Silymarin-solid dispersions: Characterization and influence of preparation methods on dissolution

DALWADI SONALI[1,*]
SONI TEJAL[2]
THAKKAR VAISHALI[2]
GANDHI TEJAL[2]

[1] *Ramanbhai Patel College of Pharmacy Charotar University of Science and Technology Changa-388421, India*

[2] *Anand Pharmacy College Anand-388001, India*

The influence of preparation methodology of silymarin solid dispersions using a hydrophilic polymer on the dissolution performance of silymarin was investigated. Silymarin solid dispersions were prepared using HPMC E 15LV by kneading, spray drying and co-precipitation methods and characterized by FTIR, DSC, XRPD and SEM. Dissolution profiles were compared by statistical and model independent methods. The FTIR and DSC studies revealed weak hydrogen bond formation between the drug and polymer, while XRPD and SEM confirmed the amorphous nature of the drug in co-precipitated solid dispersion. Enhanced dissolution compared to pure drug was found in the following order: co-precipitation > spray drying > kneading methodology ($p < 0.05$). All preparation methods enhanced silymarin dissolution from solid dispersions of different characteristics. The co-precipitation method proved to be best and provided a stable amorphous solid dispersion with 2.5 improved dissolution compared to the pure drug.

Keywords: silymarin, HPMC, solid dispersions, kneading, spray drying, co-precipitation, dissolution parameters

Seeds of milk thistle (*Silybum marianum* L. Gaertn, *Asteraceae*) have been used in medicine for over 2,000 years. Silymarin (SLM), an antihepatotoxic phytocomplex, is a mixture of flavonolignans which has been widely used as a therapeutic agent for a variety of acute and chronic liver diseases. Silymarin is practically insoluble in water; therefore, upon oral administration, its absorption rate in the gastrointestinal tract is low, providing only about 20 to 40 % bioavailability (1).

Several approaches have been attempted to improve oral bioavailability of silymarin, complexation with a phospholipid (2), formation of an inclusion complex with β-cyclodextrin and hydroxypropyl-β-cyclodextrin (3), solid dispersion with a hydrophilic polymer such as PEG 6000 (4), selfmicroemulsifying systems (5), co-precipitates (6) and a complex with crosslinked polymers (7).

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* Correspondence; e-mail: sonali.dalwadi@yahoo.com

Solid dispersions describe a family of dosage forms whereby the drug is dispersed in a biologically inert matrix of carriers such as polyethyleneglycol (PEG), polyvinylpyrrolidone (PVP), hydroxypropyl methylcellulose (HPMC), crosslinked polymers, usually with a view to enhance oral bioavailability (8). Cellulose derivatives are naturally occurring polysaccharides ubiquitous in the plant kingdom (8). Hypromellose, short for HPMC, is found in a variety of commercial products as an excipient for various purposes (8). In the present study, HPMC, E 15LV was chosen as a polymeric carrier to improve dissolution and bioavailability of several poorly soluble drugs such as carbamazepine (9), cetirizine hydrochloride (10) and felodipin (11).

The aim of the present investigation was to enhance the rate of dissolution of silymarin from solid dispersions and to assess the effect of preparation methodologies on the dissolution performance of solid dispersion.

EXPERIMENTAL

Materials

Silymarin powder (containing 78.7 % silymarin, 20.3 % silybin and isosilybin by HPLC) was a gift of Microlabs (India), HPMC E 15LV grade was a gift of Colorcon India, and methanol and dichloromethane AR grade were purchased from Atul Chemical, India. All other ingredients, solvents and reagents used were of analytical or pharmaceutical grade. Deionized double-distilled water was used throughout the study.

Solubility of silymarin

Solubility studies were performed by placing an excess amount of silymarin into 25-mL glass flasks containing HPMC E 15LV in 20 mL distilled water (0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0 and 5.0 % (m/V)). All flasks were stoppered and kept shaking at 100 rpm for 24 h in an Orbital Shaking Incubator (REMI, RIS24BL, India) at 37 °C. After equilibrium was achieved after 72 h, 5 mL of supernant was withdrawn, filtered through Whatmann filter paper (No. 1) and analyzed using a UV-visible spectrophotometer (Shimadzu UV-1650, Japan) at 286 nm (3). Experiments were performed in triplicate.

Preparation of physical mixtures

Physical mixtures of silymarin and HPMC E 15LV in 1:1, 1:3 and 1:5 mass ratios were prepared by mixing in geometric proportions, followed by passing through a 0.152-mm aperture sieve with minimum abrasion. The samples were collected and kept at room temperature in screw-capped glass vials until use.

Preparation of solid dispersions

Solid dispersions were prepared in 1:1, 1:3 and 1:5 mass ratios of silymarin to HPMC E 15LV by various methods.

Kneading method. – Silymarin and HPMC E 15LV were physically mixed, wetted with water and kneaded thoroughly for 30 minutes in a glass mortar. The paste formed was dried completely at 80 °C for 6 h, pulverized and passed through a 0.152-mm aperture sieve with minimum abrasion. The samples were collected and kept at room temperature in screw-capped glass vials until use.

Spray drying method. – HPMC E 15LV was dissolved in methanol/dichloromethane (50:50, *V/V*) and silymarin was incorporated to get 5 % (*m/V*) of total solids in the solution. The resultant solution was evaporated using a Lab Spray Dryer (LABULTIMA, LU-222 Advanced, India) at inlet temperature of 80 °C, maximum aspiration (99), pumping 45 % and feeding rate of 2.5 mL min^{-1} of HPMC E 15 LV solution. The samples were collected and kept at room temperature in screw-capped glass vials until use.

