AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Development of Sustained Released Microparticles of Diclofenac Sodium Using Polymer Complex by Spray Drier

Jitendra B. Naik[1*], Rameshwar K. Deshmukh[1], Vikas V. Kamble[2]

1. Institute of Chemical Technology, North Maharashtra University, Jalgaon-425 001, Maharashtra, India

2. Department of Chemical Technology, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad- 431 004 Maharashtra, India

ABSTRACT

Complex of Carboxymethyl cellulose (CMC) sodium salt and β-cyclodextrin (β-CD) were evaluated as sustained release polymers. Diclofenac sodium **(**DS), CMC sodium salt and β-CD were taken for the preparation of spray dried sustained release microparticles in the different ratio of 1: 0.125:0.125, 1:0.188:0.187 and 1: 0.25: 0.25 (wt/wt) respectively. The DS loaded microparticles were evaluated for particle size, surface morphology by atomic force microscopy (AFM), structural interaction by Fourier transform infrared spectroscopy (FTIR) and thermal characterization by differential scanning calorimetry(DSC). These microparticles further formulated into the tablet dosage form and evaluated for different parameters. Several kinetic models were employed to evaluate the possible changes in the release mechanism. The drug: polymer ratio of 1:0.25:0.25 shows better result of sustained release than the other ratios. The particle size of the optimized microparticles was found to be in the range of 300 nm to 5 µm. FTIR and DSC result reveals the complex formation between DS, CMC sodium and β-CD. X-ray diffraction results indicated that the degree of crystallinity was reduced and most of the drug existed in amorphous state. . The reported method is easy and reproducible and can be used for the batch scale production.

Keywords: Drug, Polymer, Micro particles, Spray-drying, Encapsulation, etc.

*Corresponding Author Email: jitunaik@gmail.com

Received 11 January 2013, Accepted 22 January 2013

Please cite this article in press as Naik JB *et al.*, Development of Sustained Released Microparticles of Diclofenac Sodium Using Polymer Complex by Spray Drier. American Journal of PharmTech Research 2013.

INTRODUCTION

Controlled or sustained release delivery system is a tool for optimizing therapeutic effect, by maximizing the bioavailability of conventional drugs and reducing side effects. Controlled release dosage forms cover a wide range of prolonged action formulation, which provide continuous release of their active ingredients at a predetermined rate and for a predetermined time[1]. Diclofenac sodium is a non steroidal anti-inflammatory agent, belongs to the class phenyl acetic acid derivatives, which is widely used in the long term therapy of rheumatoid arthritis. The biological half-life of Diclofenac sodium is 1-2 hr, therefore it requires multiple dosing to maintain therapeutic drug level in blood, necessitates preparation of a controlled release formulation. Diclofenac sodium is poorly soluble in water and practically insoluble compound in acidic solution (pKa 3.9); however, it dissolves in intestinal fluid. Gastrointestinal effects commonly observed include gastritis, peptic ulcers, bleeding, hypersensitivity reactions and renal effects[2-5].

Spray drying is a unique and important technique for microencapsulation of drugs. Spray drying can be defined as the transformation of a material from a liquid state into a dried particulate form by spraying the feed into a hot drying gas medium. Spray dryer mainly consist of spray nozzle through which we can spray solution/emulsion of drug and polymer; Solvent evaporates quickly leaving solid microparticles. The use of this technique appears to be attractive for the preparation of microparticles having narrow size distribution range[6-8].

An attempt has been made to prepare microparticles of Diclofenac sodium using spray-drying technology in aqueous system and considered as an alternative to the conventional microencapsulation methods. Information of the spray drying technique for the preparation of microparticles was found in the recent published literature[9-12]. The use of aqueous system is becoming popular for spray drying technique due to the risk of product contamination, toxicity, fire and explosion by organic solvents[13]. The purpose of the present work was to develop a new formulation of sustain release microparticles of diclofenac sodium using spray drying technique.

