



Capsulated Surface Solid Dispersion of Loperamide for Targeted Delivery

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Abstract The purpose of the study was to develop a capsulated delivery system of surface solid dispersion (SSD) of loperamide (LOP) for intestinal delivery that has potential for enhanced drug release. For the preparation of SSDs, crospovidone, croscarmellose sodium and avicel PH 101 were screened for swelling capacity and *in vitro* drug adsorption. SSDs were prepared by solvent evaporation method and the SSD prepared with crospovidone (drug to carrier ratio of 1:3) showed highest *in vitro* dissolution of 82.50% in 60 min. The optimized SSD3 was evaluated for micromeritic properties and characterized by XRD, DSC, SEM and FTIR. SSD3 was filled in Eudragit S 100 coated capsules SSD3 showed promising site specific drug delivery with release of 76.25% in 6 h. The developed dosage form has potential to protect loperamide from being released in the upper part of the GI system and thereby target to intestine.

Keywords loperamide, crospovidone, surface solid dispersion, Eudragit S100 coated capsule.

Introduction

Loperamide is opiate analogue with anti diarrheal activity. Due to its poor water solubility, it shows very little absorption in the upper part of the gut. Solid dispersion is one of the most widely used technique to enhance the aqueous solubility of drug [1] where, one or more active ingredient(s) is uniformly dispersed in an inert water soluble carrier matrix. Solid dispersion is based on the phenomenon of drug entrapment within the polymer matrix and consequently, the drug follows the additional barrier of polymer layers to cross the matrix [2]. However, the use of water soluble polymers in solid dispersion generates matrix with tackiness and follows the manufacturing difficulties, [3] especially in capsule filling and tablet making process. These difficulties should be minimized and requires a system that brings superiority over the limitations such as entrapment of drug within the polymer structure, the poor miscibility of matrix and drug, formation of handling incompatible soft tacky wet mass, lesser stable amorphous form of the drug is produced. Other limitations include laborious and expensive method with difficulty in reproducibility in formulation and poor shelf-life [4].

The problems caused by preparation of solid dispersion can be attenuated by adopting surface solid dispersion technique, which is a technique that provides deposition of the drug on the surface of water insoluble material with hydrophilic nature that can alter the dissolution characteristics of the drug. Deposition of the drug on the surface of an inert carrier leads to reduction in particle size of the drug, providing faster dissolution rate [5]. The surface solid dispersion technique has been used to increase the solubility, dissolution and consequently the bioavailability of



many practically insoluble or poorly soluble drugs such as ibuprofen [6], piroxicam [7], meloxicam [8], itraconazole [9] and aceclofenac [10]. When compared with solid dispersions, that generally generates a homogenous molecular matrix of carrier with drug; SSD can be visualized as an advantageous system as the drug is adsorbed onto the carrier surface that generates a free flowing dry powder with high dispersibility in aqueous media [2].

In literature reports, LOP was formulated as solid dispersion using PEG 6000 by spray drying technique. The observations concluded that loperamide was partly present in crystalline and partly as amorphous form in freshly prepared samples and continues to crystallize under storage conditions, which eventually resulted in poor dissolution properties [11]. This poor dissolution profile was the limitation that was aimed to overcome by surface solid dispersion of loperamide. Additionally, solid dispersions of PEG, have repeatedly reported phase separated systems having polymer in semi-crystalline state and drug in either crystalline, amorphous or a mixture of both of them. This complies with the physical stability issue. This further necessitates the development of surface solid dispersion technique which overcomes this drawback.

Materials and Methods

LOP was received as gift sample as Glenmark Pharmaceuticals Ltd., Mumbai, India. Crospovidone, Croscarmellose sodium and Avicel PH 101 was obtained as gift sample from Qualikems fine chemicals, New Delhi. All other chemicals were of analytical reagent from SD Fine Chem, Mumbai, India.

Equilibrium Solubility

Excess amount of LOP was added to 25 ml conical flask containing 10 ml of distilled water and 10 mg of each carrier was dispersed separately into the conical flask. The flasks were shaken in a water bath maintained at 37 ± 1 °C for 72 h. At the end of test period 10 ml of sample was withdrawn, filtered and analyzed spectrophotometrically at 259 nm using UV spectrophotometer (Shimadzu, Pharmaspec 1700, Kyoto Japan).

In vitro adsorption

10 mg of LOP was added to 100 ml of distilled water and tenfold weight (100 mg) of crospovidone was added to it. The mixture was magnetically stirred at 100 rpm and 37 ± 1 °C for 72 h. 10 ml of sample was withdrawn at 0, 6, 24, 48 and 72 h and assayed at 259 nm to determine the percent drug adsorbed with respect to time. The study was repeated for croscarmellose sodium and avicel PH 101.

Hydration capacity

1 g each of crospovidone, croscarmellose sodium and avicel PH 101 each was separately placed in 10 ml pre-weighed centrifuge tube. 10 ml of double distilled water was filled in each tube and stoppered. The tube was shaken manually and centrifuged for 15 min at 1000 rpm and the supernatant was decanted off. The tube was reweighed and hydration capacity was calculated using eq. 1.

$$\text{Hydration capacity} = \frac{\text{Weight of tube with sediment} - \text{weight of empty tube}}{\text{weight of sample on dry basis}} \times 100 \dots \text{eq.1}$$

Preparation of SSD

100 mg of LOP was dissolved in 10 ml of dichloromethane and 100 mg of carrier was dispersed into it as to render drug: carrier ratio 1:1. The dispersion was kept on thermostatically controlled water bath at 60 ± 1 °C to completely evaporate the solvent and obtain dry product. The procedure was repeated for each drug: carrier ratios including all carriers (Table 1).