Co-precipitation method. – HPMC E 15LV was completely dissolved in methanol to get 5 % (*m/V*) solution. Silymarin was incorporated, the solution stirred till a homogeneous mixture was formed. Water (in double methanol quantity) was added dropwise to form the precipitate. Dispersion was stirred continuously up to 30 min. Dispersion obtained was dried completely at 80 °C for 6 h, pulverized and passed through a 0.152-mm aperture sieve with minimum abrasion. The samples were collected and kept at room temperature in screw-capped glass vial until use.

Characterization of solid dispersions

Characterization was performed for pure silymarin, pure HPMC E 15LV, physical mixtures and solid dispersions prepared by kneading, spray drying and co-precipitation.

FTIR spectroscopy. – IR-spectroscopy was conducted using a FTIR spectrophotometer (Spectrum GX-FT-IR, Perkin Elmer, USA) and the spectra were recorded in the wavelength region of 4000–400 cm^{-1}. The procedure consisted of dispersing the samples in KBr and gentle grinding to prepare pellets.

Differential scanning calorimetry (DSC). – DSC was performed using a differential scanning calorimeter (DSC-PYRIS-1, Phillips, the Netherlands) to study the thermal behaviour of samples. The samples were heated in hermetically sealed aluminium pans at a scanning rate of 10 °C min^{-1} from 50 ± 0.2 to 550 ± 0.2 °C. An empty aluminium pan was used as a reference.

X-ray powder diffraction (XRPD). – X-ray diffraction study was carried out to characterize the physical form of silymarin in selected samples. The sample was allowed to spread on the glass slide in approximately 0.5 mm thickness. The slide was then placed vertically at 0° angle in the X-ray diffractometer (X"Pert Model, Philips) so that the X-ray beam fell on it. The results were recorded over a range of 0–90° (2θ) using a Cu-target X-ray tube and Xe-filled detector. The conditions were: voltage 40 kV, current 20 mA, room temperature, scintillation counter detector, non-rotating sample holder.

Scanning electron microscopy (SEM). – Surface characteristics of the samples were studied by SEM from 100 to 650x magnifications. A double sided carbon tape was affixed onto aluminium stubs. The powder sample was sprinkled onto the tape. The aluminium

stubs were placed in the vacuum chamber of a scanning electron microscope (XL 30 ESEM with EDAX, Philips). The samples were observed for morphological characteristics using a gaseous secondary electron detector (XL 30, Philips) with working pressure of 0.8 Pa and acceleration voltage of 30.00 kV.

In vitro *dissolution study*

The *in vitro* dissolution studies were carried using USP II (12) apparatus in 900 mL of distilled water, 0.1 mol L^{-1} HCl and phosphate buffer pH 6.8, thermostatically maintained at 37 ± 0.5 °C at a rotation speed of 50 rpm. Silymarin, all solid dispersions and physical mixtures, each containing an equivalent of 70 mg of silymarin, were subjected to dissolution. At predetermined time intervals, 5 mL of dissolution medium was withdrawn and filtered through Whatmann filter paper (No. 1). The same volume was replaced with fresh medium. Samples were suitably diluted and analyzed spectrophotometrically at 286 nm. Each test was performed in triplicate.

Dissolution parameters

Dissolution efficiency (%). – Dissolution efficiency (*DE*) represents the area under the dissolution curve at time *t* (measured using the trapezoidal rule) and expressed as percentage of the area of the rectangle described by 100 % dissolution in the same time (13):

$$DE = \int_{0}^{t} \frac{y \times \mathrm{d}t}{y_{100} \times t} \times 100\ \%$$

where *y* is the drug percent dissolved at time *t*.

*Mean dissolution time (*MDT*).* – The *MDT* values (in min) were calculated from dissolution data using the equation:

$$MDT = \frac{\sum_{j=1}^{n} \hat{t}_j\, \Delta M_j}{\sum_{j=1}^{n} \Delta M_j}$$

where *j* is the sample number, *n* is the number of dissolution sample times, $\hat{t}_j$ is the time at midpoint between t_j and t_{j-1} [easily calculated with the expression $(t_j + t_{j-1})\,/\,2$] and ΔM_j is the additional amount of drug dissolved between t_j and t_{j-1} (13).

Similarity factor f_2 and dissimilarity factor f_1. – A model-independent approach proposed by Moore and Flanner (14) for calculating f_1 and f_2 was used for comparison of the dissolution profiles of various samples and was defined by the following equations:

$$f_1 = \frac{\sum_{j=1}^{n} |R_j - T_j|}{\sum_{j=1}^{n} R_j} \times 100$$

$$f_2 = 50 \log \left\{ \left[1 + \left(1/n \sum_{j=1}^{n} |R_j - T_j|^2 \right) \right]^{-0.5} \times 100 \right\}$$

in which n is the number of withdrawal points, R_j and T_j are the percent of the dissolved reference and test products at each time point j.

Stability

Stability of solid dispersions was tested at 40 ± 2 °C and 75 ± 5 % RH for a period of 6 months. The samples were withdrawn at intervals of 15, 30, 60, 90 and 180 days and were evaluated for the drug content and *in vitro* drug release. Percentage drug decomposition and any change in a dissolution profile were evaluated using fit factors (f_1 and f_2 factors).