MATERIAL AND METHODS

Materials

Diclofenac sodium (DS) was provided by Emcure Pvt. Ltd. Pune as a gift sample. Carboxymethyl cellulose (CMC) sodium salt, lactose, β-cyclodextrin (β-CD), starch soluble, microcrystalline cellulose, Silicon dioxide & magnesium stearate was purchased from HiMedia laboratories Pvt. Ltd. (Mumbai, India). All other solvents and reagents were of analytical grade and used as provided.

Preparation of encapsulated microparticles

Sustained release micro particles of DS were prepared by using spray dryer (Labultima, Mumbai). DS, CMC sodium salt and β-CD in the different ratio of 1:0.125:0.125, 1:0.188:0.187 and 1:0.25:0.25 (wt/wt) were dissolved in distilled water respectively and the resulting solutions were gently stirred for 30 minutes at room temperature. This homogeneous solution then fed separately for spray drying by adjusting different parameters to obtain microparticles containing DS. The adjustable spray drying parameters are inlet and outlet drying temperature and sample feed rate. Spray drying process parameters are given in Table 1. The encapsulated microparticles were collected in collection chamber[14]. These microparticles were used for the preparation of sustained released tablets.

Table 1: Spray drying process parameters

Inlet drying temperature	130 ^{0}C ± 1 ^{0}C
Approximate outlet drying temperature	60 ^{0}C ± 1 ^{0}C
Feed rate	15 ml/min
Aspirator rate	42%
Aspirator rate	2 psi
Vacuum	90 mm Hg

Characterization of the microparticles

Drug loaded microparticles from SR tablet showing sustained drug release among all batches was used for the presentation of the characterization study.

Photomicroscopic study

The particle size of the drug loaded microparticles was determined by capturing the series of digital images using motic B1 advanced series digital microscope (Motic, China) fitted with imaging accessories equipped with computer controlled image analysis software (motic images 2000, 2.0 Version).

Atomic force microscopy (AFM)

The higher resolution images for the morphology of microparticles were obtained from Atomic Force Microscopy (AFM, Solver PRO-M scanning probe microscope, Moscow, Russia). AFM was used in semi-contact mode. Optimized drug loaded microparticles were uniformly spread on standard glass surface and particle size data were calculated from 50 µm x 50 µm and 100 µm x 100 µm scan size height image.

Fourier Transform Infrared (FTIR) spectroscopy study

FTIR spectra of DS, CMC sodium salt, β-CD and drug loaded microparticles were taken in order to find the chemical stability of drug in the microparticles using FTIR spectrophotometer (FTIR-8400; Shimadzu, Asia Pacific Pvt. Ltd. Singapore) by KBr pellet method in the scan range of

4400-500 cm^{-1}.

Differential scanning calorimetry (DSC)

The thermograms of pure DS, CMC sodium salt, β-CD and drug loaded microparticles were recorded on DSC calorimeter (DSC-60, Shimadzu Corporation, Kyoto, Japan). The accurately weighed samples (±5 mg) were hermetically sealed into aluminum pan (Sample sealer & crimper SSC-30, Shimadzu Corporation, Kyoto, Japan). The DSC runs were performed over a temperature range of 30 ^{0}C to 400 ^{0}C at a heating rate 10 ^{0}C/min under pure dry nitrogen flow of 50 ml/min.

X-ray diffraction (XRD)

In order to access the physical status characterization of drug i. e. amorphous or crystalline, X-ray diffraction patterns of DS, CMC sodium salt and β-CD and drug loaded microparticles were obtained in a X-ray diffractometer (Miniflex, Rikagu) with Cu-kα radiations (λ = 1.5406 A^0). The samples were analyzed over the angle range (2θ) 20^0 - 80^0.

Preparation & characterization of SR Tablet

Tablet formulations were prepared by wet granulation method.

Wet granulation method:

Lactose, microcrystalline cellulose and starch powder were blended and granulated according to the composition (Table 2), passed through "No. 20" mesh sieve, and uniformly wetted with certain volume of deionized water. The wetted mass was then granulated by passing it through "No. 20" mesh sieve, for getting uniform particle size and it was dried at 50 ^{0}C for 24 hrs in a tray dryer.