Evaluation of SSDs

Drug content

SSD theoretically equivalent to 10 mg of drug was weighed and extracted with 5 ml of dichloromethane. The solution was filtered and the volume was rendered up to 10 ml phosphate buffer, pH 7.4. This was diluted up to 100



ml with phosphate buffer, pH 7.4 and analyzed at 259 nm, in triplicate and mean value with standard deviation was recorded.

Table 1: Composition design and evaluation parameters of nine SSDs (SSD1-SSD9) and pure drug (LOP)

Code	Carrier	Drug: Carrier ratio	% Drug Content \pm SD*	% CDR at 60 th min \pm SD*	t _{20%} (min)	t _{50%} (min)	T _{70%} (min)	D.E at 60 min (%)	Coefficient of determination (r ²)		
									Zero Order	First Order	Higuchi
SSD1	Crospovidone	1:1	86.33 \pm 0.50	71.00 \pm 0.09	12	27	37.8	94.3	0.921	0.646	0.954
SSD2	Crospovidone	1:2	91.05 \pm 0.41	78.75 \pm 0.02	10.9	24	33.6	95.4	0.912	0.589	0.963
SSD3	Crospovidone	1:3	93.50 \pm 0.25	83.25 \pm 0.90	10	23	32.	96.3	0.902	0.630	0.948
SSD4	Croscarmellose sodium	1:1	77.50 \pm 0.17	71.25 \pm 0.10	11	29.5	41	93.3	0.957	0.633	0.973
SSD5	Croscarmellose sodium	1:2	80.33 \pm 0.44	75.00 \pm 0.50	9.5	23.5	32.9	94.6	0.891	0.589	0.973
SSD6	Croscarmellose sodium	1:3	82.26 \pm 0.42	78.75 \pm 0.05	8	20.5	28.7	95.9	0.898	0.589	0.974
SSD7	Avicel PH 101	1:1	89.04 \pm 0.50	59.98 \pm 0.50	16.5	44	61.6	90.1	0.974	0.707	0.945
SSD8	Avicel PH 101	1:2	79.66 \pm 0.43	66.25 \pm 2.16	14	37	51.8	96.25	0.986	0.689	0.947
SSD9	Avicel PH 101	1:3	79.05 \pm 0.09	67.50 \pm 0.50	12	35	49	94.0	0.966	0.664	0.963
LOP	-	-	-	22.50 \pm 0.82	55	-	-	66.6	0.960	0.980	0.872

***In vitro* dissolution**

In vitro dissolution study of all the formulated SSDs (SSD1-SSD9) was performed using USP type II apparatus (paddle type). The dissolution test was performed using 900 ml of phosphate buffer, pH 7.4 with paddle speed of 100 rpm at 37 \pm 0.5 °C. Five milliliters of sample was withdrawn at specific time intervals, 0, 10, 20, 30, 45 and 60 min. and replaced with an equal volume of fresh dissolution medium. Samples were analyzed at 259 nm in triplicate and mean value with standard deviation was recorded. The drug dissolution profile was plotted between the cumulative drug release versus time. The release data was subjected to various kinetic models to evaluate the release kinetics. The data was subjected to various kinetic models to evaluate the release mechanism of pure drug and all the nine SSDs. t_{20%}, t_{50%} and t_{70%} was determined and dissolution efficiency at 60 min was also calculated using the following equation [12].

$$\% \text{ Dissolution efficiency} = \frac{\int_0^t Q dt}{Q_{max} t} \times 100 \dots \dots \dots (\text{Eq. 2})$$

Selection and characterization of optimized SSD

Amongst the nine SSDs prepared, best SSD was selected on the basis of maximum drug content and *in vitro* dissolution and subjected to further studies. The powder properties such as angle of repose, bulk density, tapped density, Hausner's ratio, and Carr's compressibility index were assessed. Other characterization techniques used are detailed below.

Scanning Electron Microscopy

The scanning electron microscopy (SEM) of samples was conducted by using scanning electron microscope (JEOL 5400, Tokyo, Japan) operated at an acceleration voltage of 10/kV. The samples were prepared by adhering the powder on a double-sided tape stuck to aluminum stub. The stub was coated with gold ion for 5-6 min. The surface morphology of the samples was studied by observing the photomicrographs under 1000 x magnification.

Differential Scanning Calorimetry

Differential Scanning Calorimetry (DSC) of the samples was recorded using differential scanning calorimeter instrument (DSC Q-200 V 24 11 Build 124, USA). The samples were sealed in aluminium pans and analyzed. Both



the sample and reference (alumina) were kept at the same temperature and the heat flow required for maintaining the equality in temperature was measured. 5 to 10 mg of sample was sealed in aluminium pan and analyzed using a differential scanning calorimeter focused on the melting temperatures. A scanning rate of 10 °C/min from 40 °C to 390 °C under nitrogen purge was used.

X-Ray Diffraction

X-Ray diffraction patterns of the samples were recorded by X-Ray diffractometer. The samples were irradiated with monochromatized Cu-K α radiation, generated at 1.542 Å wavelength at 30 kV and 30 mA. The samples were scanned over a range of 10-90° at a chart speed of 10 mm/2 θ . The intensity of the peaks was recorded in XRD patterns and was studied for crystallinity of the samples.

Fourier Transform Infrared Spectroscopy

Fourier Transform Infrared Spectroscopy (FT-IR) analysis of the samples was examined using FT-IR spectrometer (Bruker, Alfa-T, Germany). The test samples were diluted with KBr which was mounted into the instrument. The measurements were recorded in terms of % transmittance in the range of 500-4500 cm⁻¹.