RESULTS AND DISCUSSION

Solubility of silymarin

In the present investigation, solubility of silymarin in distilled water was found to be $0.25 \pm 0.00_4$ mg mL^{-1}. The solubility plot of silymarin in HPMC E 15LV (see Fig. 1) shows that a 2.7 fold increase in solubility was found in 3 % HPMC E 15LV compared to solubility in water. As the concentration of HPMC increased from 3 to 5 %, silymarin solubility decreased, possibly due to the increase in solution viscosity (8) (Table I).
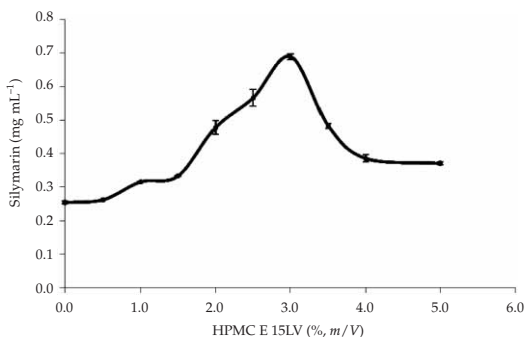

Fig. 1. Solubility plot of silymarin in HPMC E 15LV.

The values of Gibb's free energy change ($\Delta G°_{tr}$) were calculated from the following equation to understand the transfer process of silymarin from distilled water to aqueous solution of HPMC E 15LV (15):

$$\Delta G°_{tr} = -2.303 \ RT \ \log \ (S_0/S_s)$$

in which S_0/S_s is the ratio of the molar solubility of silymarin in an aqueous solution of HPMC E 15LV to that in distilled water. The $\Delta G°_{tr}$ values were all negative for HPMC E 15LV at various concentrations (Table I), indicating the spontaneous nature of silymarin solubilization (15).

Characterization of solid dispersions

FTIR. – It is well known that vibrational changes can serve as a probe of intermolecular interactions in solid materials. Characteristic peaks of silymarin appeared at 3423.36 (-OH stretching vibration), 2935 (O-H stretching), 1639.6 (C=O stretching), 1511–1465 (skeleton vibration of aromatic C=C ring stretching), 1362 (-OH in plane bending), 1274.6 (C-O-C stretching), 995 (O-H out plane bending), 1029–1161 (in plane = C-H bending) and 644–849 cm^{-1} (see Fig. 2) (8). All spectra of solid dispersions showed changes from parent spectra, that is, of silymarin and HPMC. Possible interactions would have occurred between the -OH, C-O, and -O- groups of HPMC E 15LV and of polyphenolic moiety of silymarin revealed through frequency changes of the respective functional group (7).

Table I. Solubility and $\Delta G°_{tr}$ values of silymarin

HPMC E 15LV (%, *m/V*)	Solubility of silymarin (mg mL^{-1})[a]	$-\Delta G°_{tr}$ (J K^{-1} mol^{-1})[b]
0.0	0.254 ± 0.004	–
0.5	0.262 ± 0.001	–83.9
1.0	0.316 ± 0.001	–561.2
1.5	0.333 ± 0.002	–699.5
2.0	0.479 ± 0.021	–1632.3
2.5	0.567 ± 0.025	–2069.7
3.0	0.689 ± 0.009	–2573.6
3.5	0.482 ± 0.008	–1648.2
4.0	0.386 ± 0.011	–1075.8
5.0	0.371 ± 0.004	–891.4

[a] Mean ± SD, *n* = 6.
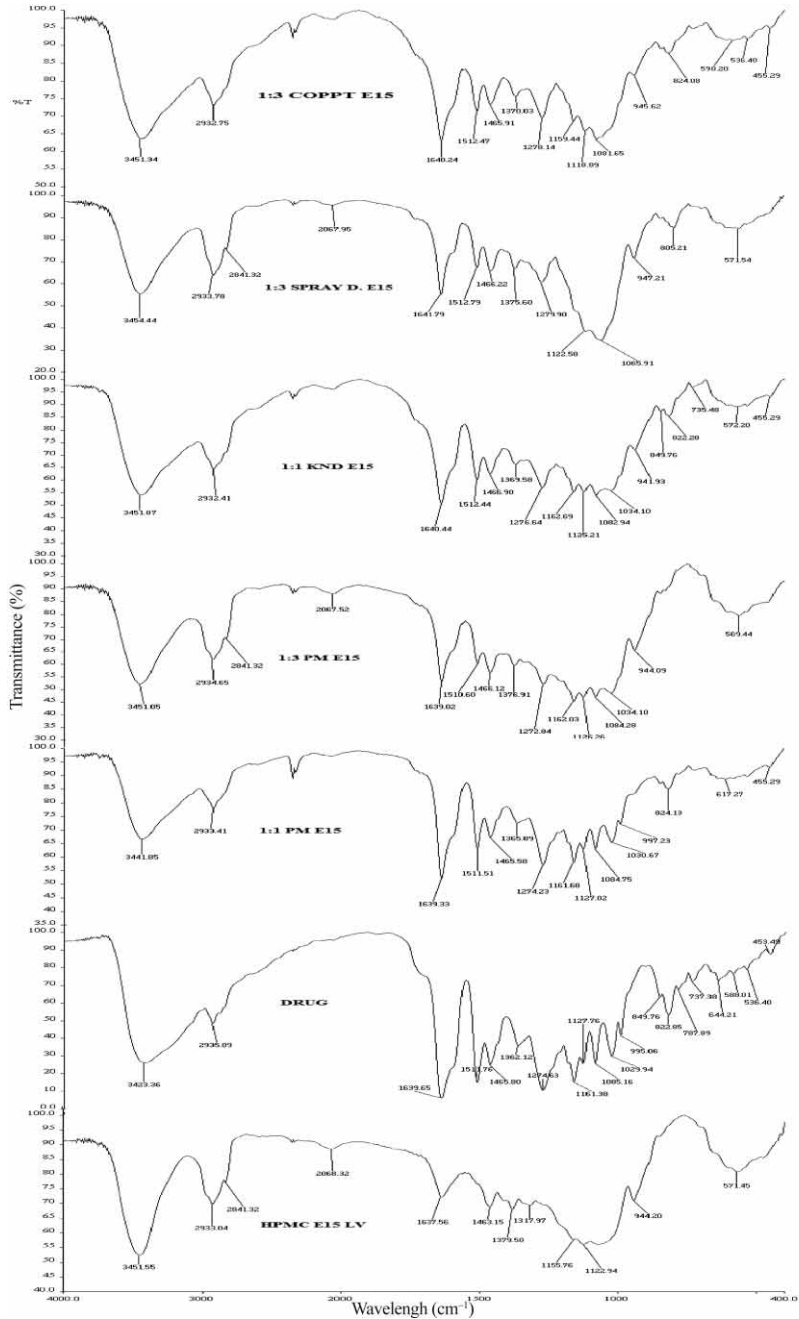[b] $\Delta G°_{tr}$ – Gibb's free energy change