Table 2: Composition details for preparation of the SR tablets

Ingredients	Sample 1	Sample 2	Sample 3
Equivalent weight of Drug	100.00	100.00	100.00
Carboxymethyl cellulose sodium salt	12.50	18.75	25.00
β-Cyclodextrin	12.50	18.75	25.00
Lactose	151.50	139.00	126.50
Starch soluble	31.50	31.50	31.50
MCC	31.50	31.50	31.50
Magnesium stearate	7.00	7.00	7.00
Silicon dioxide	3.50	3.50	3.50
Total weight	350.00	350.00	350.00

All quantities from table are in mg.

After drying, these granules were thoroughly mixed with mixture of magnesium stearate and colloidal silicon dioxide. At the end, granules and encapsulated microparticles were added and

mixed manually and compressed into tablets using 6 mm flat-faced punch on single station tableting machine (Lab press, CIP). Theoretically each tablet contained 100 mg equivalent weight of DS. Three batches were prepared for each formulation. Tablets were characterized by weight, hardness and friability. For each formulation, weight variations of the tablets were evaluated on 20 tablets with an electronic balance (Shimadzu, AUX220, Kyoto, Japan). Tablet hardness was obtained on 6 tablets using Monsanto hardness test apparatus. Friability was determined on 20 tablets by an Erweka TA Roche-type Friabilator (Adinath Industries Pvt. Ltd. Mumbai, India) at a speed of 25 rpm for 4 min.

In vitro drug dissolution studies

Dissolution test was carried out according to USP XXIII on tablets containing DS (n = 3) in dissolution test apparatus (model Vankel, India) USP type II (apparatus 1, 100 rpm, 37 ± 0.5 ^{0}C). The dissolution medium of 0.1 N HCl and phosphate buffer (pH 6.8) were prepared according to the procedure given in Indian Pharmacopoeia 2007[15]. The tablets were tested for drug release initially for 2 hrs in 0.1 N HCl (900 mL), as the average gastric emptying time is about 2 hrs. After this, all the 0.1 N HCl was replaced with 900 mL of phosphate buffer (pH 6.8) as a dissolution media and the study was continued at this pH for further 4 hrs. At the end of each hour, 5 mL samples were withdrawn from the dissolution media and were replenished with 5 mL of fresh dissolution media to maintain the sink condition. The samples were filtered through a Whatman filter paper no. 41 and filtrate was analyzed spectrophotometrically for DS at wavelength of 276 nm after suitable dilution of sample by PC based Jasco V-530 UV using a 1 cm cell. The cumulative percent drug release was determined and the mean for three tablets was used in the analysis at 30, 60, 120, 180, 240, 300 and 360 min.

Release kinetics

To study the mechanism of drug release from the SR tablets, (Eq. i) Zero order, (Eq. ii) First order, (Eq. iii) Higuchi equation and (Eq. iv) Korsmeyer-Peppas equation were selected as a model dependent approach to characterize the dissolution profile[16-24]. These selected models are often used to describe the drug release from the polymeric system when the mechanism is not well known or when more than one type of release phenomenon is involved. The model which gave the highest regression coefficient (r^2) was considered to be the most suitable kinetic model for describing the release of DS from the microparticles.

RESULTS AND DISCUSSION

Photomicroscopic study

In the characterization study of the microparticles, the particle size of the drug loaded microparticles (Figure. 1) captured using motic B1 advanced series digital microscope was found to be in the range of 2-5 µm and shows good spericity.

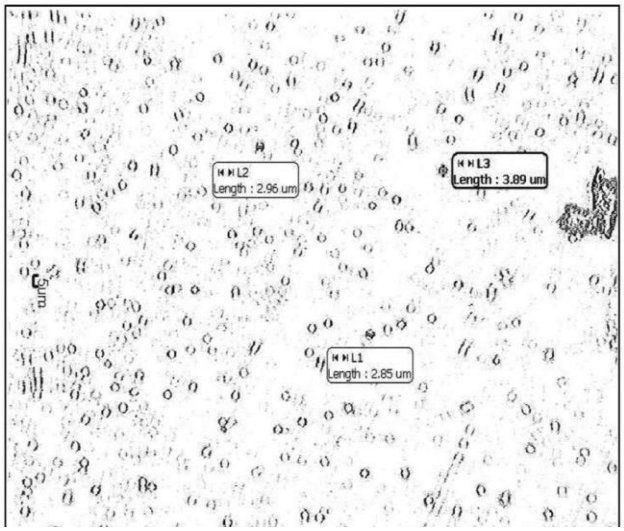

Figure 1 Particle size determination of formulated microparticles by motic microscope