Dosage form Development

Preparation of Coating Mixture

The coating mixture of 10 % w/v was prepared using Eudragit S 100 as a coating polymer, isopropyl alcohol as solvent, talc (0.1 %) as anti-adherent and triethyl citrate (10%) as plasticizer. For preparing the coating mixture, the dispersion of Eudragit S 100 was made in a mixture of isopropyl alcohol and water, a homogenous mixture of solvent, plasticizer and anti-adherent was prepared separately and finally in this homogenous mixture the dispersion was mixed and stirred to get a translucent coating mixture. After preparation of the coating solution the cap and the body of the capsule were separated and coated separately by dip coating process.

Coating of Capsules

Empty shells of hard gelatin capsules (size 3) were taken and were coated with Eudragit S 100 coating mixture. Firstly, the body of the capsule shell was coated by dip coating process leaving the portion to be inserted within the cap of the capsule uncoated. The coated portion was air dried after mono, di and tri coating layer for the specified time period for 30, 60 and 90 min, in order to evaluate the most efficient coating parameter in terms of layers of coating and time for drying. Further, the required SSD3 equivalent to the dose of the drug (4 mg) was filled in the coated body portion and was covered with the uncoated cap of the capsule shell. After complete locking of the coated body and the uncoated cap, the cap was coated with the coating mixture by dip coating process. The cap portion was then air dried for specified time period as mentioned above before being evaluated for *in vitro* release. Same procedure was repeated for coating of capsules filled with 4 mg of pure drug.

Integrity of Coated Capsule

The body of the capsule shell was coated by dip coating process leaving the portion to be inserted within the cap of the capsule uncoated and the body was filled with small amount (5mg) of methylene blue dye and was fixed with cap which then coated with the coating mixture and air dried for specified time period of 30, 60 and 90 min. The capsules were tested for their integrity in 900 ml of hydrochloric acid buffer pH 1.2 for a time period of 2 h using USP type I apparatus (basket type) at 100 rpm. At the end of the specified time period, the capsule was visually examined for release or leakage of dye and/or any other change or damage in the capsule shell.

***In vitro* release**

SSD3 (equivalent to 4 mg of LOP) filled capsules and pure drug (4 mg) filled coated capsules were subjected to *in vitro* release study using USP type I apparatus at a speed of 75 rpm in 900 ml of hydrochloric acid buffer pH 1.2, for 2 h. After 2 h, the capsule was transferred to 900 ml of phosphate buffer pH 7.4 for 4 h at 37±0.5 °C. The study



was conducted for a total duration of 6 h and 10 ml of sample was withdrawn at regular time intervals of 0.0, 0.5, 1.0, 1.5, 2.0, 3, 3.5, 4.0, 4.5, 5.0, 5.5 and 6.0 h and replaced with fresh dissolution medium after each sampling. The samples were filtered with Whatman filter paper and spectrophotometrically analyzed at 259 nm in triplicate and mean value with standard deviation was recorded. The *in vitro* release profile was plotted between the cumulative drug released versus time and subjected to kinetic modelling.

Result and Discussion

Equilibrium solubility

LOP demonstrated a solubility of 0.0098 mg/ml in distilled water which indicated its solubility dependent dissolution. With respect to pure drug, the physical mixtures of the drug with the carriers showed fair amount of enhancement in the solubility. The physical mixture of LOP with crospovidone showed maximum solubility enhancement of up to 359%, whereas that with croscarmellose sodium and avicel PH 101 showed solubility enhancement up to 206 and 87% respectively as tabulated in Table 2. The solubility enhancement by crospovidone, a water insoluble but rapidly swellable synthetically cross linked homopolymer of N-vinyl-2-pyrrolidone [13] provides efficient steric hindrance for nucleation and crystal growth was provided by repeating units in crospovidone due to its antiplasticizing effect [14]. Thus, crospovidone with porous and granular high surface area, and high interfacial activity enhanced the solubility of LOP. Thus, crospovidone with porous and granular high surface area, and high interfacial activity enhanced the solubility of LOP. Lesser enhancement in solubility by croscarmellose sodium and avicel PH 101 could be attributed to poor wetting ability in comparison to crospovidone. Furthermore, the particle size varies in the order crospovidone > croscarmellose sodium > avicel PH 101, and could be seen as one of the influencing factors. The reason why crospovidone showed highest enhancement in solubility is its particle size, surface area and the evaporation of the solvent that lead to an increase in the interfacial area of contact between the drug particles and the solubility medium.

Table 2: Solubility enhancement data of LOP in the presence of various carriers

Sample	Absorbance	Solubility (mg/ml)	% enhancement in solubility
Pure drug	0.021	0.0098	-
LOP + Avicel PH 101	0.027	0.0183	86.73%
LOP + Croscarmellose Sodium	0.034	0.0300	206.12%
LOP + Crospovidone	0.043	0.0451	359.18%

In vitro adsorption

In-vitro adsorption profiles (Figure 1) of LOP on crospovidone, croscarmellose sodium and avicel PH 101 showed highest *in vitro* adsorption of 84.33% in 72h, on crospovidone. The adsorption property of the carriers directly corresponds to the surface area of the same. Based on the literature value of specific surface area the carriers can be arranged in the increasing order (crospovidone > croscarmellose sodium > avicel PH 101) and the results of extent of *in-vitro* adsorption were found to be correlating. Since, the carriers that were used were hydrophilic in nature hence they possessed the affinity to adsorb the drug on their surface. Results were directly attributed to the large particle size of crospovidone which provided more surface area for the drug to get adsorbed. The results revealed similarity in the pattern of adsorption wherein the abundant free adsorption sites led to higher initial adsorption that later on slowed down. The larger particle size of the former provided more surface area for adsorption of LOP [15] and the fact that crospovidone swells rapidly when in contact with water due to the presence of swellable adsorbent group facilitated surface adsorption of the drug. Avicel PH 101 showed least adsorption which was attributed to its chemical structure and lesser surface area of the same.



