.31. The diffraction of the co-crystal showed obvious superstition of DFA diffraction peaks with much

lower intensity in comparison with that of the pure DFA.

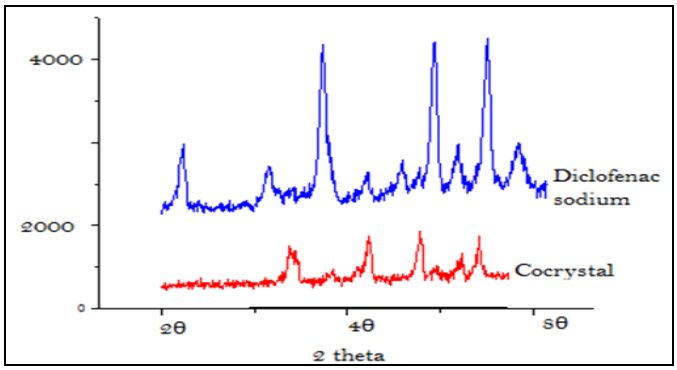

FIG. 4: XRD SPECTRA OF DFA AND CO-CRYSTAL FORMULATION

Differential Scanning Calorimetry (DSC): The DSC thermogram of DFA and co-crystal formulation are given in **Fig. 5**. The DSC of pure DFA shows a sharp melting endotherm peak that stretches from 270°C to 280°C, with a peak at maximum at 276°C, equivalent to the melting endothermic range of pure diclofenac sodium.

For the co-crystal formulation, the endothermic peak for shifted toward a lower value (135°C), due to the changes in the crystalline geometry of DFA caused by the deposition of chitosan over the DFA by hydrogen-bonded interaction of the –COOH and –NH (imidazole) group of DFA with free amino or amide group of CS. In the co-crystal formulation, the endothermic peak intensity was gradually get reduced, which shows the changing of the crystalline structure to amorphization of DFA crystal caused by the depositing of CS.

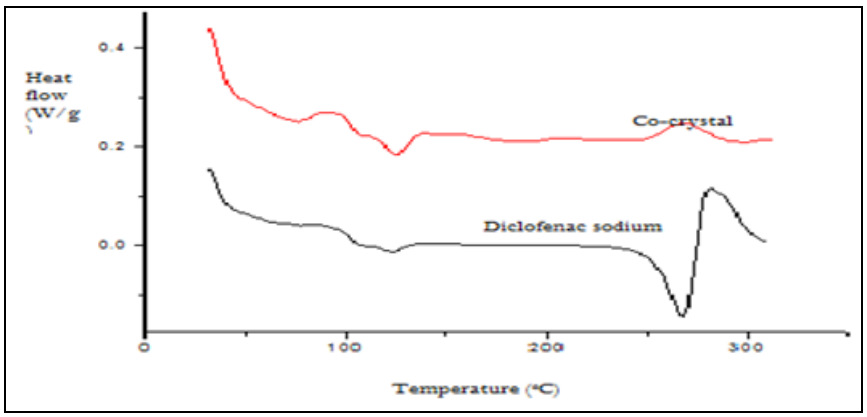

FIG. 5: DSC THERMOGRAM OF CO-CRYSTAL AND DFA

Thermogravimetric Analysis (TGA): The result of the TGA are depicted in **Fig. 6**. The TGA of the drug shows a two-step degradation profile. The first drug degradation starts near 270°C, as is supported by the DSC result; that is, it starts to melt at 275°C. After 275°C to 350°C, there is a huge weight loss of around 60%. However, for the co-crystal, the first weight loss started a little earlier than that of pure DFA 200°C, and the second weight loss was similar to DFA, but the thermogram ended before 400°C. These results show that the CS deposit over the crystals affects the crystal structure of DFA into amorphous powder.

