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Research Article

DEVELOPMENT, EVALUATION AND CHARACTERIZATION OF SURFACE SOLID DISPERSION FOR SOLUBILITY AND DISSOLUTION ENHANCEMENT OF DICLOFENAC

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ABSTRACT

The main objective of the study was to enhance the dissolution of diclofenac, a poorly water soluble drug by surface solid dispersion technique using different carriers and to study the effect of each carrier on the in vitro dissolution profile. The formulations were optimized in the preliminary trials by using various ratios of different carriers like croscarmellose sodium (CCN), crospovidone (CP) and sodium starch glycolate (SSG). Resultant formulations were evaluated using FTIR, X-ray diffraction, DSC, SEM and in vitro dissolution.

Keywords: *Diclofenac, Surface solid dispersion, Solvent evaporation, In vitro dissolution.*

INTRODUCTION

Poorly water soluble compounds have solubility, dissolution related bioavailability problems. Enhancement of solubility and dissolution rate is a challenging task in drug development. Nearly 40% of New Chemical Entities (NCE) currently being discovered are poorly water soluble[1]. The absorption rate of a poorly water-soluble drug, formulated as an orally administered solid dosage form, is controlled by its dissolution rate in the fluid at the absorption site. The dissolution rate is often the rate-determining step in drug absorption[2]. Therefore, the solubility and dissolution behaviour of a drug are the key determinants of the oral bioavailability [3].

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Among various approaches, solid dispersion has shown promising results in improving solubility, wettability, dissolution rate of drug and subsequently its bioavailability[4]. Only a few solid dispersion products are however commercially available [5,6]. The surface solid dispersion can overcome some of the shortcomings of the conventional solid dispersions. The carriers used in surface solid dispersion are water-insoluble, porous materials and hydrophilic in nature. Many commonly used tablet excipients like microcrystalline cellulose, silicon dioxide, sodium starch glycolate, potato starch, croscarmellose, crospovidone have been used as carriers for surface solid dispersion**.** The release of drug from the carrier material depends on hydrophilic nature, particle size, porosity and surface area of the carrier[7]. Larger the surface area available for surface adsorption of the drug, better is the release rate. For those carriers that have larger surface area like silicon dioxide, smaller amount of

carrier can give increased dissolution rate[8] .Surface solid dispersion technique has been extensively used to increase the solubility, dissolution and consequently the bioavailability of many practically insoluble or poorly water soluble drugs.

Diclofenac is a non-steroidal anti-inflammatory agent (NSAID) with antipyretic and analgesic actions. Act as Cyclooxygenase Inhibitors. It is use for the acute and chronic treatment of signs and symptoms of osteoarthritis and rheumatoid arthritis. Diclofenc is classified under class II according to biopharmaceutical classification system that is low solubility and high permeability. Its half life is 2 hr[9]. Results of literature survey revealed that till date, only 2 techniques have been employed, to improve solubility and dissolution rate of Diclofenac, one study reported, an improvement of solubility by complexation with Beta Cyclodextrin's & compared the effect of various complexation methods (cogrinding, kneading, co-evaporation) on drug dissolution profiles[10]. In another study an improved dissolution of a poorly water soluble drug in solid dispersions with hydrophilic carriers [11].

The drug Diclofenac was selected for enhancement of solubility and dissolution rate as it is a poorly water soluble (BCS-II) drug. The main purpose of this investigation was to increase the solubility and dissolution rate of Diclofenac by the preparation of its Surface solid dispersion with using various ratios of different carriers like croscarmellose sodium, crospovidone and sodium starch glycolate using solvent evaporation method. Ethanol was selected as a solvent of choice since the drug has highest solubility in this solvent and ethanol could be easily evaporated and recovered because of its low boiling point. Ethanol as per ICH guidelines is categorized under class III solvents thus rendering it to be less toxic& low risk to human health than other chlorinated solvents. [12]

MATERIALS AND METHOD

Diclofenac (gift sample procured from Dr. Reddy's Laboratories, Hyderabad), Crospovidone (Polyplasdone XL-ISP, Hyderabad), Croscarmellose sodium (Ac-Di-sol, Colorcon), Sodium starch glycolate type-B (Colorcon), Ethanol (Ranchem) and all the reagents used were analytical grade.