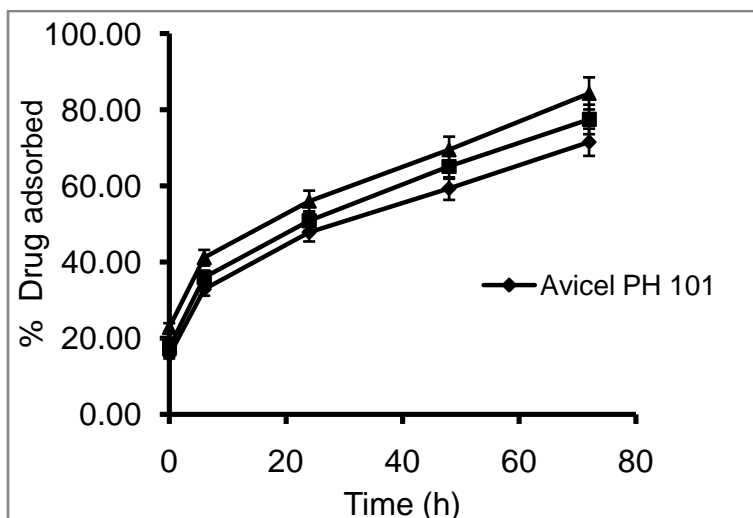


Figure 1: *In vitro* adsorption profile(s) of loperamide on croscovidone, croscarmellose sodium and avicel PH 101

Hydration capacity

The swelling ability of the each carrier was determined by hydration capacity and amongst the three carriers croscovidone showed a hydration capacity of 31 ± 0.20 %, whereas croscarmellose sodium and avicel PH 101 showed 23 ± 0.15 % and 15 ± 0.50 % of hydration respectively. Hydration capacity is an indicative of extent of solid liquid interface or the swelling power of the carriers, which is a predominant property of the carriers. Croscovidone showed the best results since croscovidone has a tendency to show both swelling as well as wicking property which is caused due to its capillary action and porosity while croscarmellose sodium and avicel PH 101 exhibit only swelling phenomenon [15]. The water holding capacity is responsible for dissolution of the drug.

SSDs

The surface solid dispersions (SSD1-SSD9) of LOP prepared by solvent evaporation method were apparently free flowing powders, and were evaluated for drug content and *in vitro* dissolution. The drug content of the SSDs (SSD1-SSD9) ranged between 77.50 ± 0.17 and 93.50 ± 0.25 % (Table 1). The drug content varied with the type of carrier and the drug: carrier ratio. Consequently, SSDs made with croscovidone afforded higher values of drug content and the least was exhibited with avicel PH101. Likewise a drug:carrier ratio of 1:3 exhibited highest drug content followed by 1:2 ratio and still lower values by 1:1 ratio irrespective of the carrier used.

In vitro dissolution

The *in vitro* dissolution profile of LOP filled capsule showed poor release of 22.50 ± 0.82 % in 60 min. The reason behind the same could be the solubility dependent dissolution exhibited by the drug in pure form. Whereas, loperamide formulated into SSD showed increased dissolution ranging from 59.98 ± 0.50 (SSD7) to 83.25 ± 0.90 (SSD3), when compared to that of the pure drug (Figure 2). The results correlated with the solubility study data as improved dissolution was a consequence of enhanced solubility facilitated by use of the carriers. The dissolution rate of loperamide increased with increase in carrier concentration, for all carriers. However, the enhancement was lesser in case of croscarmellose sodium and avicel PH 101 due to its lesser wetting ability and consequently, lesser solubility enhancement. The results correlated with those seen in previous literature work by [16]. The swelling of croscovidone, when in contact with dissolution medium, caused deaggregation of clusters of small drug particles and thus facilitating the dissolution. The improvement in dissolution rate of loperamide could also be attributed to the uniform deposition of drug particulates on the surface of hydrophilic carriers [17-18]. The drug release data fitted Higuchi model with correlation coefficient being 0.948 for SSD, which due to highest *in vitro* dissolution was



selected to be the best SSD. Model independent parameters: $t_{20\%}$, $t_{50\%}$ and $t_{70\%}$ were calculated. The dissolution efficiency was also calculated at 60 min and is mentioned in Table 1.

