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INVESTIGATING THE EFFECT OF MOLECULAR WEIGHT OF POLYVINYLPYRROLIDONE AND HYDROXYPROPYL METHYL CELLULOSE AS POTENTIAL ANTIPRECIPITANTS ON SUPERSATURATED DRUG SOLUTIONS AND FORMULATIONS USING WEAKLY ACIDIC DRUG: INDOMETHACIN

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Keywords:

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ABSTRACT: Most of the drug discovered in past decade belongs to biopharmaceutical classification system (BCS) class II. The solubility of these drugs is the limiting factor for oral bioavailability. The drug can be present in solution in a supersaturated state; however, it has a tendency to crystallize out. In this paper, we aim to study the effect of molecular weight of Polyvinylpyrrolidone (PVP) (PVP K12, PVP K29 and PVP K90) and Hydroxypropyl methyl cellulose (HPMC) (HPMC E5, HPMC E15 and HPMC E50) as potential antiprecipitant on weakly acidic drug-Indomethacin (INDO). Supersaturation assay was carried out by solvent shift and solvent casting method. These are non-formulated methods and to access their ability to generate supersaturation, spray dried solid dispersions (SD) were prepared. Supersaturation assay revealed that the ability to generate and maintain the supersaturation are concentration dependent for PVP. As the molecular weight increases the supersaturation produced is increased in PVP and decreased for HPMC polymers. On stability, PVP solvent casts are affected the most. SD were prepared and found out that processability is much better for PVP K29 and HPMC E5. PVP K90 SD and HPMC SD when stored at elevated temperature and humidity show better stability. FTIR analysis showed the presence of hydrogen bonds between the polymer and INDO. Dissolution data revealed that at higher drug-loading PVP K90 and HPMC E50 show the faster drug release in sink condition. As drug loading is decreased, high molecular weight polymers show better stability. However the drug release is governed by polymer dissolution.

INTRODUCTION: Recent advancement in high throughput screening and combinatorial chemistry, most of the drugs discovered in the past decade belong to the BCS class II. They are highly lipophilic and have low solubility and high permeability [1-3].

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The bioavailability of these drugs can be assessed in terms of fick's first law, Eq. 1

$$J=PC \quad \text{(eq. 1)}$$

Where, J=Flux across the intestinal lumen, P= Permeability of the drug and, C=concentration of drug in gastric lumen.

According to the fick's first law, flux is governed by the permeability of drug and intraluminal drug concentration. Hence designing the formulation to yield a significantly higher intraluminal drug concentration is the key to increase the

bioavailability of BCS class II drugs. For these drugs, dissolution is the rate limiting step in order to increase flux across the gastric membrane. Some researchers have demonstrated that drug present in a supersaturated state has enhanced intestinal absorption [4]. Since then has been widely studied in transdermal drug delivery systems [5, 6]. When a drug is in saturated state or equilibrium state, the drug has lowest chemical potential and hence it is stable. Whereas, in supersaturated state drug has high chemical potential and it is highly unstable. Therefore, it has high leaving tendency which eventually result in increased flux across the intestinal membrane [7]. Due to high leaving tendency, drug in supersaturated state it has a tendency to crystallize and hence if maintain the supersaturated state of the drug for certain period of time it can lead to increase absorption. This phenomena is explained by spring and parachute approach [8, 9], **Fig. 1**. Spring is a high energy form of the drug which allows rapid dissolution of poorly soluble drugs, and the parachute is the formulation component which stabilizes the metastable supersaturated system.

Various polymers are available in market which reduces crystallization and maintain the drug in supersaturated state. These polymers act as antiprecipitants (AP) and inhibit precipitation by various mechanisms like by inhibiting nucleation, which leads to crystal growth, increasing the drug solubility and thereby reducing the supersaturation produced or by decreasing the molecular mobility and diffusion coefficient by increasing viscosity; increasing cluster-liquid interfacial energy; and changing the level of salvation at the crystal liquid interface and affecting the integration of drug molecule into the crystal [10]. Some scientists have reported on literature use of polymer in in-vitro assay to evaluate supersaturation generated and to inhibit precipitation [11, 12].

In this paper, we have used polymers like PVP and HPMC to stabilize supersaturated solution. These polymers are available in various grades depending on molecular weight. The aim is to study the effect of different molecular weight of PVP (PVP K12, PVP K29 and PVP K90) and HPMC (HPMC E5, HPMC E15 and HPMC E50) to generate and maintain the stability of supersaturated solution. For the screening, we have used non-formulated methods like solvent shift and solvent casting method. These methods have advantages over conventional methods of using a minimum quantity of drugs, usually in µg and also this process can be easily automated. These are non formulated assay methods and cannot be considered as formulation and hence to study the effect of molecular weight of polymers on supersaturation of drug we have formulated these drugs along with polymers to give supersaturatable dosage form.

Supersaturatable dosage form increases the intraluminal concentration of drugs by increasing solubility. Often times, it is difficult to retain their potency and efficacy of these drug candidates while improving solubility [13]. The scientist tried many methods to improve the solubility of drugs which includes prodrug [14], salt formation [15], cocrystal [16], nanoparticle [17], nanocrystal [18], amorphous solid dispersion [19, 20]. Out of all these methods, amorphous solid dispersion is widely used to improve the solubility of BCS class II drugs which in turn increases bioavailability [21]. The amorphous solid dispersion has been defined as dispersion of one or more active pharmaceutical ingredient (API) in inert carrier. The API is converted to amorphous state in solid dispersion(SD). In SD formulation, the drug is formulated in solid dosage forms which have high patient compliance [22]. It can be prepared using various techniques like freeze drying [23], fusion method [24], spray drying [25], hot melt extrusion [26] and supercritical fluid precipitation [27].

Out of all these methods, spray drying and hot melt extrusion are scalable to large scale and hence, are widely used. Spray drying has 2 advantages over hot melt extrusions. In this method the drug is not exposed to the extreme temperature and it is possible to granulate the material in the same equipment and thus reducing the unit operation in the manufacturing of solid dispersion [28]. In this paper, we have used spray drying method for the preparation of solid dispersion by using BCS class II drug, INDO to evaluate the effect of molecular weight of PVP and HPMC to generate and maintain supersaturation of the drug. INDO is weakly acidic in nature with pKa of 4.5. The melting point of INDO is 158^0C and tg of 42^0C. It has a very low aqueous solubility, 35 µg/ml at 25^0C [29].

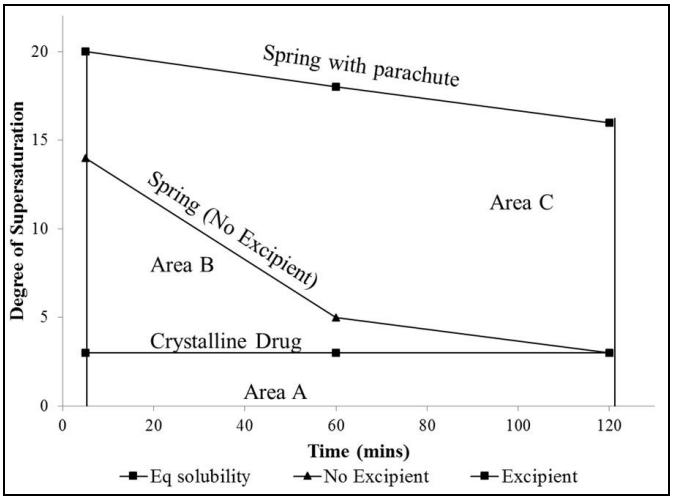


FIG.1: SPRING AND PARACHUTE APPROACH

MATERIALS AND METHODS:

Materials: INDO was procured from Spectrum chemicals Inc. PVP K12 (Plasdone® k12), PVP K29 (Plasdone® K29); PVP K90 (Plasdone® K90) was received from ISP technologies. HPMC E5 (Methocel® E5), HPMC E15 (Methocel® E15) and HPMC E50 (Methocel® E50) was received from Dow Chemicals. The reagents like sodium taurocholate, sodium dihydrogen phosphate (NaH_2PO_4), sodium chloride (NaCl), sodium hydroxide (NaOH) and HPLC grade acetonitrile and water was obtained from spectrum chemicals and lecithin was obtained from Spectrum Chemicals.

Preparation of Medium for Miniaturized Testing Methods: In this study, we have used solvent shift and solvent casting method as miniaturized testing methods. Fasted state simulated intestinal fluid (FaSSIF) was used as the test medium for these methods. FaSSIF was prepared according to the formula described by Vertzoni et.al [30]. It was prepared using following composition: 3mM sodium Taurocholate, 0.75 mM Lecithin, 29mM Sodium dihydrogen phosphate (NaH_2PO_4), 13.8 mM sodium hydroxide (NaOH), 106 mM sodium chloride (NaCl), pH was adjusted to 6.5 by 1 N Sodium hydroxide (NaOH) or 1N hydrochloric acid (HCl).

Quantification of Drug: Quantification of INDO was carried out by high performance liquid chromatography (HPLC). The Agilent 1100 series chromatographic system was used for chromatographic separation. It was equipped with a binary pump, plate auto sampler, thermostat in the column compartment and diode array detector controlled by Chem Station version A.10.02. INDO detection was carried out in Supleco C18 Column of 4.6 mm X 150mm with a particle size of 5µm. The mobile phase is composed of 70% acetonitrile and 30% water with 0.1 % trifluoroacetic acid with a flow rate of 1ml/min, 10µL injection volume and 6 min of run time. The column temperature was maintained at 25^0C and UV detection was carried out 319nm.