Fig. 2. FTIR spectra of: pure HPMC E 15LV, silymarin, physical mixtures (PM), solid dispersions (KND – kneading, SPRAY D. – spray drying, COPPT – co-precipitation), bottom to top.

In the spectra of physical mixtures, characteristic peaks substantially corresponded to the superimposition of the peaks of both components, silymarin and HPMC. The band which appeared at 3000–3600 cm^{-1} (assigned to -OH stretching) in the spectrum of silymarin was found at higher frequency in the case of dispersions. This revealed the formation of H-bond between the drug and -OH group of HPMC E 15LV in dispersion (14). The characteristic peaks at 1600–1300 and below 1300 cm^{-1} were found to change their intensity in the following order: co-precipitated < spray-dried < kneaded solid dispersion, but the H-bond interaction which occurred in solid disperions resulted in lower peak intensity (7, 15). The IR spectra also demonstrate disruption of the crystal lattice (8). In fact, the splitting phenomenon in frequency regions below 1300 cm^{-1}, a typical feature of the crystal lattice present in silymarin, was still present in physical mixtures, but its intensity was reduced in kneaded, spray-dried and co-precipitated solid dispersions.

DSC. – The DSC thermograms of silymarin, HPMC E 15LV, physical mixtures and solid dispersions are shown in Fig. 3. There was a considerable shift in the endothermic peaks in the kneaded solid dispersion and physical mixture (1:1 ratio). The maximum shifted from 369.7 °C to 349.2 °C and 349.9 °C in thermograms of kneaded solid dispersion and physical mixture, respectively, depicting the change in the crystal form of the drug (17). Due to low silymarin enthalpy (ΔH = 27.280 J g^{-1}) found from thermograms, the DSC technique could not be used for characterization of silymarin solid dispersion since suppression and disappearance of peaks could not be identified in the thermogram (Fig. 3).

XRPD. – XRPD pattern of silymarin, HPMC E 15LV, physical mixtures and solid dispersions prepared by different methods are shown in Fig. 4. Silymarin is crystalline, as demonstrated by the sharp and intense diffraction peak at 2θ of 72.3°. HPMC E 15LV was found as an amorphous powder having no diffraction peak. Physical mixtures showed diffraction peaks consistent with the presence of crystalline silymarin. The lower intensity of diffraction peaks of physical mixtures was the result of a dilution effect with amorphous HPMC E 15LV (18). The intensity of peak height was found to be reduced at 2θ = 72,3° in kneaded and spray dried solid dispersions as compared to silymarin. The XRPD pattern of co-precipitated solid dispersion showed complete disappearance of the diffraction peak at the same 2θ value, confirming the existence of the amorphous form of silymarin.

The relative degree of crystalinity (RDC) of all solid dispersions and physical mixtures at the same 2θ value are shown in Table II. The rank order of the relative degree of crystallinity in dispersions could be given as: spray dried > kneaded > co-precipitated solid dispersions. Co-precipitation produced amorphous particles compared to the pure drug, which might be responsible for improved dissolution of the drug (19).