Preparation of Surface Solid Dispersion of Diclofenac:

Required amount of Diclofenac was dissolved in 10 ml of Ethanol. Accurately weighed carrier corresponding to different drug: carrier ratio by weight was dispersed in drug solution. The solvent was allowed to evaporate on water bath under occasional stirring at temperature of 40-420C in a protected environmental condition containing an exhaust system. The dried mass was pulverized and was passed through a #100-mesh. The powder was subsequently dried at 400 C for 3 hours in a tray drier. The powder was stored in desiccators for further studies.

Characterization Of Surface Solid Dispersions (SSD):

- ***Production yield:***

Production yield was determined by following formula:

Yield = (a x b+c)×100

where,

a - weight of solid dispersion sifted through a # 100.

b - weight of diclofenac taken for solid dispersion preparation,

c - weight of polymer taken for solid dispersion preparation.

- ***Assay:***

Accurately weighed samples equivalent to 10 mg of drug was taken in a 100ml volumetric flask, 10ml methanol was added and sonicated for 20min to dissolve the drug. The volume was made to 100ml with 0.1N HCl. The dispersion was filtered using Whatmann filter paper. A 10ml aliquot of the above solution was taken and diluted to 100ml with 0.1N HCl. The absorbance of sample solution was determined at 285nm against acid blank.

- ***In Vitro Dissolution Studies:***

Diclofenac a pure drug & surface solid dispersions of diclofenac were subjected to dissolution test using in-vitro dissolution rate apparatus-II. (Paddle method). This test was performed using 900 ml of dissolution medium (0.1N HCL) at 37±20C. Accurately weighed samples (plain drug and surface solid dispersions) of drug were added in 900 ml

capacity jar of dissolution apparatus which paddle was rotated at 50rpm. A 5ml aliquot of dissolution medium was withdrawn at appropriate time intervals. An equal volume of fresh dissolution medium was immediately replaced. It was suitably diluted and analyzed spectrophotometrically by measuring absorbance at 285nm.The experiments were performed in triplicate. With the help of standard curve equation concentration were found using absorbance values.

- ***FTIR Spectroscopy***

FTIR spectra of drug, SSD were obtained. About 1mg of sample was mixed thoroughly with 100 mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Perkin Elmer USA Spectrum 65 IR spectrophotometer and the IR spectrum was recorded from 4000 cm-1 to 400 cm-1 in a scan time of 12 minutes. The resultant spectra were compared for any spectral changes.

- ***Powder X-Ray Diffraction Analysis:***

X- ray diffraction of drug (Diclofenac), SSG, Drug: SSG in different formulation was recorded by using "PANalytical X'pert pro". The cross section of the samples was exposed to X-ray radiation with scanning range of 0-50θ

- ***Differential Scanning Calorimeter*:**

Thermograms of Diclofenac, and Drug: SSG formulation was recorded by using "Perkin-Elmer differential scanning calorimeter with a pyris workstation". Thermal behavior of the samples was investigated under a scanning rate of 10 0C/ min, covering a temperature range of 100- 3000C.

- ***Solvent Residue:***

The determination of ethanol was performed by gas chromatography on a Agilent GC 6890N with 7694E Head space sampler, fitted with flame ionization detector. Carrier gas was nitrogen. Headspace GC is used to detect solvent residues. The packed column was BD-624 capillary column. Temperature of oven was 600C injection port 140 0C and detector 2500C. Oven was programmed at 5 0C/min for 10min, 15℃/min up to 250 0C with a hold time of 7min.

RESULT AND DISCUSSION

- ***Production yield:*** Production yield was calculated according to the formula and results are given in Table 3.
- ***Assay*:** Assay was done according to procedure and results are given in table 2.