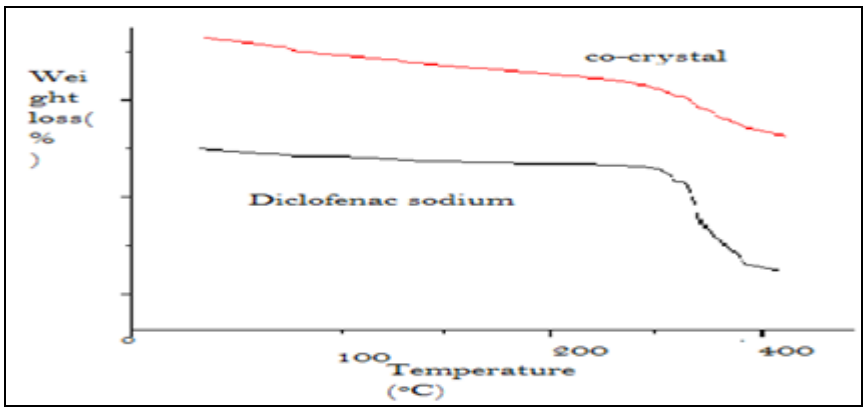

FIG. 6: TGA OF CO-CRYSTAL AND DFA

Solubility Studies: The different batches of co-crystals were prepared to contain CS (100-300mg) and DFA (400mg) shown in **Table 1**. The pure DFA dispensed a solubility of 18.6 µg/ml in water at room temperature, whereas the PM showed a solubility of 30.9 µg/ml. The PM presented solubility higher than the pure drug because of the CS. However, the co-crystal conferred solubility values ranging from 34.6-46.6 µg/ml. This increase may be due to the formation of a soluble complex between the drug and CS. Bar graph of solubility is shown in **Fig. 7.**

TABLE 1: SOLUBILITY, *IN-VITRO* RELEASE, % RELEASE AND % EE OF DIFFERENT BATCHES

Batch	Conc. Of chitosan (mg)	Conc. Of DFA (mg)	Solubility (µg/ml)	% release in 60 min.	EE (%)
1	100	400	38.9	80.7	87.9
2	300	400	46.6	84.8	91.7
3	500	400	34.6	72.5	81.5
PM	400	400	30.9	58.7	80.4
DFA			18.6	27.8	

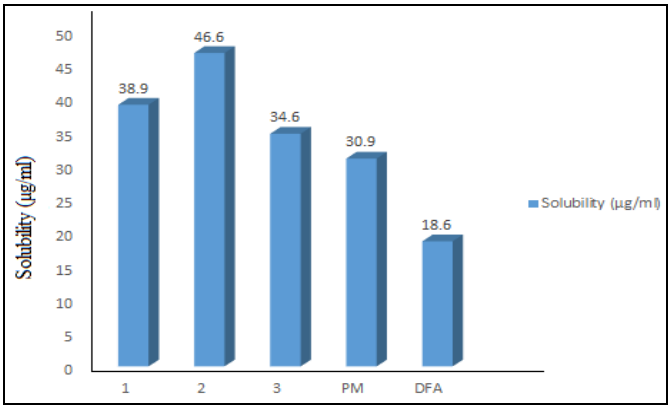

FIG. 7: SHOWN THE BAR GRAPH OF SOLUBILITY OF DRUG (DFA), PM AND DIFFERENT BATCHES OF CO-CRYSTAL FORMULATION

***In-vitro* Drug Release:** All the formulations batches (1 to 3) of the prepared co-crystals of DFA were subjected to *in-vitro* release studies, which were carried out using a USP dissolution apparatus type II using pH 7.4 buffer for 1 h shown in **Fig. 8**. The drug release increased when the concentration of CS increased. CS is a well-known biocompatible co-former used to prepare co-crystals that increases the dissolution rate of DFA by increasing its wettability by its hydrophilic nature thereby altering the surface morphology of the drug, and reducing particle size. The depositing of the CS polymer over the drug particles was higher and stronger when associated with sodium citrate. The reaction of CS with multivalent anion sodium citrate leads to the formation of bridges between the polymeric chains, which results in the efficient deposition of CS by forming a three-dimensional network on the drug crystals. This might have eventually resulted in efficient adsorption of CS on the drug crystals. Hence, these co-crystals can improve the solubility of the drug. Adsorption of chitosan on the drug's surface was improved by adding an anionic cross-linker i.e., sodium citrate. The cross-linker bridges thus formed over the chitosan improved the deposition of chitosan molecules on drug particles. Suppose the concentration of the polymer is further increased the dissolution decreases due to the formation thick gel layer of the chitosan on the surface of the drug. This gel structure will increase the distance between the core DFA crystals from the outside solvent imbibing. These results are well corroborated by a previous study that described acyclovir co-crystals prepared by chitosan [41].