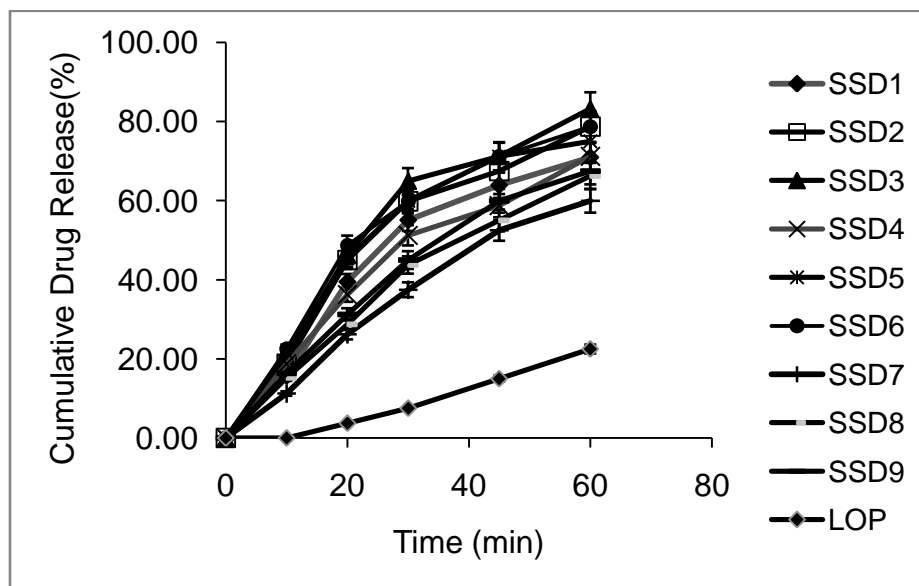


Figure 2: In vitro dissolution profiles of SSDs (SSD1-SSD9) of loperamide

Selection of optimized SSD

Amongst the nine SSDs prepared, SSD3 was found to be the optimized SSD on the basis of highest drug content and % cumulative drug release.

Micromeritic properties of the optimized SSD (SSD3)

The angle of repose of SSD3 was found to be $18.8^{\circ} \pm 2.1^{\circ}$, which suggests excellent flow property of SSD ($<25^{\circ}$) and that there is no need of any incorporation of flow activators in the manufacturing lines of SSD. Good flow characteristics of SSD3 was also be confirmed by low Carr's compressibility index of $20.3\% \pm 2.3$ which lies in the range for good particle flow (18-23%). Furthermore, the Hausner's ratio of SSD3 was 1.33 ± 0.041 , which is less than 1.25 and indicated good flow characteristics of the powder. All these results demonstrated good powder properties of SSD3. The reason for good flow properties was the use of water insoluble carrier (crospovidone). The carrier does not support formation of soft and tacky powder as seen with SDs [19]. This definitely proves to be advantageous aspect in the manufacturing facilities of SSD over SD.

Table 3: Micromeritic properties of optimized SSD (SSD3)

Parameter	Value
Tapped density (g/cc)	0.348 ± 0.012
Bulk density (g/cc)	0.259 ± 0.006
Hausner's Ratio	1.33 ± 0.041
Carr's Compressibility index (%)	20.3 ± 2.3
Angle of repose ($^{\circ}$)	18.8 ± 2.1

Scanning Electron Microscopy

SEM of pure drug inflected irregular crystals with regular plain surfaces and sharp edges clearly seen in Figure 3(a). SEM micrograph of crospovidone as shown in Figure 3(b) revealed partially agglomerated particles in bundles. The amorphous surface probably played an important role in providing larger surface area for drug deposition [20]. Porous and amorphous surface allowed the deep penetration and restricted the drug recrystallization during the



processing of SSD [21]. Micrograph of optimized SSD (SSD3) revealed deposition of very fine microcrystals of loperamide on to the crospovidone particles, Figure 3(c). Small microscopic cracks and crevices, formed due to solvent evaporation, further provided additional surfaces for the drug to get adsorbed. Thus, it can be concluded from SEM pictures that SSD3 leads to increase in solubility as well as dissolution characteristics due to presence of free form particles of crospovidone.

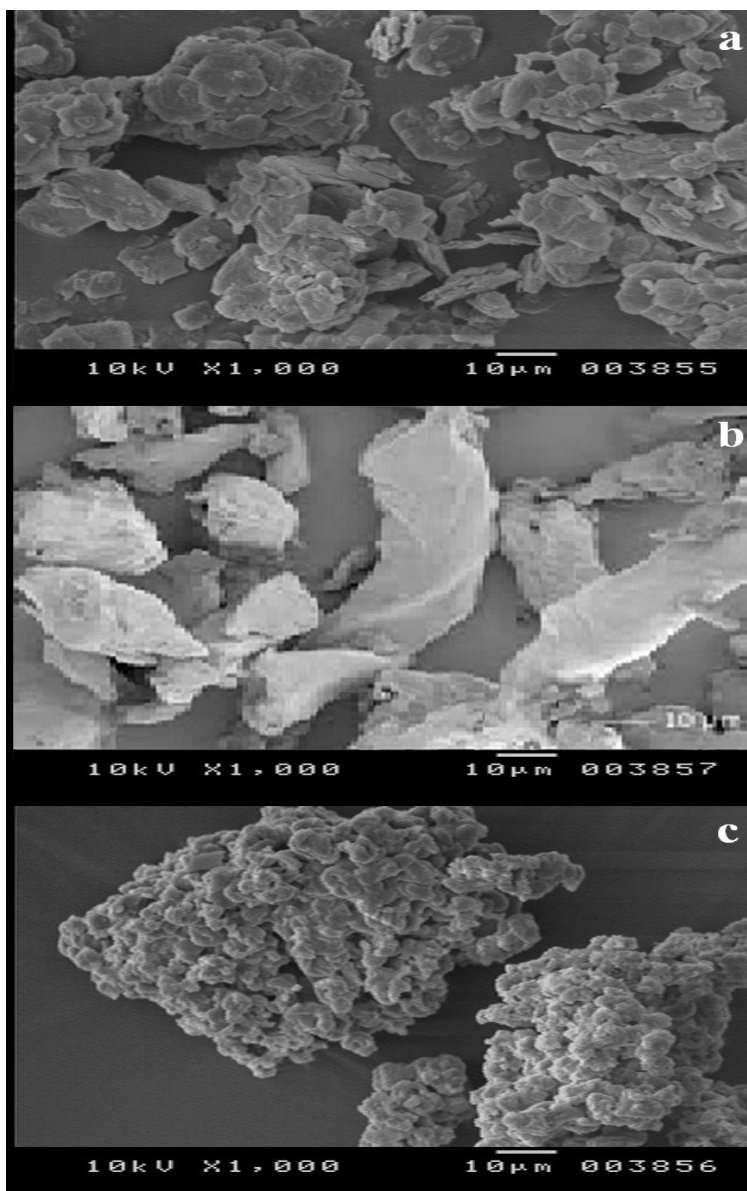


Figure 3: SEM images of (a) pure drug, loperamide, (b) crospovidone, and (c) SSD3