Antiprecipitant Screening Methods:

Solvent Shift Method: All polymer used was dissolved in FaSSIF at a concentration of 0.01%, 0.1%, 1%, 2% w/v and INDO was dissolved in dimethyl sulfoxide (DMSO) at a concentration of 125 mg/ml. 30 ml of polymer solution was placed in a beaker and stirred continuously with the help of magnetic stirrer. An organic solution, i.e. INDO dissolved in DMSO was then added drop wise to the polymer solution until visible precipitate is noticeable. 1 ml of sample was withdrawn after 5, 30, 60, 90,120 min post drug addition. Samples were filtered using 0.45µm GHP filter and diluted immediately with the mobile phase and analyzed by HPLC. In all cases only 2% of organic phase was added.

Viscosity Measurement of Antiprecipitant solution: Polymer solution viscosity measurements were performed using Gilmont Falling Ball viscometer, size 1. Viscometer consists of a glass tube with two fiduciary lines. Viscometer was filled with 5-10 ml and stainless steel ball was dropped into the viscometer. The time required by a stainless steel ball to pass between two sets of fiduciary line is measured with a stop watch and viscosity was calculated by Eq 2.

$$\eta = K (\rho_1-\rho) t \text{ (eq. 2)}$$

Where, K= 0.3 (size 1), ρ_1= density of stainless steel ball, ρ= Density of the liquid, t=time of descent (minutes).

Density of polymer solution was measured with the help of glass pycnometer.

Solvent Casting Method: Solvent cast of the INDO-polymer were prepared in 96 well plates. A stock solution of INDO-polymer was prepared in ethanol. Stock solution with INDO-polymer was prepared and 200 µL was dispensed in each plate.

20% of water was added to ethanol for HPMC polymer. The drug concentration in each plate was kept 0.2 mg/ml and polymer varies according to drug load in each well. After Dispensing of the liquid, the solvent was evaporated in vacuum oven at 50^0C for 2.5 hrs. After drying, each well contains a film or pellet which was sealed with paraffin film and kept at room temperature overnight. This step gives unstable formulation an opportunity to crystallize out of the solution. Replicates of the plates were prepared and stored at room temperature and humidity and dissolution testing was performed after 15 days and 1 month. These solvent casts were also stored at accelerated stability conditions, 40^0C and 75% RH and analyzed after 2 weeks, 4 weeks and 6 weeks of storage.

Drug Release Testing from Solvent Cast: Dissolution testing of solvent casts was performed by adding 200 µL of FaSSIF (pH 6.5) in each well and then the plates were shaken in the belly dancer shaker for 0.5 hr, 1 hr and 4hr at 95 rpm respectively. After shaking the contents of the plate were then transferred to 0.45 µm GHP membrane filter plate (Pall Life sciences). The samples were pulled through the filter with the help of vacuum. 100µL of the sample was diluted with the mobile phase immediately to avoid precipitation and analyzed by HPLC. 4 hr sample was considered as infinity time point. Solvent cast stored at room temperature and 40^0C and 75% RH was tested at infinity time points. Assay was performed on all the solvent cast by adding 200 µL of ethanol in each well and then plates were shaken in the belly dancer shaker for 2 hr at 95 rpm and filtered through the GHP membrane filter plates and analyzed by HPLC.

Solid Dispersion Preparation: Solid dispersion was prepared using Buchi spray dryer B-290 (Buchi Laboretechnik AG, Flawil, Switzerland) equipped with inert loop B-295. Spray drying solution was prepared by dissolving polymer and drug in ethanol with 5% feed concentration, i.e. solid content was used for PVP K12 and K29 and 1% feed concentration was used for PVP K90. In case of HPMC polymers, INDO and HPMC was dissolved in ethanol with 20% of water and 3.2% feed concentration was used for HPMC E5 and HPMC E15 and 2% feed concentration was used for HPMC E50. The inlet temperature was set as 110^0C and solution was sprayed at 10ml/min flow rate. The aspirator rate was set to 100% and nozzle size of 0.7mm with drying air flow (473L/Hr) was used for all experiments. The resulting spray dried powder were collected and stored in tightly closed vials and stored over desiccators at room temperature (RT).

Stability Studies: Stability studies of formulation were performed at 40^0C and 75% Relative humidity (RH) in a sealed glass chambers. A saturated NaCl salt solution was prepared by using chemically pure NaCl and distilled water. This solution was placed in glass chambers and allowed to equilibrate at 40^0C to maintain the accelerated stability condition of 40^0C and 75% RH. SD was stored in these glass chambers in open glass vials and samples were pulled after 1, 2 and 6 weeks. The solid dispersions collected were gently separated and screened through USP mesh no 30. All stability samples were then thoroughly dried, by placing them on silica gel (0% RH) desiccators for 48hrs. These samples were then stored in sealed glass vials in 0% RH desiccators until further analysis. 0% RH was maintained using silica gel.

Characterizations of Spray Dried Solid Dispersions:

Powder X-ray Diffraction:

Powder X-ray diffraction (PXRD) was done using scanning diffractometer (Advanced Diffraction system, Scintag Inc, Model XI Cupertino, CA, USA) controlled by a computer with diffraction management system software for windows NT. X-ray radiation used was generated by copper Kα filter with a wavelength 1.54A0 at 45KV and 40mA. Solid samples were placed on a sample holder with a dimension of 2cm X 2cm X 2mm. The powder was placed on a glass slide and flattened using a spatula and glass slide was then placed in the holder. Samples were scanned over the range of 10 to 50^0 2θ degree using a scan rate 2^0/min and scan step of 0.05.

Modulated Differential Scanning Calorimetry: Modulated differential scanning calorimetry (MDSC) analysis was performed using Q200 (TA instruments, USA) equipped with a cooling system. Nitrogen was used as a purge gas with flow rate of 20 ml/min.

5-10 mg of samples were weighed into an aluminum pan with pinhole and hermetically sealed. Samples were heated from 20-250^{0}C at a heating rate of 5^{0}C/min with modulation of 1.59^{0}C every 60s. Heat-cool-heat cycle was used to analyze all samples.

Fourier Transform Infrared Spectroscopy: Fourier transform Infrared spectroscopy (FTIR) spectra for all solid dispersion were obtained using MAGNA-IR-60 spectrophotometer (Nicolet Instrument Corp, Madison WI). Small quantity of each sample was triturated with pure potassium bromide in mortar and pestle and compressed to form a pellet. These pellets were scanned in the region of 400 to 4000cm^{-1}. 64 scans were collected for each sample.

Dissolution Testing of Solid Dispersion: *In-vitro* release experiments were carried in USP apparatus 2 (Distek dissolution systems 2100A, NJ, USA). The release behavior of the physical mixture, pure drug, SD and its stability samples was assessed in two media, 0.1N HCL and phosphate buffer pH 6.8. To ensure sufficient wetting media was conditioned at 37^{0}C with stirring speed of 50rpm. A sample amount equivalent to 25 mg of INDO was used throughout the studies in 250 ml of media. 3 ml of sample volume was drawn through a stainless steel cannula at 15, 30, 45, 60, 90 and 120 min.

samples were filtered through 0.45 µm PTFE syringe filter. The first milliliter of the sample was discarded and rest of the sample was diluted with MP and analyzed by HPLC. Assay of all the SD prepared was performed on sample equivalent to 25 mg of INDO. This sample was dissolved in 25 ml of ethanol by continuous stirring on magnetic stirrer for 2 hr, samples were then filtered through PTFE membrane and analyzed by HPLC.

Particle Size Analysis: Particle size analysis was performed using Flowcam (Scarborough, ME). Drug particle and dispersions were suspended in mineral oil and particle size analysis was performed as flow rate of 0.5ml/min using 4X optical lens. Data was analyzed using flowcam software version 3.4.5.

RESULT AND DISCUSSION:

Solubility of INDO: The thermodynamic solubility of INDO was determined in FaSSIF with or without the presence of 2% polymer at 25^{0}C. Thermodynamic solubility of INDO in FaSSIF was found out to be 312 µg/ml ± 16.2 µg/ml. Polymers did not affect the thermodynamic solubility of INDO at 25^{0}C (data not shown). Solubility of INDO was also determined in pH 6.8 at 37^{0}C at 734 µg/ml ± 40 µg/ml.

Antiprecipitant Effect of Polymers:

Solvent Shift Method: Solvent Shift method was used to generate supersaturated state of the drug. It is described by degree of supersaturation ratio (SR), expressed as the concentration of the INDO in the solution divided by the equilibrium solubility of INDO, Eq 3.

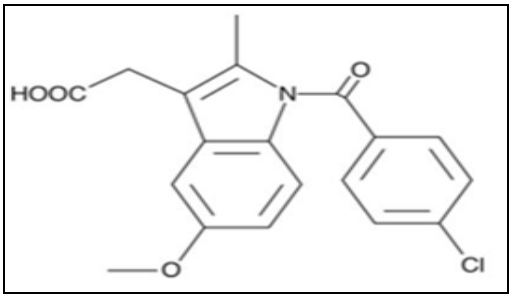
$$SR = \frac{C}{C_{eq}} \text{ (eq. 3)}$$

Where C is the drug concentration and C_{eq} is the equilibrium drug concentration.
It also represents the state of drug in solution.
SR=0, Drug is in a state of saturation,
SR<1, Drug is in an unsaturated state,
SR>1, Drug is in a supersaturated state.