- ***In Vitro Dissolution Studies:***

Dissolution data of surface solid dispersions on excipients were reported in Fig 1 All theprepared surface solid dispersion showed an enhancement in the dissolution rate of the drug compared to plain drug. Surface solid dispersions prepared by using sodium starch glycolate (1:7 ratio) showed enhanced dissolution rate when compared to other carriers. Surface solid dispersions of diclofenac were prepared with various carrier concentrations and the effect of increasing carrier concentration on dissolution rate was determined. The rank order of dissolution rate improvement for various carriers are; SSG>CCS>CP. The D: SSG 1:7 ratio, both showed near 100% drug release in 20 min. So Drug: SSG 1:7 selected as optimized formulation.

From drug release pattern it was concluded that Drug: SSG at the ratio 1:7 shows good result.

- ***FTIR Study:***

Fig. 2 shows the FTIR spectra of the I) drug II) carrier III) Surface Solid Dispersion. There was no significant change in the spectrum of Surface solid dispersions, as incorporation of Diclofenac into the carrier (SSG) did not modify the position of its functional groups.

- ***X-Ray diffraction studies:***

X-ray diffraction patterns revealed that pure Diclofenac was in crystalline state as it showed sharp distinct peaks notably at 2θ diffraction angles of 7.43°, 9.73°, 16.18°, 24.27°. The reflections (specific peaks) corresponding to the drug and SSG were also found in the formulation diffractogram with reduced

intensity as compared to drug alone. The reduction in intensity and number of typical diffraction peaks in formulation diffractogram suggests reduction in crystalline nature of drug and may be converted from crystalline to amorphous form.

- ***Differential scanning calorimeter*:**

The thermogram of pure Diclofenac showed a sharp peak at 283℃, which corresponds to the melting temperature of Diclofenac, sharpness of the peak indicating crystalline nature of the drug. The thermogram of sodium starch glycollate (SSG) showed a peak at 82℃, which corresponds to the melting temperature. In the optimized formulation Drug: SSG (1:7) 2 peaks were observed one at 82.36℃, another one at 285.47℃, which corresponds for SSG and Diclofenac respectively. And the area and sharpness of the peaks were decreased, which indicated that the crystallinity of the drug was reduced and might be converted to amorphous form. There was no change in the peak temperature of the optimized formulation (SSD-S4) when compared to the pure drug, which indicates no interaction between drug and excipients.

- ***Residual Solvent Study:***

Residual solvent concentration in surface solid dispersion of Diclofenac prepared using ethanol was performed by gas chromatography. The level of ethanol was below detectable limits that is 5000ppm . Hence, can be concluded that solvent evaporation method was efficient in removal of solvents from SSD well below permissible levels.

Table 1: Coding formulations for SSD of Diclofenac

Drug		***Diclofenac***	***Diclofenac***	***Diclofenac***
Carrier		SSG	CCN	CP
Code	1	SSD-S1	SSD-C1	SSD-P1
Code	2	SSD-S2	SSD-C2	SSD-P2
Code	3	SSD-S3	SSD-C3	SSD-P3
Code	4	SSD-S4	SSD-C4	SSD-P4
Code	5	SSD-S5	SSD-C5	SSD-P5
Drug:Carrier ratio	1	1:1	1:1	1:1
Drug:Carrier ratio	2	1:3	1:3	1:3
Drug:Carrier ratio	3	1:5	1:5	1:5
Drug:Carrier ratio	4	1:7	1:7	1:7
Drug:Carrier ratio	5	1:9	1:9	1:9

Table 2: Result of Production Yield & Assay of Surface solid dispersion

Drug	*Carrier*	*Code*	*Ratio*	*Production Yield (%)*	*Assay (%)*
DICLOFENAC	Sodium Starch glycolate	SSD-S1	1:1	95.04	97.64
		SSD-S2	1:3	95.40	91.67
		SSD-S3	1:5	96.38	94.92
		SSD-S4	1:7	92.50	96.33
		SSD-S5	1:9	96.20	98.85
	Croscarmellose sodium	SSD-C1	1:1	96.04	98.34
		SSD-C2	1:3	93.20	91.57
		SSD-C3	1:5	88.43	97.34
		SSD-C4	1:7	96.70	92.98
		SSD-C5	1:9	89.20	94.56
	Crospovidone	SSD-P1	1:1	95.20	95.39
		SSD-P2	1:3	93.80	102.04
		SSD-P3	1:5	97.80	98.93
		SSD-P4	1:7	91.56	90.33
		SSD-P5	1:9	92.51	96.36