Differential Scanning Calorimetry

The DSC thermogram of pure drug (LOP) showed sharp melting peak at 231°C, Figure 4 (a). The sharp melting endotherm of loperamide was sharp due to its crystalline nature and unlike the DSC thermograph of crospovidone, Figure 4 (b), was a broad sharp endotherm because of its amorphous nature. The peak of crospovidone was retained in optimized SDD, SSD3, seen in Figure 4 (c). This was seen without any shifting or occurrence of any new peak that confirmed the compatibility between the drug and the carrier, which was due to the inertness of crospovidone. The shifting of the peak of the pure drug from 231°C to 228°C could be attributed to the poor re-crystallization of drug during its deposition on the amorphous carrier particles that was further confirmed by XRD.



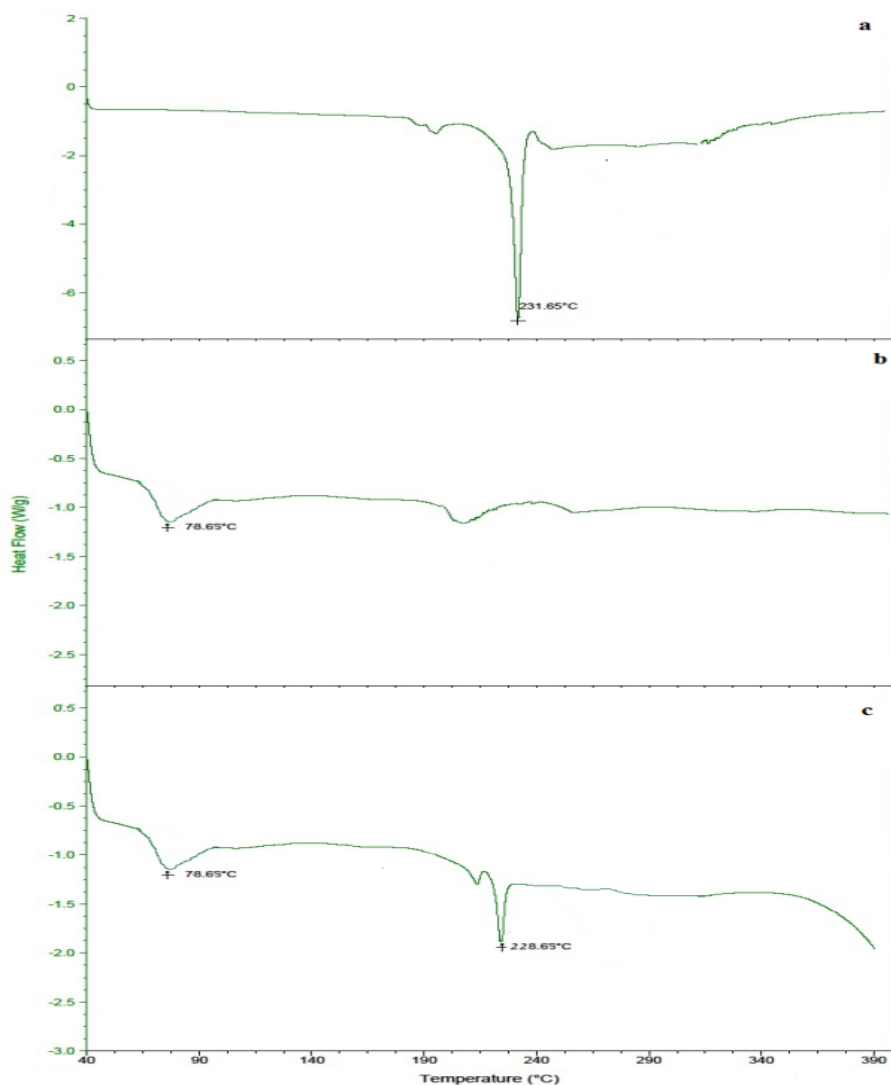


Figure 4: DSC thermographs of (a) pure drug loperamide, (b) crosopovidone, (c) SSD3

X-Ray Diffraction

Numerous distinctive peaks of pure drug (loperamide) were seen in the diffraction pattern throughout the scanning range at diffraction angle 2θ , Figure 5(a), whereas, in the XRD spectrum of SSD3, Figure 5(c), prominent peaks were clearly visible at nearly the same positions but with reduced intensities and halo areas in the spectrum. The sharpness in the peaks of pure drug denoted its crystalline nature which correlated to the images obtained in SEM and the DSC thermographs. An appropriately visible decrease in the intensities of the peaks seen in Figure 5(c) was probably due to dilution, some change in crystal habit or conversion of the product to an amorphous form. Any conversion to polymorphic form was clearly ruled out due to non occurrence of any new peaks. The SSD was prepared using dichloromethane as solvent and this showed reduced crystalline properties as compared to pure drug. This accounted for increased dissolution efficiency of the SSD prepared with dichloromethane as solvent.