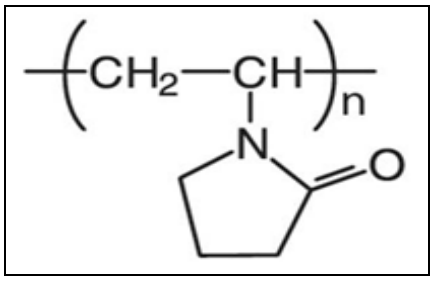
In this method the anti-precipitants to be screened were dissolved in various concentrations in FASSIF and 2 % of organic phase was added and concentration was monitored for the period of 2 hrs. The SR is expressed as a ratio of the concentration of INDO in solution after 5 minute post drug addition to the equilibrium solubility of INDO in the solution. This method was able to generate the supersaturation in all the solutions due to a concentration gradient. As described earlier, when the drug is in a supersaturated state in the solution, it has a tendency to precipitate out due to high chemical potential; this process can be hindered by increasing viscosity of the solution. Viscosity of polymer solution is dependent on the concentration of polymer in solution and hence in these experiments we have studied the different concentration of polymer in the solution, i.e. 0.1 mg/ml, 1 mg/ml, 10 mg/ml and 20 mg/ml. Blank experiments were also performed without the addition of any polymer in the solution, this experiment was performed to determine the ability of this method to generate supersaturation.

In the blank experiment, the concentration of INDO in solution after 5 min was 1591 µg/ml ± 18 µg/ml (SR=5.1) which was subsequently reduced to 1462 µg/ml ± 78 µg/ml (SR=4.7) at the end of 2 hr. Saturation solubility of INDO is 312 µg/ml ± 16.2 µg/ml. Hence, the solvent shift method was able to create supersaturation without the addition of any polymer and it was maintained fairly well till the end of 2 hr. The concentration of the INDO at 5 minutes is given in Table 1. From the data; it is evident that PVP and HPMC polymers were able to generate the supersaturation. As we discussed earlier, drug in a supersaturated state in solution tends to crystallize out, which in turn leads to low concentration of the drug in the solution at the end of 2 hr. The concentration of drug at the end of 2 hr in the presence of the polymer is given in **Table 2.**

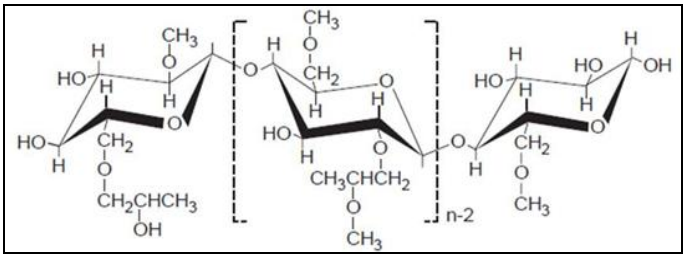
The physical property of different grades of PVP and HPMC is shown in the **Table 3** and structures of INDO, PVP and HPMC is given in **Fig. 2**. The viscosity of the solution is concentration dependent and it is seen that as the concentration of PVP increases supersaturation increases. All higher concentration of PVP were able to sustain more drug in the dissolved state, hence the ability of PVP to generate and maintain supersaturation is concentration dependent. However, this is not the case with HPMC polymers. It is seen that as concentration increases the supersaturation produced increases till 1mg/ml after which there is decrease observed for all the polymers studied in HPMC family. This can be attributed to high viscosities of HPMC. As molecular weight increases, supersaturation produced decreases HPMC polymers. The experiment using the solvent shift method gives us the idea how PVP and HPMC polymers behave with respect to their molecular weight.



(a) INDO



(b) PVP



(c) HPMC

FIG. 2: STRUCTURE OF INDO, PVP & HPMC - (a) INDO; (b) PVP; (c) HPMC

TABLE 1: SUPERSATURATION OF DRUG CREATED IN THE PRESENCE OF POLYMERS

Supersaturation produced 5 mins post drug addition				
Polymer	**0.1 mg/ml (n=3)**	**1 mg/ml (n=3)**	**10 mg/ml (n=3)**	**20 mg/ml (n=3)**
PVP K12	5.2	5.2	5.3	5.4
PVP K29	5.2	5.3	5.3	5.5
PVP K90	5.2	5.4	5.4	5.5
HPMC E5	5.3	5.4	5.3	5.3
HPMC E15	5.0	5.4	5.3	5.3
HPMC E50	5.1	5.4	5.2	5.2

TABLE 2: STABILITY OF SUPERSATURATED DRUG SOLUTION AT THE END OF 2 HOURS

Supersaturation at the end of 2 hrs				
Polymer	**0.1 mg/ml (n=3)**	**1 mg/ml (n=3)**	**10 mg/ml (n=3)**	**20 mg/ml (n=3)**
PVP K12	4.8	4.9	5.0	5.1
PVP K29	4.9	5.0	5.1	5.2
PVP K90	5.0	5.1	5.2	5.3
HPMC E5	5.0	5.0	4.7	4.7
HPMC E15	4.8	4.9	4.9	4.7
HPMC E50	4.9	5.0	4.7	3.9

TABLE 3: PHYSIOCHEMICAL PROPERTIES OF POLYMERS

Polymer	Tg (^{0}C)	Molecular Weight (Da)	Viscosity in mpa.s			
			0.1 mg /ml (n=3)	1 mg/ml (n=3)	10 mg/ml (n=3)	20 mg/ml (n=3)
PVP K12	117	4,000	0.91	0.91	1.1	1.42
PVP K29	176	58,000	1.03	1.13	1.24	1.87
PVP K90	181	1,300,000	1.08	1.33	3.07	7.37
HPMC E5	150	28,700[a]	0.97	1.11	2.06	5.02
HPMC E15	154	60,000[a]	1.06	1.26	4.02	15.00[a]
HPMC E50	164	86,700[a]	1.03	1.38	ND	50.00[a]

[a] values are taken from published literature [31], ND: not determined

Casting Method: The solvent casting method is a miniaturized testing method to determine efficiency of polymers. In this method both drug and polymer is dissolved in common solvent and solvent is evaporated to yield solvent casts. However, the films prepared by this method cannot be considered as formulation, the manufacturing procedure of solvent cast mimics solvent evaporation method of preparation of solid dispersion. We have used these films to perform the release rate studies and to evaluate the stability of drug in the polymers. In this study, we had prepared solvent cast with various drug loads, 80%, 60%, 40% and 20% drug loading. The drug release versus time profile for INDO-PVP and INDO-HPMC solvent casts at various drug loadings is shown in **Fig. 3** and **4** respectively. From **Fig. 3**, it is seen that at all the drug loading studied, PVP K29 shows higher rate and higher amount of drug release as compared to PVP K12 and K90. If we compare **Fig. 3a-3d**, it is seen that PVP K90 solvent casts shows the complete release of drugs at 20% drug loading; at higher drug loading PVP K90 solvent cast did not show complete release of INDO. PVP K12 was able to release only 91% of the drug at 20% drug loading; at higher drug loading the drug release form PVP K12 solvent casts was much slower. The molecular weight of PVP K12 is low as compared to PVP K29 and PVP K90. As the molecular weight increases, it is expected that rate at which drug release will be slower, which is evident from **Fig.3** for PVP K29 and PVP K90 polymer.

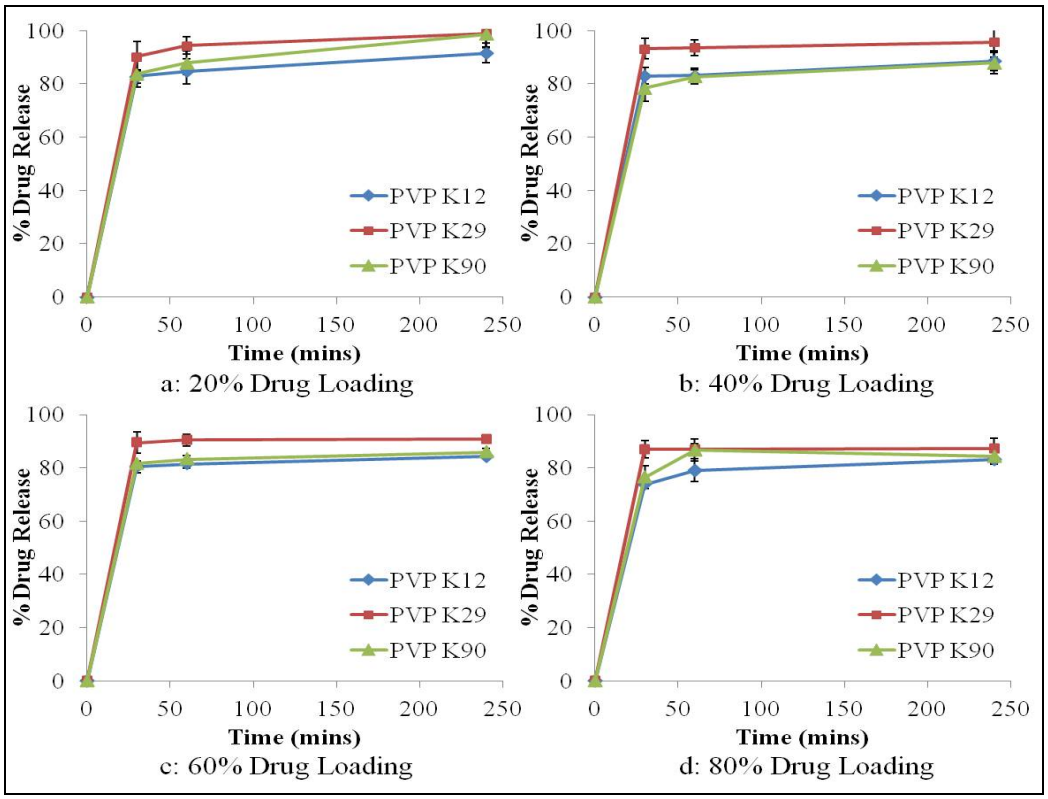


FIG. 3: DRUG RELEASE VS TIME PROFILE OF INDO-PVP SOLVENT CASTS AT VARIOUS DRUG LOADINGS AT - (a) 20% DRUG LOADING; (b) 40% DRUG LOADING; (c) 60% DRUG LOADING; (d) 80% DRUG LOADING