Table 3: Comparison studies of Dissolution profiles of different SSD in 0.1 N HCL

Code	*D:C Ratio*	*T5*	*T20*	*T30*	*T45*	*T60*	*T90*
SSD-S1	1:1	34.03	71.30	77.98	86.10	92.03	99.20
SSD-S2	1:3	43.26	74.70	82.05	90.40	99.26	-
SSD-S3	1:5	34.20	91.30	94.87	99.70	-	-
SSD-S4	1:7	36.80	99.93	-	-	-	-
SSD-S5	1:9	33.97	97.85	99.87	-	-	-
SSD-S2	1:3	43.26	74.70	82.05	90.40	99.26	-
SSD-C1	1:1	25.20	47.57	59.50	64.48	74.93	78.60
SSD-C2	1:3	30.06	49.50	57.43	63.70	78.20	83.55
SSD-C3	1:5	25.60	63.02	72.16	80.50	87.14	92.60
SSD-C4	1:7	35.03	69.30	75.30	81.45	91.50	97.51
SSD-C5	1:9	43.80	77.66	86.10	97.20	-	-
SSD-P1	1:1	20.50	44.30	47.00	59.10	68.60	79.36
SSD-P2	1:3	23.45	54.10	62.70	72.20	78.20	83.40
SSD-P3	1:5	19.65	57.20	65.82	74.41	79.72	89.55
SSD-P4	1:7	30.12	60.59	65.89	75.60	83.90	93.98