SEM. – The representative photomicrographs of silymarin, HPMC E 15LV, physical mixtures and solid dispersions prepared by different methods are presented in Fig. 5. The image of silymarin revealed drug particles with a reduced specific surface area due to some aggregation and agglomeration. Morphological images of HPMC E 15LV exhibited cylindrical shape and similar to fiber (20). The photomicrographs of physical mixtures showed individual particles of silymarin and carrier without any surface adsorption.
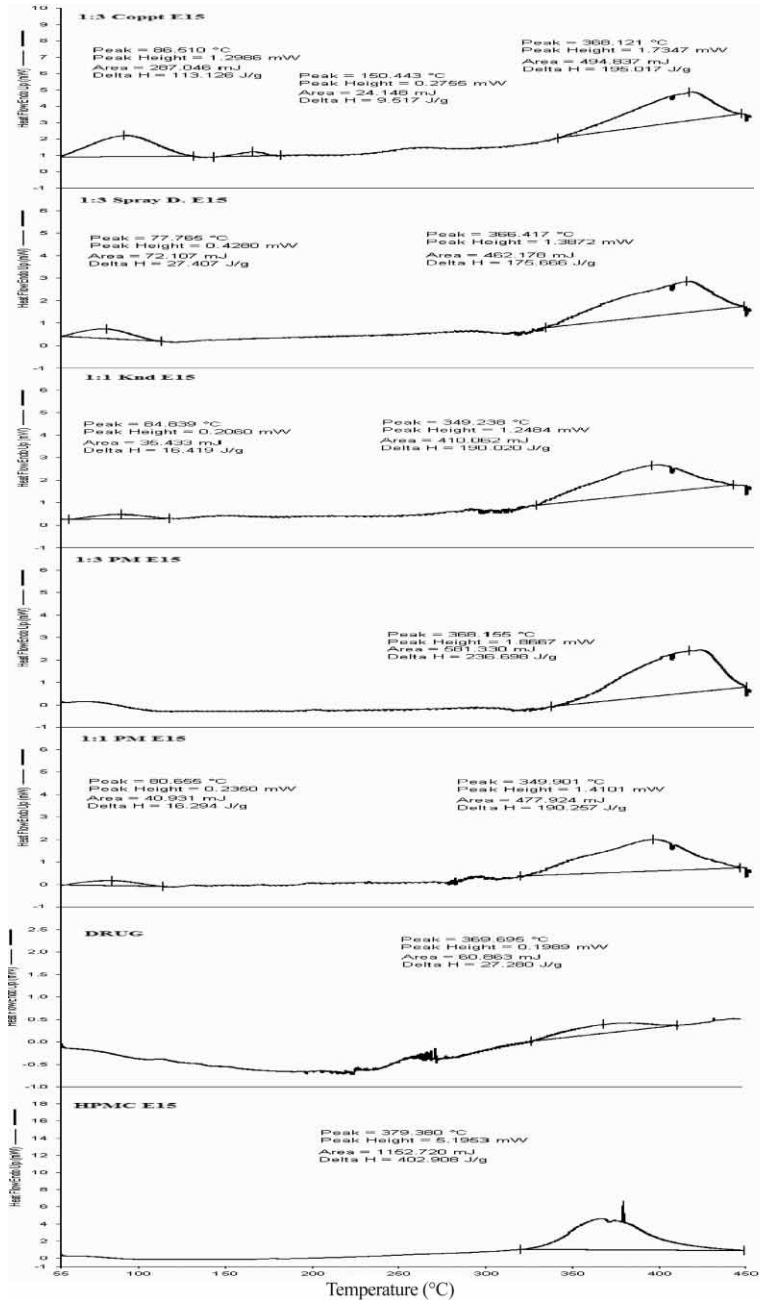
Fig. 3. DSC thermograms of: pure HPMC E 15LV, silymarin, physical mixtures (PM), solid dispersions (KND – kneading, SPRAY D. – spray drying, COPPT – co-precipitation), bottom to top.
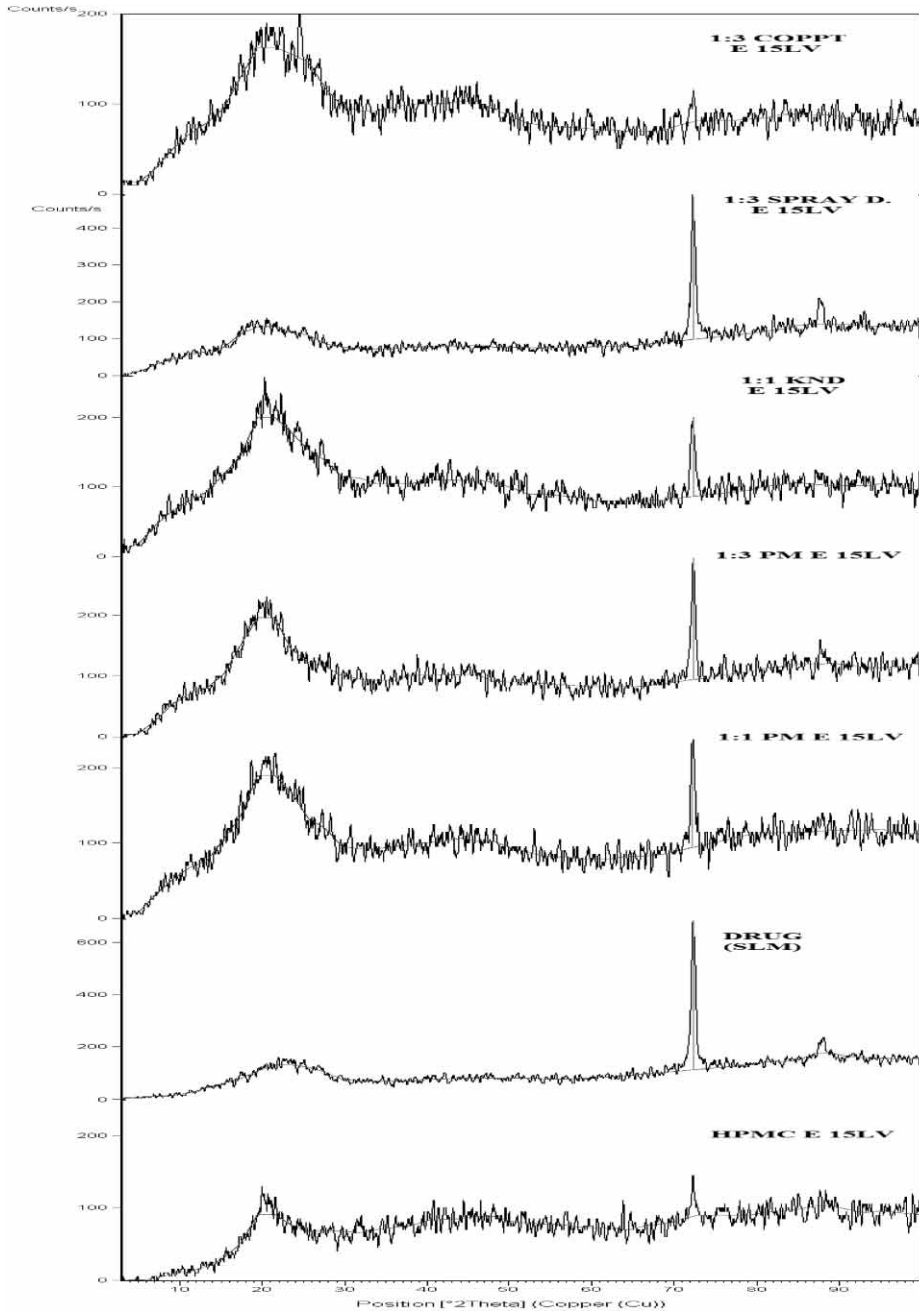
Fig. 4. XRPD patterns of: pure HPMC E 15LV, silymarin, physical mixtures (PM), solid dispersions (KND – kneading, SPRAY D. – spray drying, COPPT – co-precipitation), bottom to top.