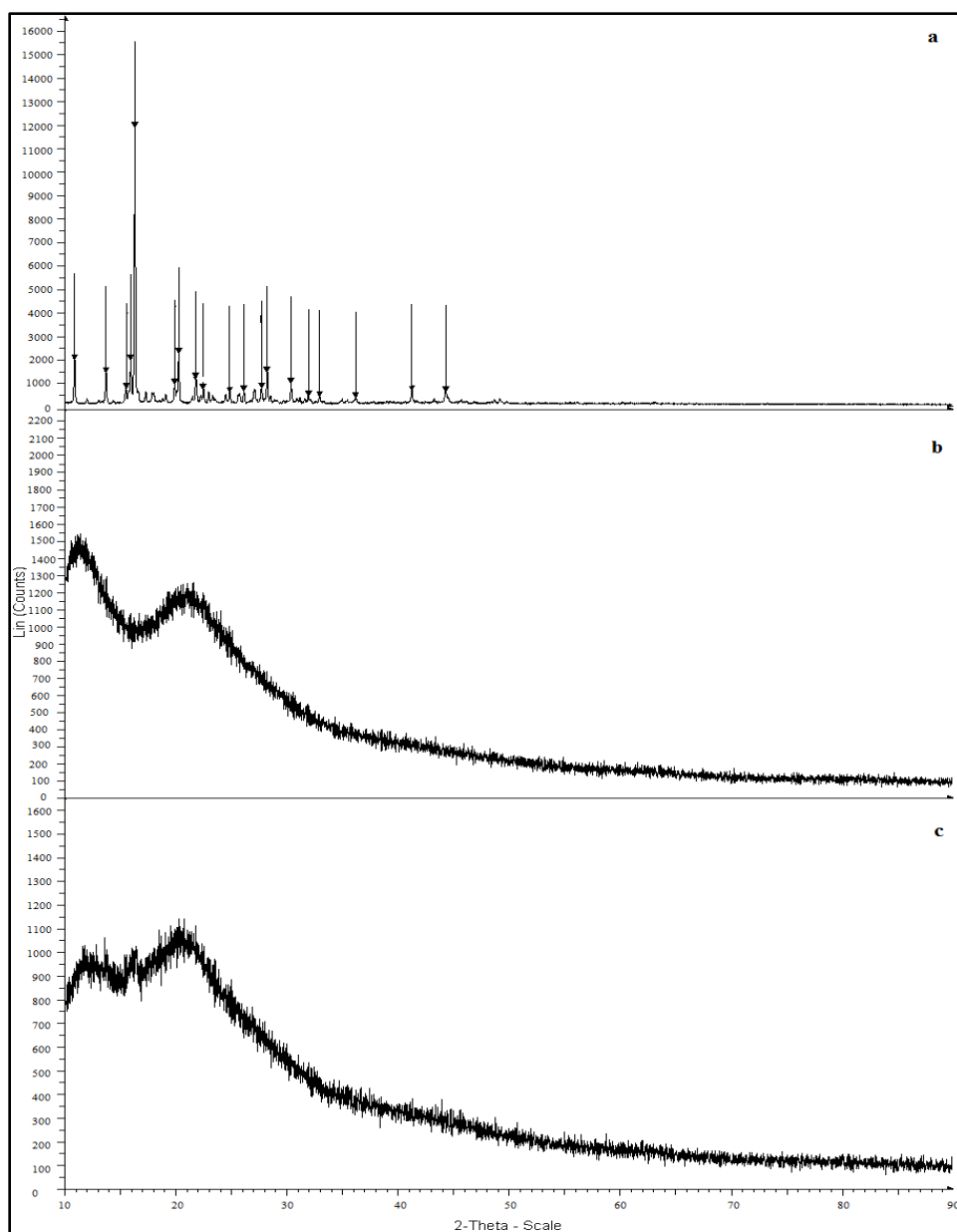


Figure 5: XRD diffraction patterns of (a) pure drug loperamide, (b) crospovidone, (c) SSD3

Fourier Transform Infrared Spectroscopy

The major IR peaks for LOP and crospovidone as observed in Fig. 6(a, b) respectively were also retained in SSD3 spectrum (6c). Fig. 6(a) showed characteristic peak at wave number at $750\text{--}735\text{ cm}^{-1}$ that showed characteristic aromatic hydrocarbon, 1404 cm^{-1} for C-O-H stretching, peak at 1710 cm^{-1} showed peak of --C=O which is aliphatic ketone [22]. The presence of these peaks thus, indicating no evidence of chemical interactions between the drug and carrier (crospovidone). No specific conclusions could be drawn from the IR spectra of SSD3 related to drug-carrier interactions. The spectra predominantly revealed significant peak of crospovidone as well as LOP. There were no new bands observed in the spectrum, which confirms that no new chemical bonds were formed between the drug and the carrier.



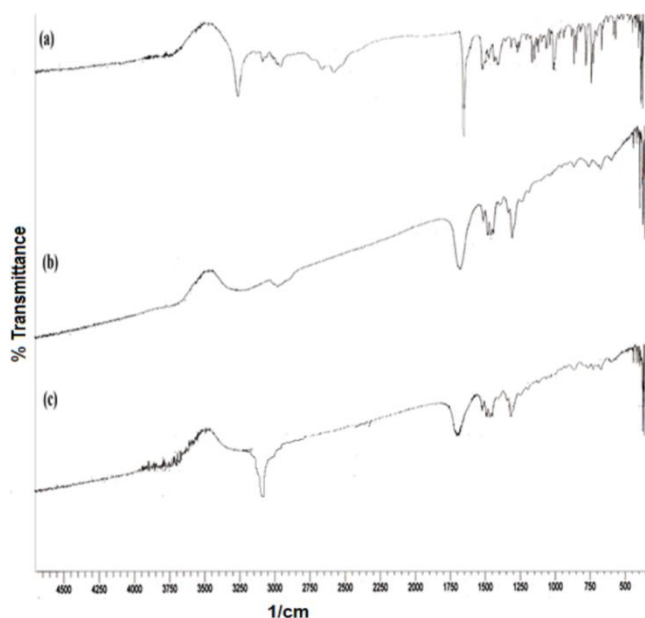


Figure 6: FT-IR spectrographs of (a) pure drug loperamide, (b) crospovidone, (c) SSD3