Hence, the drug release from PVP K90 is slower as compared to PVP K29. This data shows K29 is more suitable polymer for solid dispersion of INDO. From HPMC family, HPMC E5 shows the highest rate of drug release as compared to HPMC E15 and HPMC E50 at all the drug loading studied, **Fig. 4**. This can be attributed to the molecular weight difference between these polymer HPMC E5 being the lowest shows the highest rate of drug release followed by HPMC E15 and HPMC E50 respectively. The complete release of INDO is seen at 20% drug loading for HPMC polymers. At 80% drug loading, HPMC E50 shows the highest rate and amount of drug release as compared to HPMC E15 and HPMC E5. At higher drug load, i.e. 80% drug loading, the HPMC E50 is more effective than HPMC E5. This method gives us about an idea of the how dispersions of this polymer will perform at different drug loading.

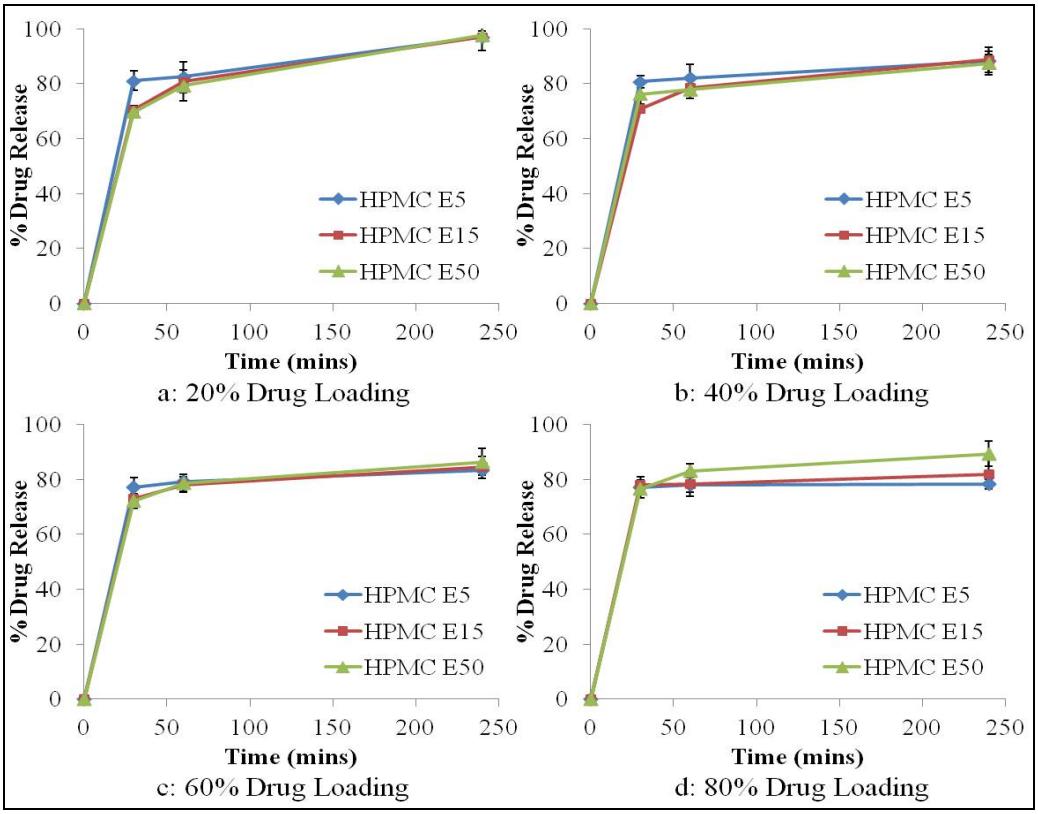


FIG.4: DRUG RELEASE VS TIME PROFILE OF INDO-HPMC SOLVENT CASTS AT VARIOUS DRUG LOADINGS AT- (a) 20% DRUG LOADING; (b) 40% DRUG LOADING; (c) 60% DRUG LOADING; (d) 80% DRUG LOADING

Stability of Solvent Cast: Stability of solvent cast was carried out at room temperature in 96 well plates. These 96 well plates are made up of polystyrene and it does not protect the material from humidity. Hence it is expected that at room temperature, humidity varies and it will have an effect on the performance of these solvent cast. These solvent casts were also stored in open condition at 400C at 75% RH. These studies were carried out to see the effect of temperature and humidity on the performance of these solvent cast.

Table 4, gives the drug release at the end of 4 hr for solvent casts are stored at different conditions. From the data, it is evident that the PVP K12 cast were affected the most by temperature and humidity followed by PVP K29 and PVP K90 in PVP family. However, the drug release from these casts decreases on storage. As described earlier, the method of preparation of solvent casts resembles the solvent evaporation technique of solid dispersion formation, hence it is expected that drug is in the amorphous state. This is the reason for the increase in drug solubility. If the solubility is reduced on storage, it is possible that drug crystallizes out. It is evident from **Table 4,** as molecular weight increases, the molecular mobility of the drug is reduced and which in turn, increases the shelf life of the drug. Hence, the stability of PVP K90 was much better followed by PVP K29 and PVP K12.

In HPMC family, at 20 % drug loading the drug release reduced to 90% for all the grades of the HPMC on storage. At 80% drug loading, the drug release decrease for all grades of HPMC, E50 solvent casts are affected the most, followed by E15 and E5 respectively.

TABLE 4: STABILITY OF SOLVENT CASTS

Polymer	Initial	RT 15 days	RT 1 month	40^{0}C & 75% RH 2 week	40^{0}C & 75% RH 4 week	40^{0}C & 75% RH 6 week	Polymer	Initial	RT 15 days	RT 1 month	40^{0}C & 75% RH 2 week	40^{0}C & 75% RH 4 week	40^{0}C & 75% RH 6 week
20% Drug Loading							**60% Drug Loading**						
PVP K12	92	87	86	77	72	72	PVP K12	84	80	74	63	60	60
PVP K29	99	99	95	95	91	91	PVP K29	91	90	85	84	83	83
PVP K90	99	96	95	95	95	93	PVP K90	86	85	85	84	84	84
HPMCE5	97	94	92	92	91	91	HPMC E5	83	80	80	83	83	77
HPMCE15	97	91	91	90	90	90	HPMC E15	84	84	84	83	83	77
HPMCE50	98	94	92	93	92	92	HPMC E50	86	84	82	83	73	67
40% Drug Loading							**80% Drug Loading**						
PVP K12	89	83	78	64	63	63	PVP K12	83	80	59	52	52	52
PVP K29	96	92	90	91	87	87	PVP K29	87	84	81	72	70	71
PVP K90	88	88	87	87	88	86	PVP K90	84	85	85	83	84	82
HPMCE5	88	88	88	83	83	82	HPMC E5	78	76	73	66	66	61
HPMCE15	89	85	84	83	83	83	HPMC E15	82	82	72	66	66	60
HPMCE50	87	85	82	82	82	80	HPMC E50	89	73	74	66	67	60

Spray Dried Solid Dispersion: Spray dried Solid dispersion were prepared by using buchi 290 equipped inert loop. In this process have many factors like inlet temperature, flow rate, solvent selection, nozzle size, drying gas flow rate and feed concentration which affects the properties of spray dried dispersion. However, in order to minimize variation parameters like inlet temperature, flow rate, solvent, drying gas flow rate and nozzle size were kept constant. The feed concentration was changed in order to increase the processability. PVP K90 has very high viscosity and due to which we have to reduce the feed concentration to 1% for INDO and 2% for HPMC E50. The % yield for INDO is given in **Table 5.** It is evident from table 5 that the yield of PVP K90 is low as compared to PVP K29 and K12 in PVP family and HPMC E50 yield is less as compared to HPMC E15 and E5 in HPMC family. All high molecular weight polymers have low yield. The feed concentration used for PVP K90 and HPMC E50 solid dispersion is low and hence in dilute solution very small particles are formed and which escapes the cyclone and gets deposited on the filter used [25, 32], this might be the reason for low yield. The % yield for HPMC E5 is higher as compared to HPMC E15. HPMC E15 has a higher viscosity as compared to HPMC E5 and hence the viscosity of the feed solution is higher for E15 and hence due to higher viscosity most of the dispersion was lost due to sticking in the drying chamber of the spray dryer and hence, we get lower yield.