Atomic force microscopy (AFM)

AFM technique has been used to provide the size and surface morphology of particles in three dimensions and on nanometer scale. Figure. 2 & 3 shows the three dimension pattern and Figure 4 shows the maximum size of the optimized drug loaded microparticles performed with the AFM in the scan size area of 50 x 50µm. The particles were found to be in the range of 300nm to 5µm.

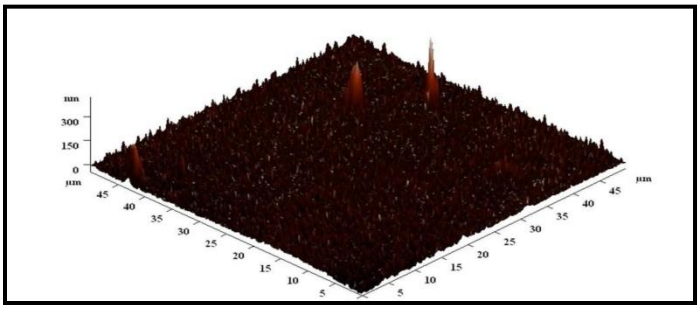

Figure 2 Three dimensional pattern indicating size of optimized drug loaded micropartilces

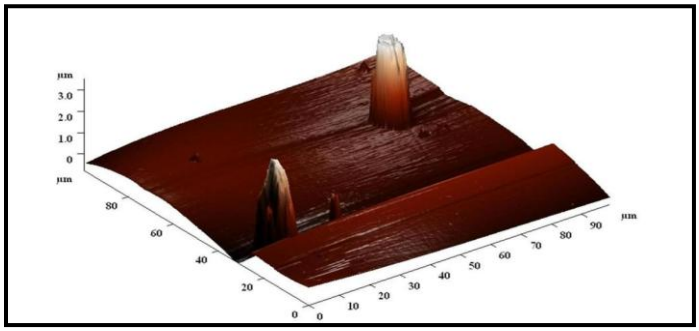

Figure 3 Three dimensional pattern indicating size of optimized drug loaded micropartilces

Figure 4 Maximum size of optimized drug loaded microparticls performed with the AFM

Fourier Transform Infrared (FTIR) spectroscopy study

FTIR spectra of materials were obtained in order to analyze the prepared microparticles. Figure 5 shows typical spectra of pure DS (A) and encapsulated DS (D) in the micro particles. In the spectrum of DS (A), principal peaks were found at the range of 700-800 cm^{-1} attributed to substituted phenyl group, aromatic amines exhibit two strong bands at 1180-1360 cm^{-1} due to C-N stretching, signal at 1575 cm^{-1} attributed to C=C stretching of aromatic ring, at 3080 cm^{-1} attributed to C-H stretching of aromatic ring, at 3385 cm^{-1} attributed to N-H stretching of amines. In the FTIR spectra of CMC sodium (B), wide absorption band between 3000-3600, associated with free and bonded hydroxyl groups, was observed. The bands at 1336 attributed to C-O