Dosage form Development

Coating mixture

10% w/v mixture of Eudragit S 100 (10ml) was prepared and was successfully used as the coating mixture for coating of capsules. Using 10% w/v Eudragit S 100 mixture, the capsules (size 3) were successfully coated with mono, di and tri layer. Optimization of mono, di and tri layered coated capsules filled with methylene blue dye was carried out. It was seen that tri layered coated capsules with drying time of 90 min did not show any release of the dye or any damage to the capsule shell for 2 h in 900 ml of hydrochloric acid buffer, pH 1.2 (Table 3). The detainment of the integrity for 2 h in acidic pH is vital in offering protection to the drug until it leaves the stomach which is attenuated to the property possessed through the use of the pH dependant polymethacrylates polymer i.e. Eudragit S 100 [23]. These intact coated capsules were further used for carrying out the *in vitro* release of the formulation.

Table 3: Optimization of coating of capsule shell

Number of coats applied	Time of drying after each coat (min)	Time of release of dye from capsule in SGF (min)	Parameter for integrity in 0.1N hydrochloric acid buffer, pH 1.2, for 2 hr	Result
1	30	< 25	Time (min) for release of methylene blue (dye) from capsule in SGF	Fail
1	60	< 45		Fail
1	90	< 80		Fail
2	30	< 30		Fail
2	60	< 45		Fail
2	90	< 90		Fail
3	30	< 30		Fail
3	60	No release of dye		Pass
3	90	No release of dye		Pass

In vitro release

Prepared coated capsule formulation filled with SSD3 (drug to carrier ratio of 1:3 and drying time of 90 min) was subjected to preliminary *in-vitro* release studies. The test was carried in two media, acidic buffer, pH 1.2 for the



first two hours, and in phosphate buffer, pH 7.4 for the subsequent 4 h. After introduction of the capsule, there was no drug release in the acidic media due to the acid resistibility of the coating layer of Eudragit S 100 solution. The acid resistibility indicated the efficiency of Eudragit S 100 as coating material. The use of this polymer proved that the drug was not released in the stomach which helped it reach the site of action i.e. intestine avoiding the degradation in acidic pH. It is well established that the average residence time of the formulation in the stomach, 2h, was achieved [24] as seen in the release profile of the formulation in Figure 7. The drug release was negligible in first 2 h followed by release of the drug in next span of 4h. The property of Eudragit S 100 to get dissolved in basic pH 7.4 allowed the penetration of dissolution medium into the capsule and caused fast but steady release of the drug [25]. Furthermore, the drug release was twice as much from the LOP filled capsulated dosage form in comparison to SSD3 formulation highlighting higher drug release efficiency from the developed dosage form.

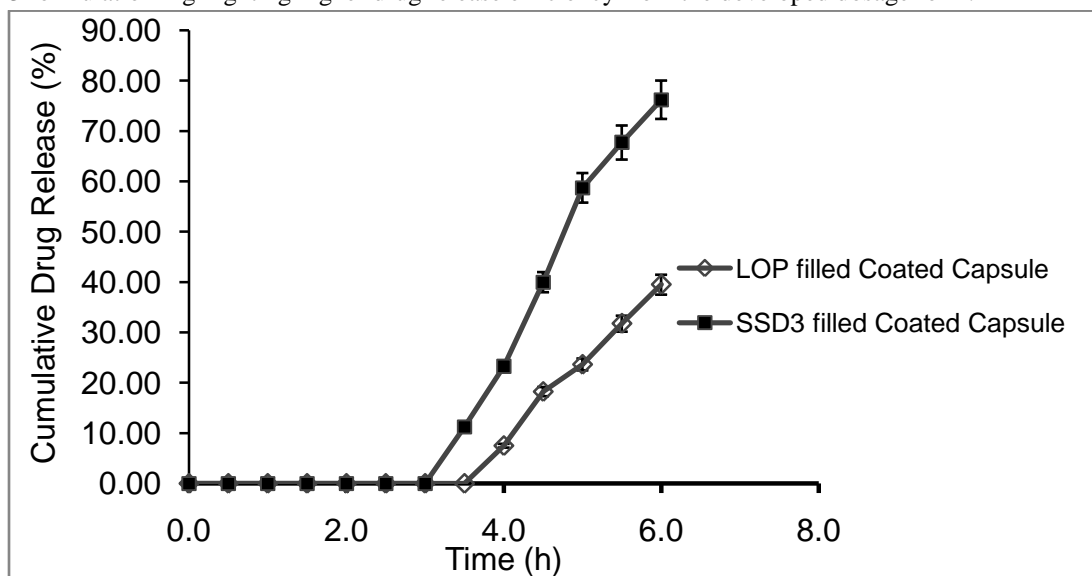


Figure 7: Comparative *in vitro* cumulative drug release from SSD3 filled coated capsule and pure drug filled coated capsules

Conclusion

Conclusively, surface solid dispersion) of loperamide was successfully prepared by solvent evaporation method. Both the solubility and the dissolution rate were enhanced due to deposition of the microcrystals of the drug on the amorphous carrier (crospovidone). Hydrophilicity as well as large surface area proved to be the key highlighting point in development of SSDs. Further, the Eudragit S 100 coated capsules of the optimized SSD offered protection to the drug in the acidic media and the released the drug in basic pH thus offering potential of targeted delivery of loperamide at the site of action.

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