TABLE 5: % YIELD OF INDO-SD

Polymer	75% Drug Loading		50% Drug Loading		25% Drug Loading	
	% yield	Stdev	% yield	Stdev	% yield	Stdev
PVP K12	69	3.46	65	1.59	67	1.02
PVP K29	75	1.26	72	1.17	78	1.30
PVP K90	43	0.88	49	1.13	49	1.11
HPMC E5	62	1.75	64	1.07	79	0.91
HPMC E15	49	0.80	50	0.47	60	0.47
HPMC E50	50	0.87	50	1.26	46	1.52

Characterization of Solid Dispersions:

Powder X-ray diffraction: The PXRD was performed on all the solid dispersion, to check for presence of crystalline INDO. The PXRD was also carried out for physical mixture and solid dispersion and stability samples of INDO-PVP and INDO-HPMC. INDO is crystalline in nature. When it is physically mixed with PVP it doesn't change

in crystallinity of the INDO (data not shown). However, the PXRD patterns of solid dispersion and its stability samples did not show the presence of crystalline INDO (data not shown), which states that drug all the solid dispersion and its stability samples is in anamorphous in nature.

Modulated Differential Scanning Calorimetry: MDSC was performed on all the spray dried dispersions to study the thermal behavior of the dispersions as well as to detect the crystallinity of INDO. MDSC was used in addition to PXRD to detect crystallinity of INDO SD, since it has been reported in the literature that PXRD might be able to detect the small crystals, even if it is above the limit of detection [33].

The overlay of MDSC thermogram of INDO-PVP and INDO-HPMC spray dried solid dispersion at different drug loading is shown in **Fig. 5**. All the polymers shows absence of drug melting peak which indicates the drug is in amorphous state for all the solid dispersions except HPMC polymer at 75% drug loading. Amorphous systems tend to exhibit optimal conditions for nucleation and crystal growth above tg, where molecular mobility is greater. The tg of pure INDO and INDO-PVP and INDO-HPMC spray dried solid dispersions is given in Table 6. From the **Table 6**, it is evident that the polymer has the antiplasticising effect on INDO, the tg increases as we increase the polymer content. Zografi et.al has shown that storage of amorphous INDO at temperature about 40-50^{0}C below tg near refrigerator temperatures, prevent crystallization over very long time periods [34]. The melting point of INDO was found to be 160.71^{0}C, it is reported in literature γ polymorph of INDO have melting point of 160-162^{0}C and α polymorph of INDO have melting point of 152-154^{0}C [35].

MDSC thermograms of INDO-PVP SD and INDO-HPMC SD at drug loading and its stability samples are shown in **Fig. 6** and **7.** From **Fig.6**, it is seen that 75% drug loading all the PVP shows peak near the drug melting point on storage for all the PVP studied. At 50% and 25% drug loading there is no peak near drug melting point after the stability of INDO-PVP SD samples (data not shown). It shows that PVP polymer were able to maintain a solid dispersion in the amorphous state at 50% and 25% drug loading. **Table 7** and **8** gives tg of INDO-PVP SD stability samples at 50% and 25% drug loading, respectively. PVP K29 and K12 shows the presence of two tg at 50% and 25% drug loading in stability samples, **Table 6.** The presence of 2 tg indicates immiscibility. PVP K90 shows the only presence of 1 tg after storage.

Hence, PVP K90 dispersion shows better stability at 50% and 25% drug loading as compared to other two polymers in PVP family.

MDSC thermograms of INDO-HPMC SD shows presence of a peak near drug melting point at 75% and 50% drug loading HPMC, which says that the drug is not in an amorphous state, **Fig 7**. At 25% drug loading, thermogram does not show any peak and drug is in an amorphous state, tg of these dispersions are given in Table 9. In **Fig. 7a-7c,** it is seen that there are presently two peaks seen near drug melting point for INDO-HPMC SD stored at elevated temperature and humidity at 75% drug loading. The presence of polymer alters the melting point of drug. INDO-HPMC dispersions show the presence of crystalline INDO which is characterized by the presence of a peak near the melting point of pure INDO. These dispersions when kept in the stability it is seen that the drug present in amorphous form is trying to crystallize out in less stable polymorph and hence we see two peaks in stability samples of 75% drug loaded INDO-HPMC SD. From **Fig.7d-7e** it is seen that at 50% drug loading, initially the dispersion is amorphous in nature; on stability the drug is crystallizing out. 25% drug loaded INDO-HPMC SD shows presence of one tg even after storage of dispersions for 6 weeks (DSC thermogram data not shown). This shows HPMC SD is more stable as compared to PVP dispersions

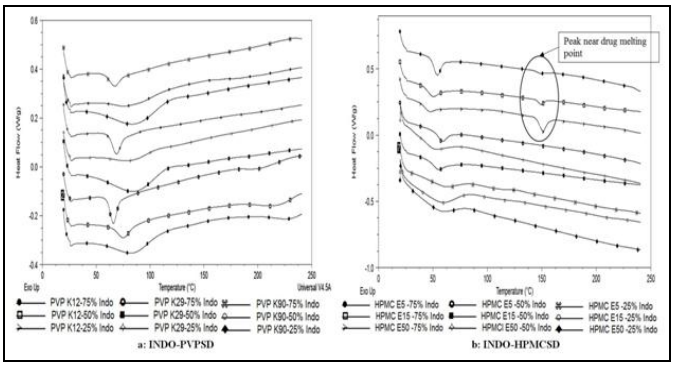


FIG. 5: OVERLAY OF MDSC THERMOGRAMS OF INDO-SD- (a) INDO-PVP SD; b) INDO-HPMC-SD

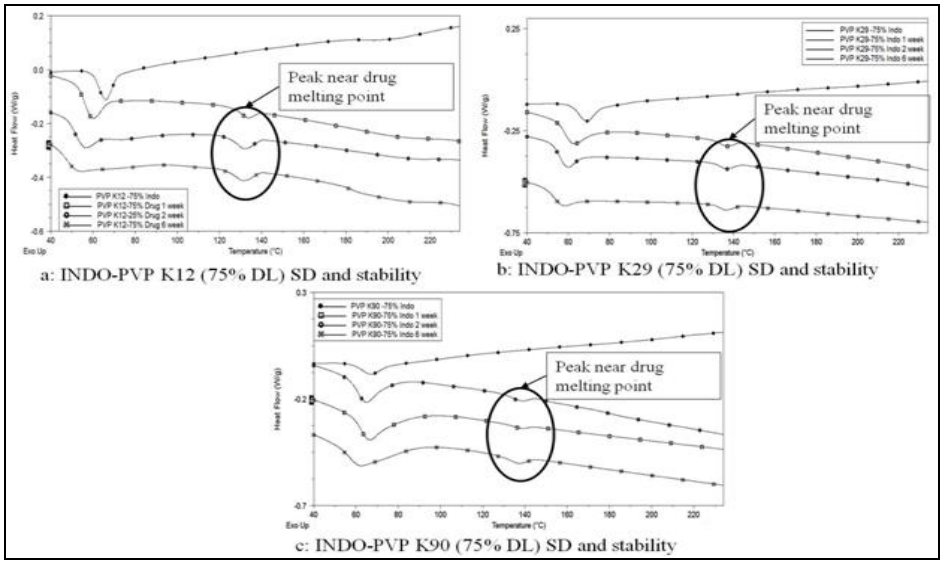


FIG. 6: DSC THERMOGRAMS OF INDO-PVP SOLID DISPERSIONS AT 75% DRUG LOADING AND ITS STABILITY SAMPLES STORED AT 40^0 C % 75% RH FOR 1 WEEK, 2 WEEKS, AND 6 WEEKS (TOP TO BOTTOM) - (a) INDO-PVP K12 (75%DL) SD and stability; (b) INDO-PVP K29 (75%DL) SD and stability; (c) INDO-PVP K90 (75%DL) SD and stability