Table II. Relative degree of crystallinity of physical mixtures and solid dispersions

Sample	Relative degree of crystalinity at $2\theta = 72.3°$
Co-precipitation (1:3)	–
Spray drying (1:3)	0.68
Kneading (1:1)	0.20
Physical mixture (1:3)	0.35
Physical mixture (1:1)	0.25
Silymarin	1.00
HPMC E 15LV	–

RDC – relative degree of crystalinity [ratio of the peak height in solid dispersion and the peak height of silymarin alone, at the same angle (11)].

In the case of kneaded solid dispersions, photomicrographs showed that silymarin particles were physically adsorbed over the respective carrier and formed porous solid dispersion particles with a hard surface having crevices and fissures. The morphological
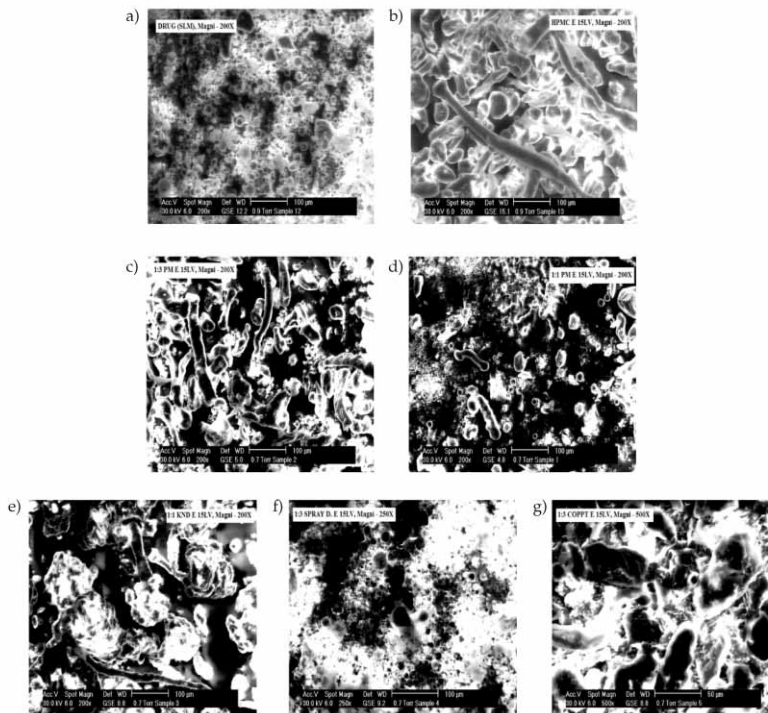

Fig. 5. SEM of: a) drug (SLM), b) HPMC E 15LV, c, d) physical mixtures (1:1, 1:3) and e, f, g) solid dispersions (kneading, spray drying and co-precipitation).

images of the spray-dried solid dispersion revealed that drug particles were distributed uniformly on the surface of carrier. Therefore, size reduction and uniform adsorption of the drug over carrier were found in solid dispersion prepared by spray drying (21). The SEM photomicrographs of the co-precipitated solid dispersion showed fully amorphous and porous nature with an irregular, coarser and hard surface full of crevices. The images further suggest the existence of an amorphous product with the presence of a single component in the solid dispersion (16).

In vitro *dissolution and dissolution parameters*

The *in vitro* dissolution profiles of pure silymarin, physical mixtures, and optimum ratios in solid dispersions prepared by kneading, spray drying and co-precipitation in distilled water (Fig. 6a), 0.1 mol L^{-1} HCl (Fig. 6b) and phosphate buffer pH 6.8 (Fig. 6c) over a period of 90 min are shown. It was evident that the *in vitro* dissolution of pure silymarin was very low in all dissolution media (drug released after 60 min was 46.8, 45.3 and 43.3 % in water, 0.1 mol L^{-1} HCl and PBS 6.8, resp.). The kneading, spray drying and co-precipitation methods improved silymarin dissolution within 90 min in all three dissolution media. Co-precipitation method showed maximum dissolution enhancement as compared to other preparation methods (> 80 % silymarin was released within 10 min from solid dispersion in three different dissolution media). This suggests that preparation methodology has an effect on drug dissolution improvement.

The drug release from physical mixtures after 10 min was enhanced compared to pure silymarin in all dissolution media.

The value of DE_{10min} for pure silymarin was enhanced in physical mixtures as well as in solid dispersions prepared by different methods significantly ($p < 0.05$) (Table III). Among the different preparation methodologies used, increased in the following order: co-precipitation > spray drying > kneading.