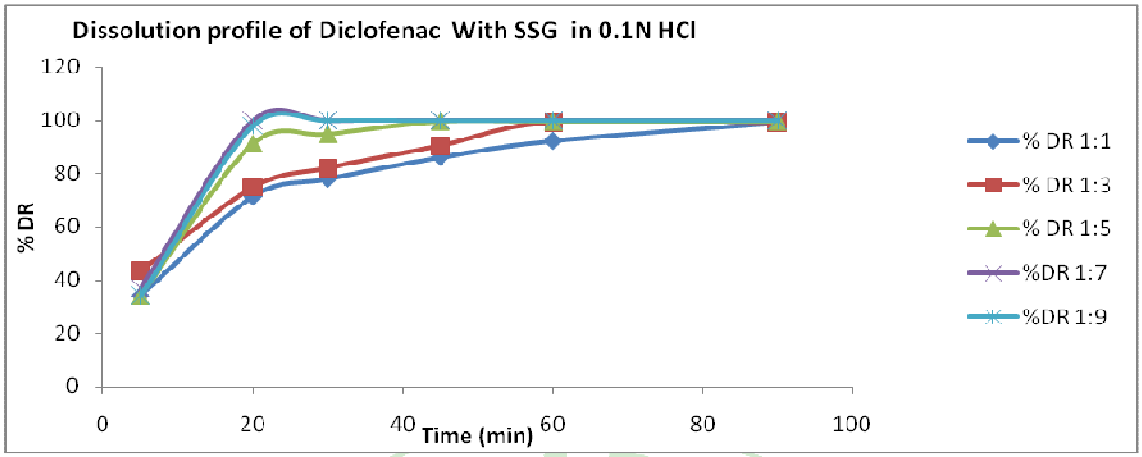


Fig 1: Dissolution profiles of Diclofenac with SSG in 0.1 N HCL

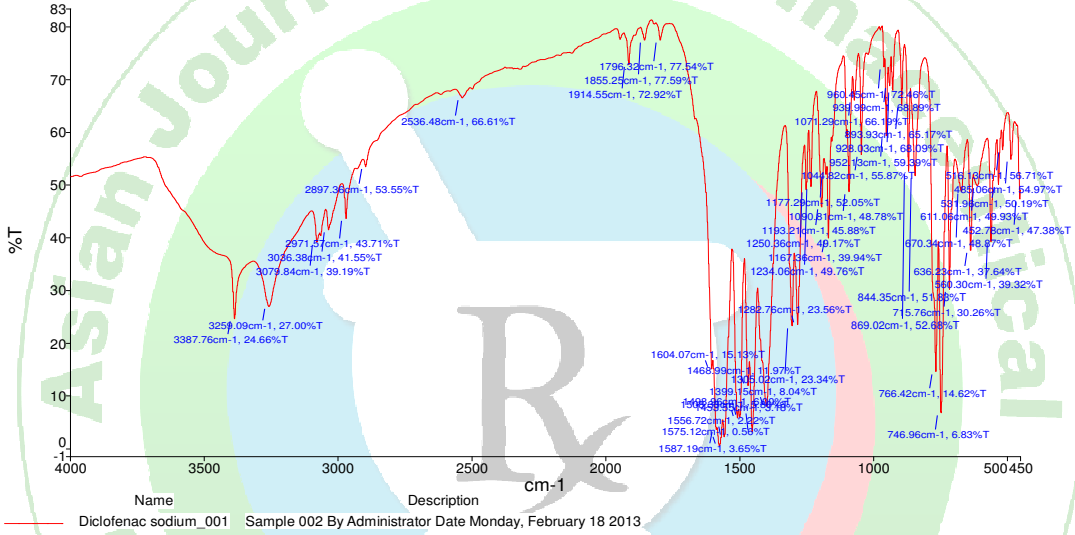
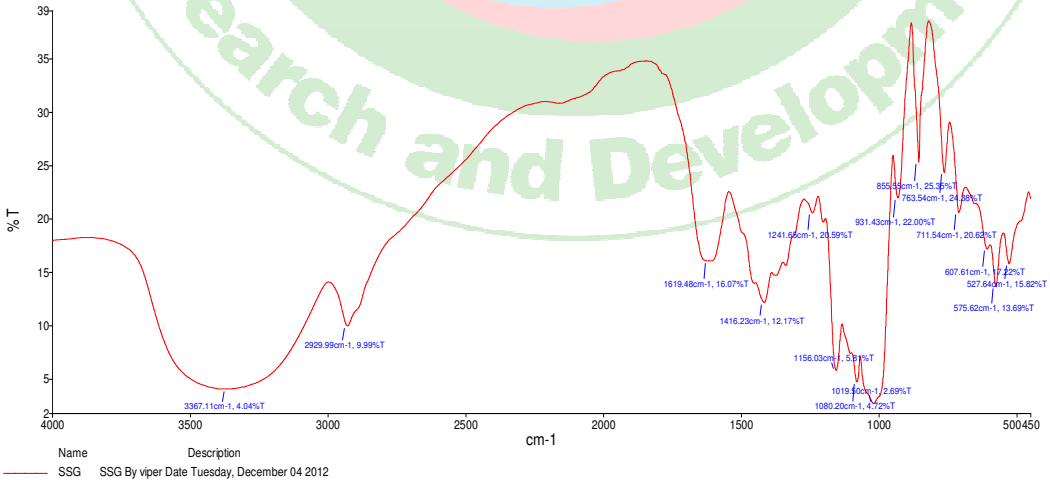
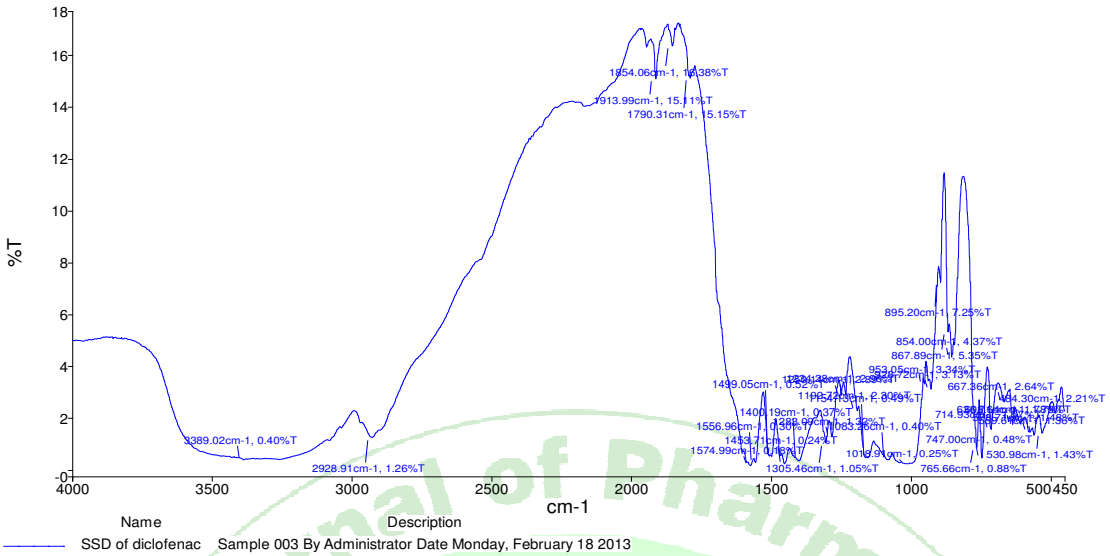