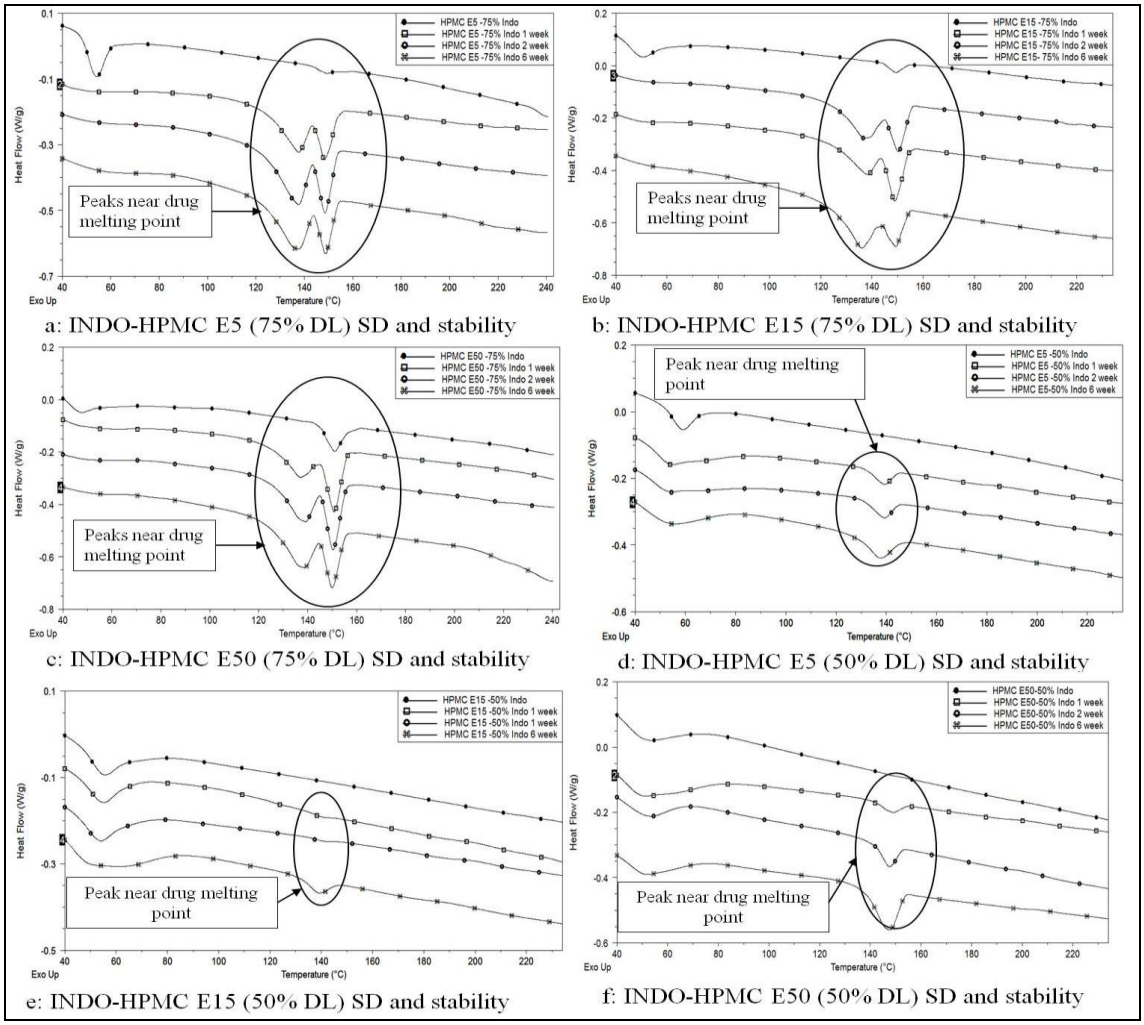


FIG.7: DSC THERMOGRAMS OF INDO-HPMC SOLID DISPERSIONS AT 75% AND 50% DRUG LOADING AND ITS STABILITY SAMPLES STORED AT 40^0 C % 75% RH FOR 1 WEEK, 2 WEEKS, AND 6 WEEKS (TOP TO BOTTOM)- (a) INDO-HPMC E5 (75%DL) SD and stability; (b) INDO-HPMC E15 (75%DL) SD and stability; (c) INDO-HPMC E50 (75%DL) SD and stability; (d) INDO-HPMC E5 (50%DL) SD and stability; (e) INDO-HPMC E15 (50%DL) SD and stability; (f) INDO-HPMC E50 (50%DL) SD and stability

Table 6: Effect of storage on glass transition temperature of INDO-PVP SD and INDO-HPMC SD

Polymer	Tg (^{0}C)			
	75 % Drug Loading	50 % Drug Loading	25 % Drug Loading	0 % Drug Loading
PVP K12	54.76	77.32	91.43	117
PVP K29	60.73	94.46	128.55	176.07
PVP K90	61.84	98.82	133.64	178.49
HPMC E5	40.78	60.66	91.65	143.75
HPMC E15	-	60.62	93.37	153.16
HPMC E50	-	62.47	89.17	156.95

TABLE 7: EFFECT OF STORAGE ON GLASS TRANSITION TEMPERATURE OF INDO-PVP SD AT 50% DRUG LOADING

Storage: 40^{0}C & 75% RH	PVP K12		PVP K29		PVP K90	
	Tg^1 (^{0}C)	Tg^2 (^{0}C)	Tg^1 (^{0}C)	Tg^2 (^{0}C)	Tg^1 (^{0}C)	Tg^2 (^{0}C)
Initial	77.32	-	94.46	-	98.82	-
1 week	58.63	113.02	66.52	140.31	98.11	-
2 week	59.3	114.52	67.69	139.98	98.34	-
6 week	58.72	121.01	66.46	142.1	97.35	-

TABLE 8: EFFECT OF STORAGE ON GLASS TRANSITION TEMPERATURE OF INDO-PVP SD AT 25% DRUG LOADING

Storage: 40^{0}C & 75% RH	PVP K12		PVP K29		PVP K90	
	Tg^1 (^{0}C)	Tg^2 (^{0}C)	Tg^1 (^{0}C)	Tg^2 (^{0}C)	Tg^1 (^{0}C)	Tg^2 (^{0}C)
Initial	91.43	-	128.55	-	133.64	-
1 week	63.71	126.81	121.09	177.75	129.88	-
2 week	62.37	127.48	119.82	176.88	130.64	-
6 week	62.7	128.79	124.38	176.47	128.74	-

TABLE 9: EFFECT OF STORAGE ON GLASS TRANSITION TEMPERATURE OF INDO-HPMC SD AT 25% DRUG LOADING

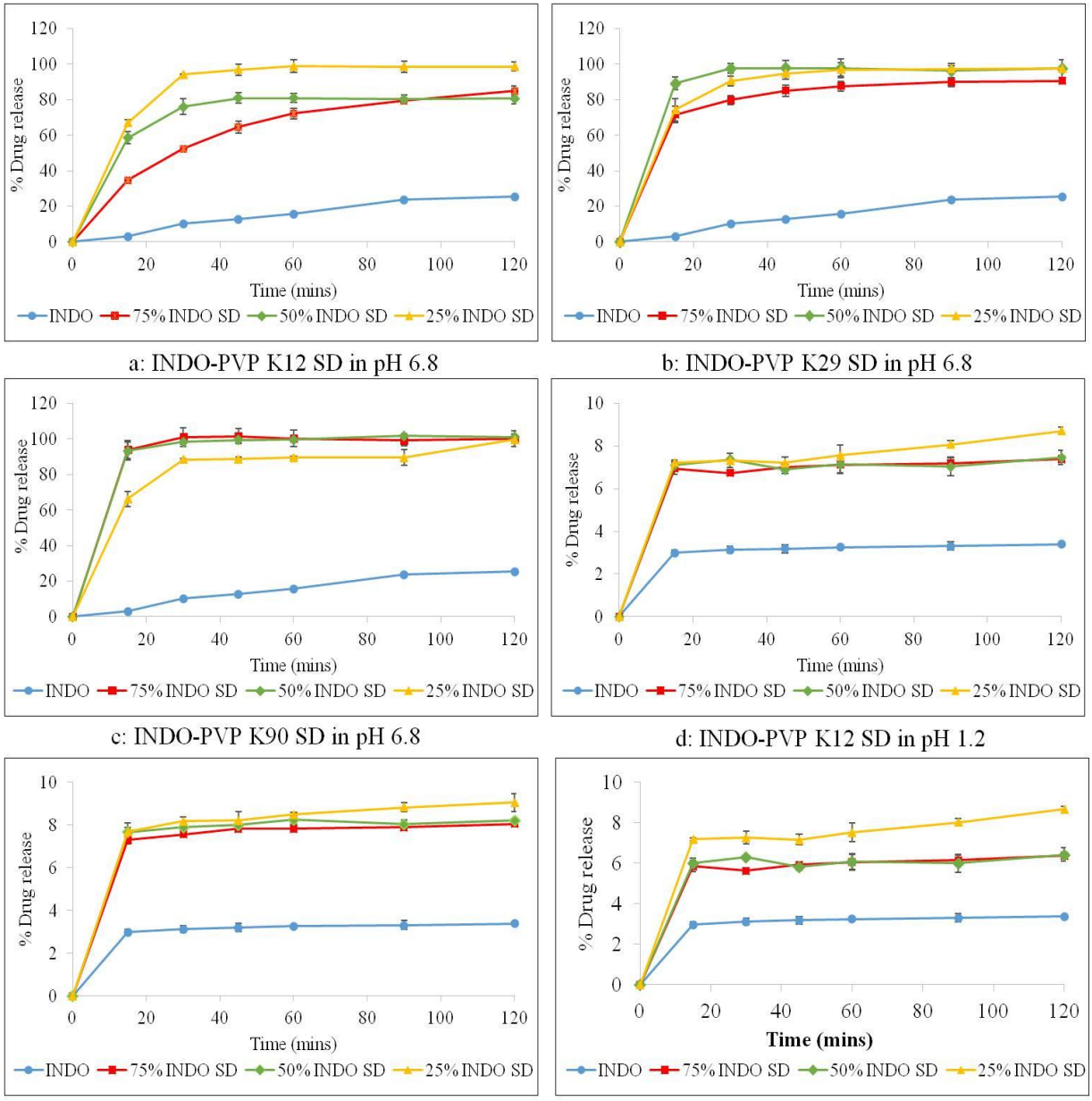
Storage: 40^{0}C & 75% RH	HPMC E5		HPMC E15		HPMC E50	
	Tg^1 (^{0}C)	Tg^2 (^{0}C)	Tg^1 (^{0}C)	Tg^2 (^{0}C)	Tg^1 (^{0}C)	Tg^2 (^{0}C)
Initial	91.65	-	93.37	-	89.17	-
1 week	91.73	-	91.92	-	88.25	-
2 week	91.73	-	93.03	-	89.21	-
6 week	90.13	-	93.78	-	89.26	-