The mean dissolution time (*MDT*) is a measure of drug release retarding ability of the dosage form (15). The value of *MDT* in three dissolution media for pure silymarin, physical mixtures and solid dispersions prepared by different methods is presented in

Table III. Dissolution efficiency of solid dispersions prepared by various methods

| Dissolution medium	DE (%) after time (min)								
	Water			HCl (c = 0.1 mol L^{-1})			PB pH 6.8		
Parameter	10	30	60	10	30	60	10	30	60
Silymarin	15.6	43.6	63.4	38.8	67.5	80.1	31.6	58.2	73.1
Kneading (1:1)	48.9	73.5	78.5	35.5	63.2	77.9	35.4	60.8	72.8
Spray drying (1:3)	37.9	67.6	81.3	37.6	65.1	76.8	37.6	65.1	76.8
Co-precipitates (1:3)	44.8	77.8	87.5	43.1	76.1	87.6	42.6	74.3	86.3
Physical mixture (1:1)	26.0	49.4	66	36.8	62.8	72.5	39.6	67.3	79.8
Physical mixture (1:3)	25.6	49	65	34.8	59.8	69.6	39.0	66.6	78.6

DE – dissolution efficiency
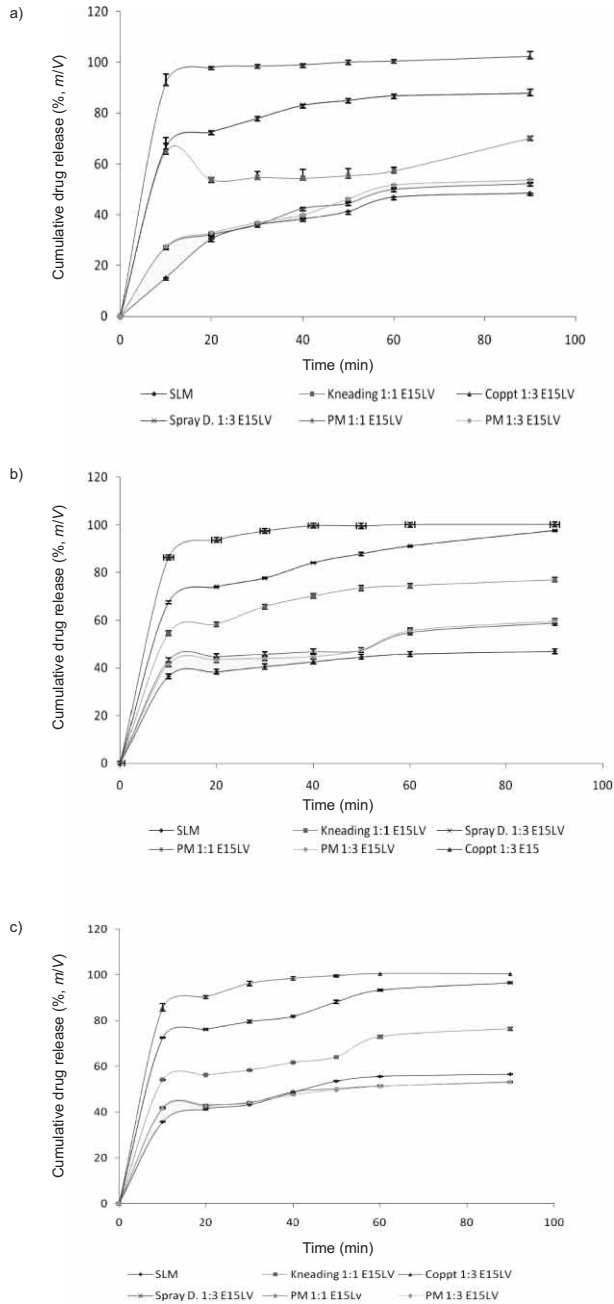
Fig. 6. *In vitro* dissolution profiles of solid dispersions in: a) water, b) 0.1 mol L^{-1} HCl, c) PB pH 6.8 (Mean ± SD, *n* = 3).

Table IV. It is evident that higher silymarin release was obtained (*MDT* = 7.4–8.3 min). The *MDT* value increased from spray drying to kneading. The physical mixtures also showed a considerably lower *MDT* value compared to pure silymarin.

It is evident from dissimilarity and similarity factors that the release profiles of silymarin prepared by all methods were significantly different (exception: physical mixtures) from that of silymarin (Table IV). Co-precipitation method showed maximum dissimilarity (f_1 value higher than 100) and therefore is the best method to improve dissolution of silymarin in all dissolution media.

Analysis of variance revealed that the drug release profiles of kneaded solid dispersion (1:1 drug to polymer ratio), co-precipitated (1:3 drug to polymer ratio) and spray dried solid dispersion (1:3 drug to polymer ratio) were significantly different ($p < 0.05$) from that of pure silymarin. They showed improved drug release compared to that of pure drug and other ratios of the respective methods. It is evident that *in vitro* dissolution of silymarin from co-precipitated solid dispersion was also significantly different ($p < 0.05$) from that of pure silymarin and physical mixtures in different dissolution media.

The improved dissolution of silymarin from solid dispersion prepared by kneading, spray drying and co-precipitation was attributed to the solubilizing effect of the carrier. The improvement of powder wettability could result from formation of a gel layer around the drug substance particles modifying the hydrophobicity of surfaces (11). Solid dispersions using HPMC E 15LV became gelatinized in the dissolution media. The gelatinized solid dispersion is constantly crushed by attrition during stirring and the finely gelatinized solid dispersion diffuses to bulk solution through the diffusion layer. Being water retentive, gelatinized dispersion also increases drug wetting, which is attributable to the increase in dissolution (8). In addition, other factors such as increased surface area, the absence of aggregation and agglomeration between hydrophobic drug particles, conversion of drug to the amorphous form and good dispersibility of the dispersed drug might have also contributed to the observed increase in the dissolution rate of silymarin from solid dispersions prepared by different methods (15).