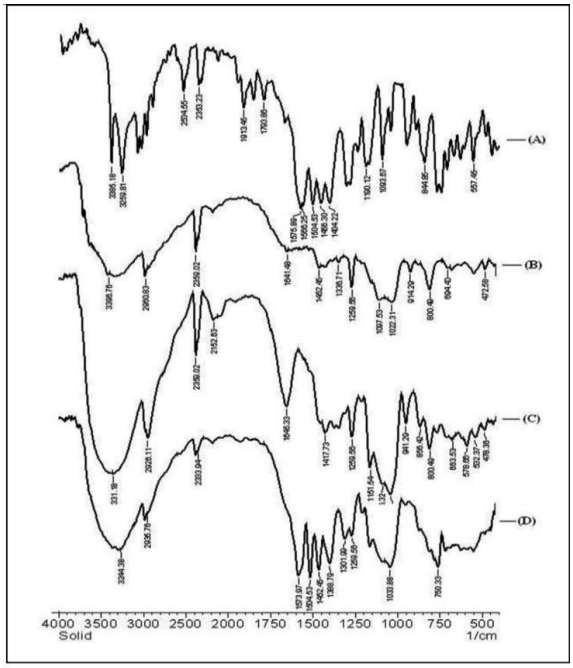

Figure 5 FTIR spectra of Diclofenac sodium(A), CMC, sodium salt(B), b- cycodextrin(C) and optimized drug loaded microparticles(D)

stretching, a wide band due to the ether group (C-O-C stretching) was observed at 1022 cm^{-1} for CMC. From the IR data of β-CD (C), a wide band at 3331 due to O-H bonds stretching and complex band at 1000-1260 due to C-O bond stretching were observed in the spectra. These values remained same in the FTIR spectra of optimized drug loaded micro particles (D), indicating no existence of different association form of DS with polymers.

Differential scanning calorimetry (DSC)

In order to determine the physical state of drug, DSC examination was conducted for the pure drug, polymers and optimized drug loaded microparticles. Thermograms of the single components and optimized drug loaded microparticles are shown in Fig. 6. An exothermic peak of melting was located at 281^{0}C in DSC curve of DS followed by the sharp endothermic peak of decomposition start at 289^{0}C (Curve I). CMC sodium salt showed an endothermic peak (Curve II) at 74^{0}C due to water evaporation and one exothermic peak at 307^{0}C (with shoulder exothermic peak at 319^{0}C) corresponds to the polymer thermal decomposition. In the thermogram of β-CD (Curve III), two broad endothermic transitions were observed in the temperature range between 110-120^{0}C due to the loss of water and near 308^{0}C that corresponds to the β-CD fusion. The thermal decomposition started at 285^{0}C and melting occurred at 308^{0}C (with shoulder endothermic peak at 316^{0}C) respectively. A DSC thermogram of optimized drug loaded microparticles (Curve IV) showed a broad endothermic peak at 80^{0}C and two sharp exothermic peaks at 251^{0}C and 264^{0}C which might be the displaced peak of the CMC sodium confirm the presence of CMC sodium salt inside the optimized drug loaded microparticles. One sharp exothermic peak of melting of DS at 282^{0}C in the optimized drug loaded microparticles suggesting that drug is well distributed in the polymer throughout the system.

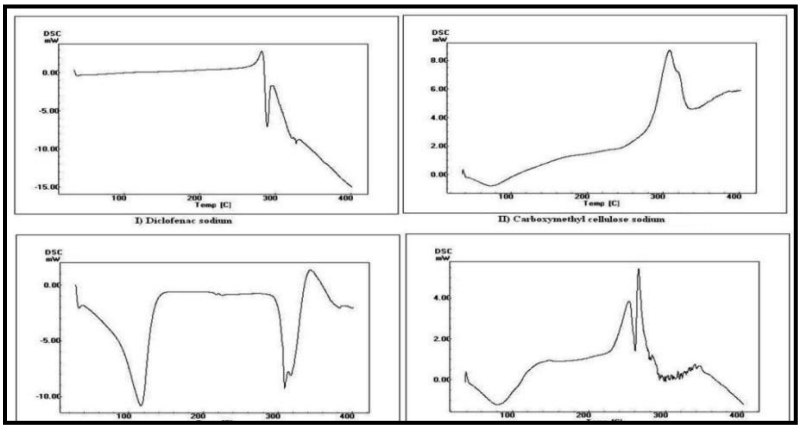

Figure 6 result of DSC analysis

In DSC thermogram of optimized drug loaded microparticles containing β-CD did not reveals any melting endotherm, suggesting the complex formation between DS, CMC sodium and β-CD.