INDO is acidic in nature and hence it is poorly soluble in acidic media. It is also poorly soluble in water. Here we have used two medium 0.1N HCL to represent simulated gastric fluid and phosphate buffer 50mM pH 6.8 was considered as a simulated intestinal fluid. The solubility of INDO in 0.1N HCL is not detectable in HPLC whereas solubility at pH 6.8 is 733µg/ml at 37^{0}C. The dose of INDO used is 25 mg in 250 ml of media, hence pH 6.8 represents sink conditions and 0.1N HCL represent the non-sink condition. The dissolution profile of pure INDO, INDO-PVP SD at 75%, 50% and 25% drug loading in 0.1N HCL and pH 6.8 is shown in **Fig.8**. Dissolution of INDO in 0.1 N HCL and pH 6.8 was variable and found to be dependent on the weakly acidic nature of drug. It is seen that in pH 6.8 all the PVP used were able to achieve 100% drug release at the end of 2 hr. PVP K90 shows 94% of drug release in 15 min in contrast to 72% drug release of PVP K29 and merely 34% drug release of PVP K12 at 75% drug loading. In sink conditions, drug release increases as we go from PVP K12 to K90, however, in 0.1N HCL PVP K90 SD shows 6% of drug release in 15 min, whereas PVP K29 SD and K12 SD shows 7% of the drug release in first 15 min at 75% drug loading. In non-sink conditions the drug release follows the order of PVP K29>K12>K90. After 6 weeks of stability it is seen that drug release decrease for all the polymer studied, however the order remains the same for all the drug loading (data not shown).

The dissolution profile of pure INDO, INDO-HPMC SD at 75%, 50% and 25% drug loading in 0.1N HCL and pH 6.8 is shown in **Fig.9.** It is seen that at pH 6.8 all the HPMC SD with 50% INDO were able to achieve 100% drug release at the end of 2 hr, however SD containing 75% INDO shows only 86%, 90% and 92% of drug release for HPMC E5, E15 and E50 respectively. At 25% drug loading

only E5 shows 93% of drug release in pH 6.8 and the release form E15 and E50 was very low. At 25% and 50% drug loading E5 shows the highest drug release in 15 mins but at 75% drug release E50 shows highest drug release at pH 6.8. In non-sink conditions HPMC E5 shows the highest drug release at the end of 2 hr at all drug loading studied. The amount of INDO released from HPMC E5 dispersions in 0.1N HCL increases as we increase the polymer concentration. HPMC E5 SD shows almost 12% of release at the end of 2 hr, which is higher than any of PVP polymers.

On the storage of dispersions to elevated temperature and humidity the drug release from all INDO-HPMC dispersion decreases (data not shown). Overall, it can be said that as we increase the polymer content drug release increase for lower molecular weight polymers like PVP K12, PVP K29 and HPMC E5. At the higher drug loading, drug release is faster in higher molecular weight polymer like PVP K90 and HPMC E50. As we decrease the drug content in SD, drug release is dictated by dissolution of the polymer in the dissolution media.



a: INDO-PVP K12 SD in pH 6.8

b: INDO-PVP K29 SD in pH 6.8

c: INDO-PVP K90 SD in pH 6.8

d: INDO-PVP K12 SD in pH 1.2

e: INDO-PVP K29 SD in pH 1.2

f: INDO-PVP K90 SD in pH 1.2

FIG. 8: COMPARISON OF DISSOLUTION PROFILES OF INDO-PVP SOLID DISPERSIONS - (a) INDO-PVP K12 SD in pH 6.8; (b)INDO-PVP K29 SD in pH 6.8; (c) INDO-PVP K90 SD in pH 6.8; (d) INDO-PVP K12 SD in 0.1N HCL; (e)INDO-PVP K29 SD in 0.1N HCL; (f) INDO-PVP K90 SD in 0.1N HCL

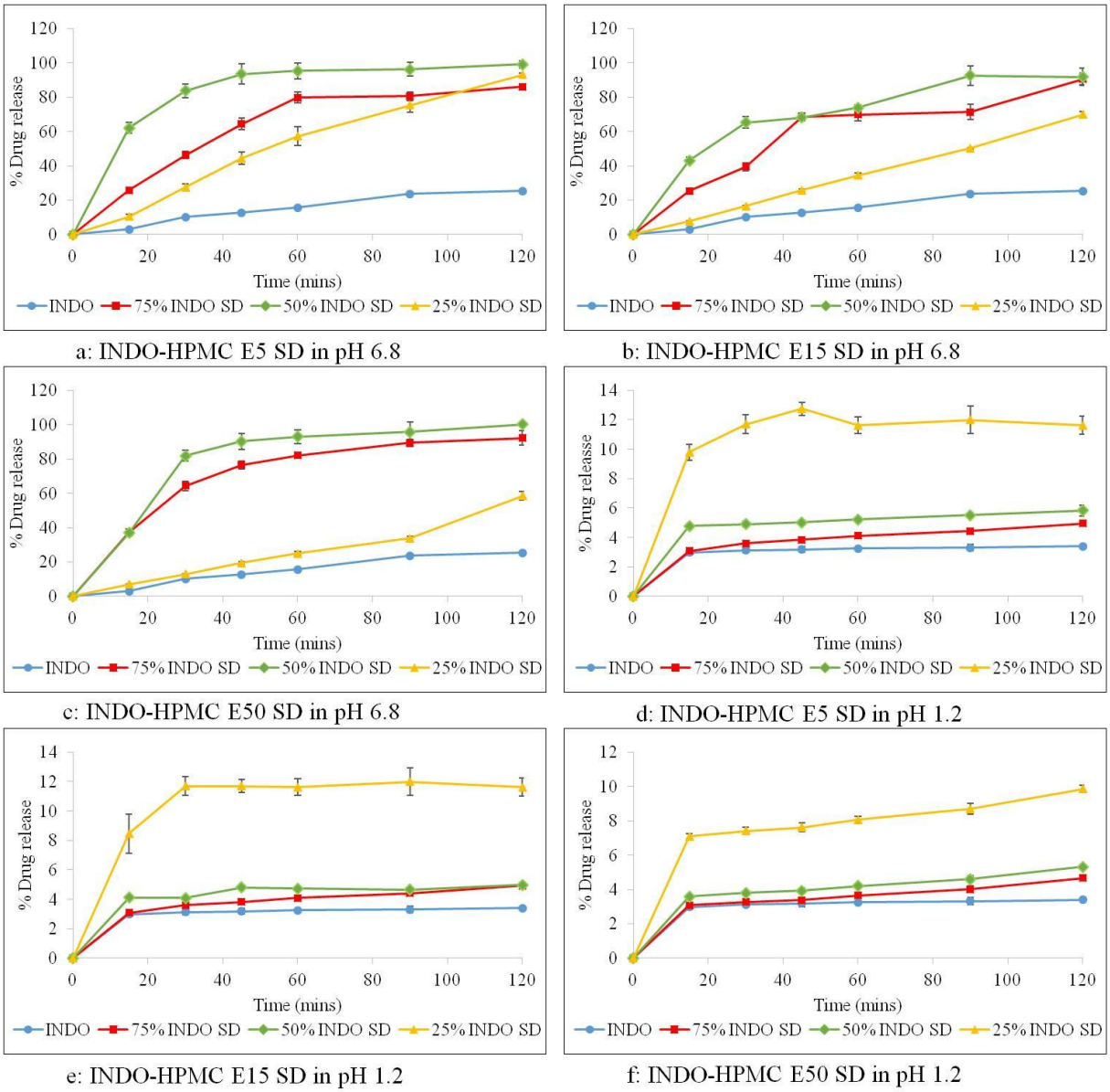


FIG.9: COMPARISON OF DISSOLUTION PROFILES OF INDO-HPMC SOLID DISPERSIONS - (a) INDO-HPMC E5 SD in pH 6.8; (b)INDO-HPMC E15 SD in pH 6.8; (c) INDO-HPMC E50 SD in pH 6.8; (d) INDO-HPMC E5 SD in 0.1N HCL; (e)INDO-HPMC E15 SD in 0.1N HCL; (f) INDO-HPMC E50 SD in 0.1N HCL

Fourier transform infrared spectroscopy: FTIR spectra were used to investigate the potential interactions between the polymer and INDO SD. In order to evaluate and understand these spectra we need to study the structure of these polymer and drug, **Fig. 2**. PVP structure can act as a proton acceptor (through either the O or N atoms of the pyrrole ring) and INDO can act as a proton donor site (through –OH group of the carboxylic acid). INDO shows the peak at 1691cm-1 due to the carbonyl group of amide and at 1710 cm-1 due to carbonyl group of acid. PVP carbonyl group shows the peak at 1680 cm-1. Shifts in these peak positions of INDO indicate a possible breakage of the hydrogen bond between crystalline INDO molecule and formation of the hydrogen bond between INDO and PVP [36]. The FTIR spectra of INDO-PVP and INDO-HPMC solid dispersion at the different drug loading is given in **Fig.10**. We observed the shift in amide carbonyl group peak to 1680 cm-1 and carbonyl group of acid to 1724cm-1in all the INDO-PVP SD. There is peak present at 1636 cm-1 in solid dispersions containing 50% or more drug loading for INDO-PVP SD. This peak represents hydrogen bonded PVP carbonyl group. Therefore, it is prominently seen in 75% drug loading and as the concentration of the PVP increases, it is seen as shoulder which represents non hydrogen bonded carbonyl group of PVP. The FTIR spectra of physical mixture of INDO and PVP seems to be additions of the spectra of pure

INDO and PVP, which states absence of any physical interactions between them (data not shown).