Table IV. Dissolution parameters for solid dispersions prepared by various methods

Dissolution medium / Dissolution parameter	Water			HCl (c = 0.1 mol L^{-1})			PB pH 6.8		
	MDT (min)	f_1	f_2	*MDT* (min)	f_1	f_2	*MDT* (min)	f_1	f_2
Silymarin	22.4	–	–	12.3	–	–	15.	–	–
Kneading (1:1)	18.3	60.2	30.0	13.7	60.1	29.4	17.4	32.5	39.9
Spray drying(1:3)	11.4	118.5	18.0	16.2	96.1	19.3	14.4	75.5	22.1
Co-precipitates (1:3)	7.8	169.4	10.2	7.4	128.7	13.2	8.3	91.4	17.4
Physical mixture (1:1)	20.9	11.3	62.9	17.6	15.7	56.8	12.5	5.9	72.2
Physical mixture (1:3)	21.5	12.6	61.4	19.2	4.5	57.8	13.4	6.2	72.2

MDT – mean dissolution time.
f_1, f_2 – dissimilarity and similarity factor.

Table V. Drug content and dissolution parameters of co-precipitated solid dispersion during stability study

Day		0		15		30		60		90		180	
Condition		Room[a]	Test[b]	Room[a]	Test[b]	Room[a]	Test[b]	Room[a]	Test[b]	Room[a]	Test[b]	Room[a]	Test[b]
Silymarin (%, *m/m*)		99.04	99.04	99.24	99.01	99.04	98.59	99.04	98.59	99.05	98.59	99.14	98.59
Dissolution parameter	f_1	–	–	0.19	0.19	0.19	0.19	0.19	0.024	0.19	0.45	0.192	0.98
	f_2	–	–	96.18	93.83	96.18	94.72	96.18	96.18	96.18	91.29	96.18	96.38

[a] 25 ± 2 °C and 40 ± 5 % RH

[b] 40 ± 2 °C and 75 ± 5 % RH

f_1 and f_2 – dissimilarity and similarity factor

Stability

The silymarin content in solid dispersions was higher than 98 % (*m/m*) over a period of 15, 30, 60, 90 and 180 days and implies stability of prepared dispersions (Table V). Difference in drug release between aged and freshly prepared dispersions was evaluated by similarity and dissimilarity factors (*f₁* and *f₂*). The results indicate similarity in the dissolution profile of dispersions over a period of 6 months.

CONCLUSIONS

In conclusion, preparation methodologies have an effect on the physicochemical characteristics of the dispersion and rate of dissolution of silymarin. Aqueous solubility of silymarin was favoured by the presence of HPMC 15LV and spontaneous drug solubilization was also confirmed by the negative value of Gibb's free energy. Among various drug to polymer ratios, the most favourable condition was found in 1:1 for the kneading method and 1:3 for other methods. The reduced intensity without shifting of characteristic peaks justifies weak hydrogen bond formation between the drug and polymer. The X-ray diffraction pattern clearly demonstrates reduction in crystallinity and formation of partial amorphism in dispersions prepared by kneading, spray drying or co-precipitation. SEM photographs also support the amorphism in solid dispersions. Preparation methodology clearly affects the dissolution parameters. Improvement in the rate of dissolution can be attributed to the increased surface area, increased solubility and reduction in crystallinity. The increased dissolution rate observed in the case of physical mixtures might be due to the close contact of HPMC with silymarin, which improves wetting and dissolution or might be caused by one or more of the characterization factors mentioned previously. Statistical evaluation suggested enhancement in silymarin dissolution in co-precipitation (2.5 fold) > spray drying (1.9 fold) > kneading (1.5 fold). Mean dissolution time (in min) was as follows: 8.3 for co-precipitation, 14.2 for spray drying and 17.4 for kneading.

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S A Ž E T A K

Čvrste disperzije silimarina: Karakterizacija i utjecaj načina priprave na oslobađanje

DALWADI SONALI, SONI TEJAL, THAKKAR VAISHALI i GANDHI TEJAL

U radu je ispitivan utjecaj načina priprave čvrstih disperzija silimarina na brzinu oslobađanja. Čvrste disperzije silimarina pripravljene su pomoću hidrofilnog polimera HPMC E 15LV metodom gnječenja, sušenja sprejom i koprecipitacijom. Pripravci su karakterizirani pomoću FTIR, DSC, XRPD i SEM. Profili oslobađanja uspoređivani su statistički i pomoću metoda koje su neovisne o modelu. FTIR i DSC studije otkrile su postojanje slabih vodikovih veza između lijeka i polimera, dok su XRPD i SEM potvrdile da je silimarin u čvrstim disperzijama amorfan. Poboljšano oslobađanje u odnosu na čisti lijek uočeno je ovim slijedom: koprecipitacija > sušenje sprejom > metoda gnječenja (*p* < 0.05). Iz svih pripravaka oslobađanje je bilo sporije, bez obzira na metodu priprave. Pripravci dobiveni metodom koprecipitacije bili su stabilni, a oslobađanje silimarina iz njih bilo je 2,5 bolje u odnosu na čisti lijek.

Ključne riječi: silimarin, HPMC, čvrste disperzije, gnječenje, sušenje sprejom, koprecipitacija, parametri oslobađanja

Ramanbhai Patel College of Pharmacy, Charotar University of Science and Technology Changa-388421, India

Anand Pharmacy College, Anand-388001, India