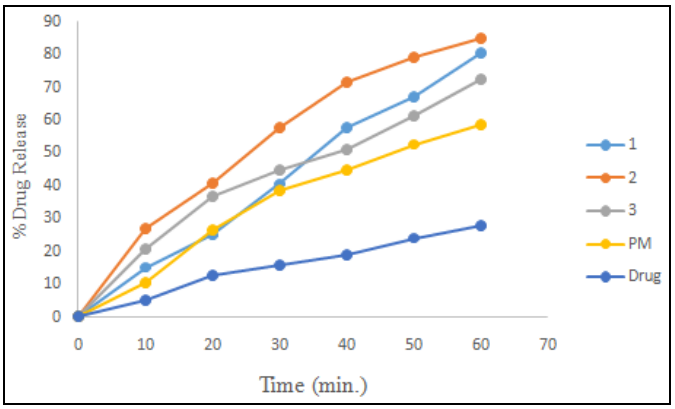

FIG. 8: *IN-VITRO* RELEASE PROFILE OF DRUG (DFA), PM AND DIFFERENT BATCHES OF CO-CRYSTAL

The release data were fitted into various release kinetic models to determine their release kinetics and drug release mechanism from the co-crystal formulation's optimized batch. The kinetic release data of the optimized formulation was best fitted into the Higuchi's square root release kinetic model based on the regression coefficient (R^2 of 0.982). Further, the value of release exponent n ($0.43 < n < 0.85$) determined the fickian diffusion mechanism of drug release [42] **Table 2.**

TABLE 2: RELEASE KINETICS AND MODELING DATA OF OPTIMIZED CO-CRYSTAL BATCH-2

Formulation	Zero order R^2	First order R^2	Higuchi R^2	Korsmeyer Peppas R^2	n value
Co-crystal	0.952	0.791	0.982	0.957	0.450

Anti-inflammatory Activity: Fig. 9 shows the *in-vitro* anti-inflammatory activity of the drug DFA and co-crystal through the egg albumin denaturation method. The results demonstrated that the % inhibition of formulation co-crystal is much more than the model drug DFA. It is observed from the study that increasing the concentration of DFA in the formulation and DFA alone shows an increase in anti-inflammatory activity. But comparing the effect, it is clear that co-crystal is more effective than drug DFA in its pure form. Hence, it is concluded that the formulation co-crystal is more active than the drug. Therefore, co-crystal shows higher anti-inflammatory activity than the model drug DFA.

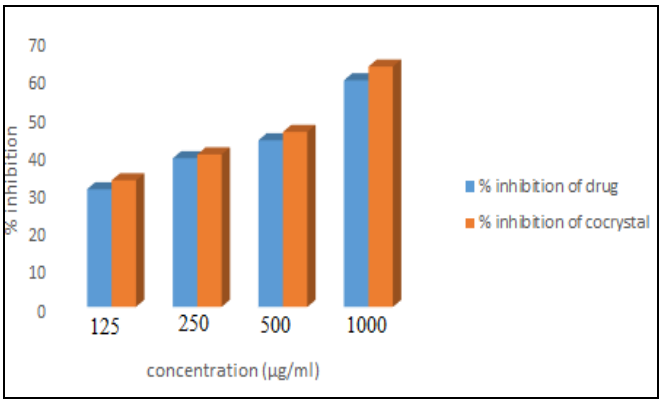

FIG. 9: ANTI-INFLAMMATORY ACTIVITY OF DRUG (DFA) AND CO-CRYSTAL FORMULATION

CONCLUSION: In summary, from the results obtained, it was strongly evidenced that the formed chitosan-DFA co-crystals have improved solubility and bioavailability with a certain concentration of drug and polymer used.

In our case, the concentration from 100 to 300 mg weight of the drug to polymer supports the continual improvement of the solubility of the drug, while the same on further increasing the polymer will tend to decrease the solubility; hence we chose the 300 mg as the favorable highest drug-polymer weight for excellent solubility.

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