Exothermic peak of CMC sodium was shifted to the lower wavelength might be due to intra and intermolecular interaction between polymers and drug and when the temperature of 280^{0}C was reached the decomposition of optimized drug loaded microparticles started in DSC thermogram.

X-ray diffraction (XRD)

The presence of numerous distinct peaks in the XRD patterns of DS, CMC sodium and β-CD were present as crystalline material with characteristic diffraction peaks shown in Fig 7. XRD patterns of optimized formulation showed weak signals at the respective scattering angles to that observed with DS, CMC sodium and β-CD. Thus, XRD data suggested that the degree of crystallinity of DS, CMC sodium and β-CD were reduced and most of the drug existed in amorphous state and distributed homogenously in the polymers. This was expected, as powders generated through spray drying are known to be predominantly amorphous in nature[25].

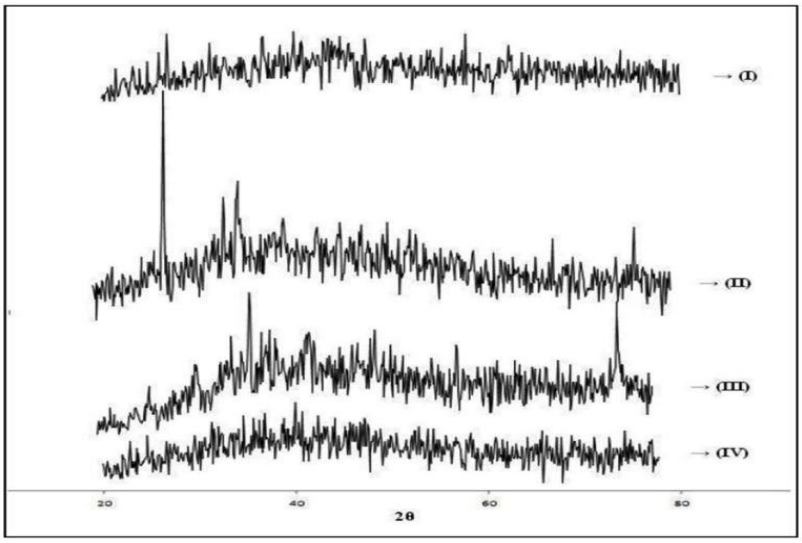

Figure 7 XRD spectra of Diclofenac sodium (A), CMC, sodium salt (B), b- cycodextrin (c) and optimized drug loaded microparticles

Physical characterization of tablets & In-vitro drug dissolution study

In this study, the effect of polymer concentration on the release behavior as well as kinetics of DS from SR tablets was evaluated. Table 3 shows the results of physical property of SR tablets. Weight variation, hardness and friability test of all prepared tablets were within pharmacopoeial specification[26]. From the results it was observed that hardness of the tablet increases with increase in polymer concentration in the tablet. The SR tablet-containing drug: polymer (1:0.25:0.25) ratio (optimized drug loaded microparticles inside) shows good hardness and friability as compare to other ratios. The percentage friability of tablets increases as the hardness decreases. Figure 8 shows the cumulative % drug release as a function of the dissolution time

from the SR tablets. From the figure, it was observed that as the time increases, the cumulative % drug release also increases from all the compositions. It was also found that the release rate of diclofenac sodium was extremely low at acidic pH (less than 10 % of drug was released in 2 hrs). This was an expected result[27], since the solubility of the diclofenac sodium in the acidic medium is very less (< 2.0 mg/L). However, when the pH was changed to 6.8, the drug was released more for the subsequent period of time. The encapsulated microparticles showed a delayed drug dissolution rates, sustaining the drug for several hours.