Fig 2: FTIR Spectra of I) Drug (Diclofenac)



II) Carrier (SSG)



III) Surface solid Dispersion

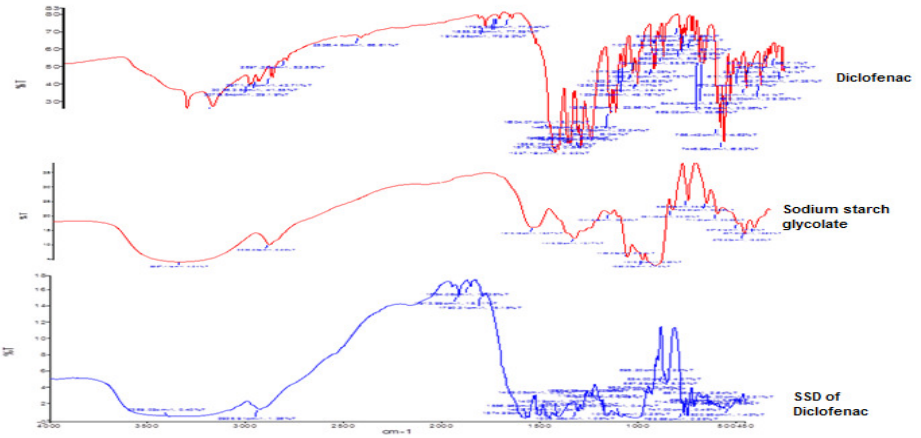


Fig. 3. Comparative FTIR spectra of Diclofenac, Sodium starch glycolate & Surface solid dispersion of Diclofenac

CONCLUSION

The enhancement of dissolution rate and oral bioavailability of poorly soluble drugs remains one of the most challenging aspects of the drug development. Among the different methods of dissolution enhancement, Surface solid dispersion technology was found to be more successful with number of drugs. SSD's of Diclofenac with three different super disintegrant prepared by solvent evaporation method showed significantly higher drug dissolution in comparison with pure drug. FTIR and DSC showed no evidence of interaction between the drug and carrier.

Among the super disintegrant tested SSG gave highest enhancement of dissolution rate and efficiency of Diclofenac (1:7 ratio). In each case the dissolution rate and DE 30% were increased as the concentration of carriers in the surface solid dispersions were increased. The basic reason behind improvement in solubility were a) Drug get deposited on surface of inert carrier leading to reduction in particle size of drug & there by enhance dissolution. Here polymers used were superdisintegrants. b) Higher dissolution rate observed with superdisintegrant might be due to rapid disintegration & fine dispersion of particle formed after disintegration. C) Because of

good hydration capacity of polymer drug was in longer time contact with GI fluid . d) Sodium starch glycolate swell in three dimensional way , it having less capacity to transmit fluid to next particle because it retained the water/ fluid itself therefore ideal for surface solid dispersion. The order of increase in dissolution rate with various super disintegrant is SSG>CCS>CP. This surface solid dispersion could then be incorporated successfully into a capsule or tablet, either in conventional or sustain release formulation.

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