Table 3: **Physical properties of diclofenac sodium SR tablets**

Samples	weight (mg)	Hardness (Kg/cm2)	Friability (%)
Sample 1	346±1.15	8.5±0.24	0.80 ±0.09
Sample 2	348±1.24	8.6±0.20	0.78±0.09
Sample 3	342±1.55	8.9±0.23	0.77±0.11

All values are expressed as mean ± SD

The results of dissolution studies indicated that sample 1, 2 and 3 shows less than 10 % of drug release in acidic medium at the end of 2 hrs. At 6 hrs of study, sample 1 show 27.8 % and sample 2 shows 25.1 % while sample 3 shows only 20.4 % of drug release. From these results, it was found that as the polymer concentration increases the cumulative % drug release decrease. Four different kinetic models were employed to evaluate the possible changes in release mechanism. As clearly indicated in Figure 8, the formulations did not follow a zero order release pattern. The release rate kinetic data and different release kinetic models along with its equations are illustrated in Table 4 and Table 5. Sample 1 shows first order kinetic while sample 2 and 3 shows Higuchi's kinetic. To confirm the diffusion mechanism, the data were fit in to Korsmeyer-Peppas equation. Sample 2 and 3 showed good linearity (R^2: 0.973 and 0.981) with slope (n) values of 0.5 and 0.4. This n value, however, appears to indicate that diffusion is the dominant mechanism of drug release with these formulations.

Table 4: **Kinetic parameters of diclofenac sodium release from SR tablet**

Samples	Zero order	First order	Higuchi	Koresmeyer-Peppas	
	R^2	R^2	R^2	R^2	Slope (n)
Sample 1	0.955	0.965	0.952	0.923	0.5
Sample 2	0.934	0.952	0.973	0.944	0.5
Sample 3	0.847	0.878	0.981	0.940	0.4

Table 5: **Different release kinetic models**

Eq. No.	Kinetic	Equation
i	Zero order	$M_t = k_0 t$
ii	First order	$\ln M_t = \ln M_0 - k_1 t$
iii	Higuchi equation	$Q = kt^{1/2}$
iv	Korsmeyer-Peppas equation	$M_t / M_0 = kt^n$

Where, M_t = Percentage of drug is released at time t

$k/k_0/k_1$ = release rate constant;

Q = Amount of drug release

M_0 = Original mass of the drug particles at respective time t

n = Release exponent depend on drug release mechanism

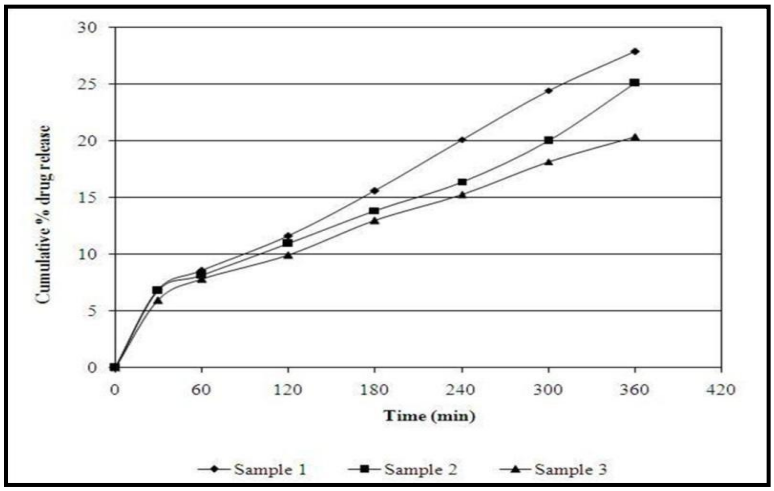

Figure 8 Cumulative % drug release from SR tablets of different concentration of polymer

CONCLUSION

This work shows that spray-drying is a suitable technique for the preparation of microparticles containing diclofenac sodium which result in particles to be in size range of (300 nm-5 µm) and is more desirable for controlled release. All the formulations show better sustained release of diclofenac sodium. Hardness increases while friability decreases with increase in polymer concentration. The cumulative % drug release decreases with increase in polymer concentration. The drug: polymer (DS: CMC sodium and β-CD) ratio 1: 0.25: 0.25 shows better result of sustained release than the other ratios. These results suggest that CMC sodium salt and β-CD blended microparticles are potential carrier for efficient delivery of diclofenac sodium.

ACKNOWLEDGEMENT

Authors are very much thankful to University Grants Commission (UGC), New Delhi for providing financial assistance to carry out this research work. Authors gratefully acknowledge the Emcure Pvt. Ltd. for providing the gift sample of Diclofenac sodium for the research work.

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