There was no difference seen in the FTIR spectra of solid dispersion of PVP K12, K29 and K90. On subjecting these dispersions to elevated temperature and humidity, no change in IR spectra was observed for INDO-PVP SD for all the PVP grades and drug loading studied (data not shown). Spectra at all drug loading seems to have physical interactions between drug and polymer molecule, the strength of physical bonding cannot be determined by FTIR and there is need of some other spectroscopic method to be evaluated for these systems.

FTIR spectra of INDO-HPMC SD shows shift in carbonyl of INDO peak to 1684 and carbonyl group of acid to 1734 at all the drug loading, which indicates the physical interactions of INDO and HPMC. On the storage of INDO-HPMC dispersion, FTIR spectra did not show at any change in spectra at 50% and 25% drug loading. The FTIR spectra of INDO-HPMC dispersion at 75% drug loading and their stability samples at 1 week, 2weeks, and 6 weeks of storage in 400C % 75% RH is shown in **Fig. 11.** It is seen that FTIR spectra of 75% drug loading stability samples shows peak at 1684, 1692 and 1734. The peak at 1691 is also seen in pure crystalline INDO, it can be said that INDO is getting converted to crystalline form and hence peak at 1691 is seen as shoulder in 1 week and it became prominent in 6week stability samples. There was no difference seen in the FTIR spectra of INDO-HPMC SD at 50% and 25% drug loading. On subjecting these dispersions to elevated temperature and humidity, no change in IR spectra was observed for INDO-HPMC SD for all the HPMC grades studied at 50% and 25% drug loading (data not shown).

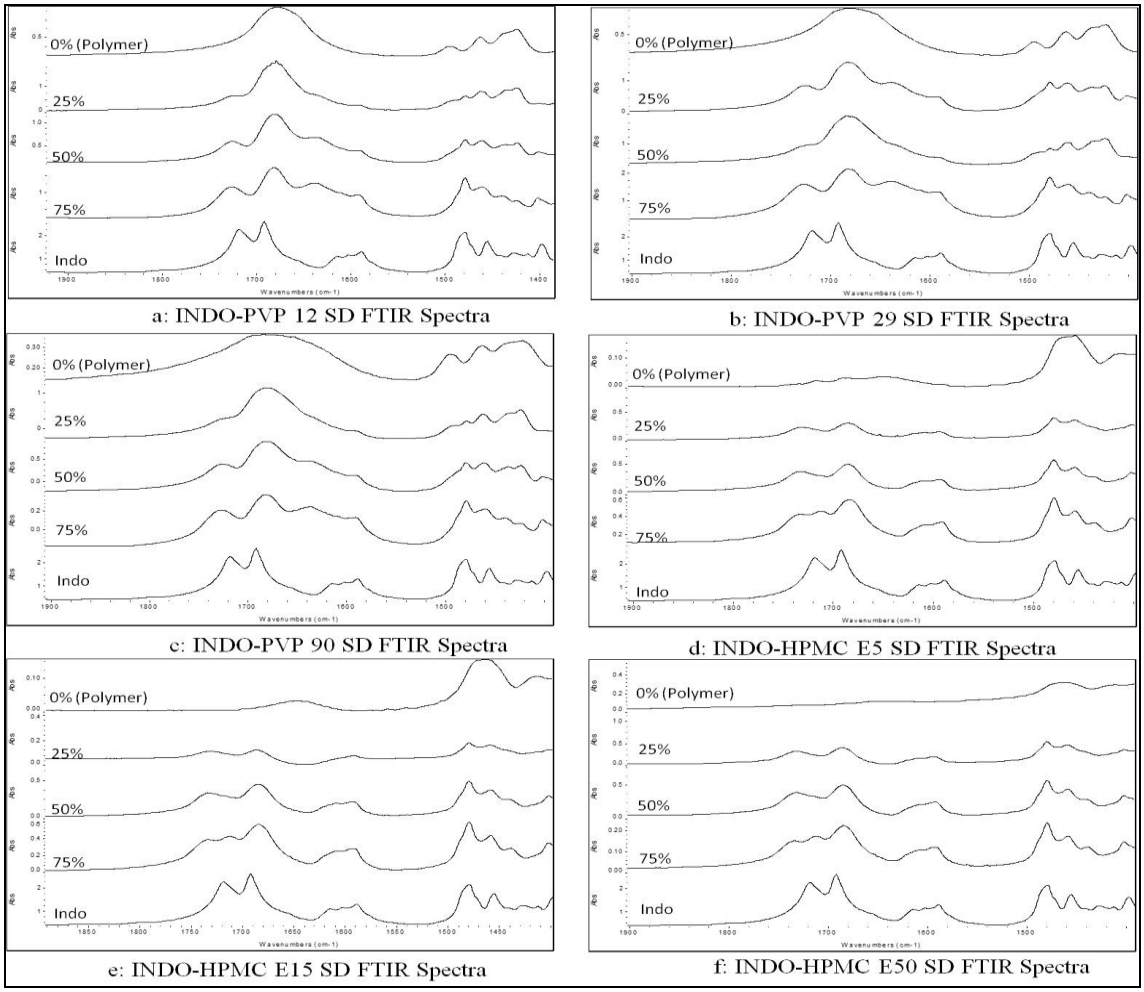


FIG.10: FTIR SPECTRA OF INDO-PVP AND INDO-HPMC SD'S AT DIFFERENT DRUG LOADING - (a) INDO-PVP K12 SD FTIR spectra; (b) INDO-PVP K29 SD FTIR spectra; (c) INDO-PVP K90 SD FTIR spectra; (d) INDO-HPMC E5 SD FTIR spectra; (e) INDO-HPMC E15 SD FTIR spectra; (f) INDO-HPMC E50 SD FTIR spectra

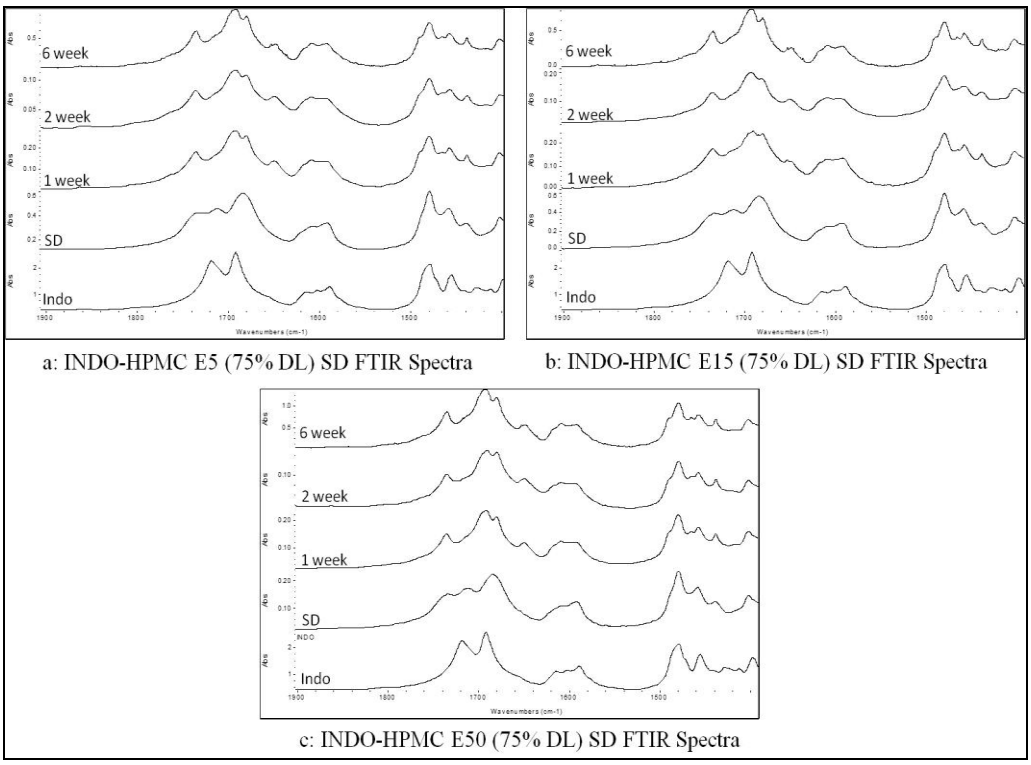


FIG.11: FTIR SPECTRA OF INDO-HPMC SD'S AT 75% DRUG LOADING AND THEIR STABILITY AT 1 WEEK, 2 WEEKS, AND 6 WEEKS OF STORAGE AT 40^0 C % 75% RH - (a) INDO-HPMC E5 SD FTIR spectra; (b) INDO-HPMC E15 SD FTIR spectra; (c) INDO-HPMC E50 SD FTIR spectra

Particle Size: Particle size of INDO and SSD were performed. INDO has a mean particle size of 17.29µm ± 0.04 µm. Mean Particle size of INDO-SD is given in table 10. The particle size of INDO was reduced to a certain extent. Since the parameters used for spray drying were same there is no much difference in particle size of different drug loaded dispersions and hence the difference in different solid dispersion formed is due to polymers themselves

CONCLUSION: In this study, we have evaluated the effect of molecular weight of PVP and HPMC using miniaturized testing method. The solvent shift method was able to generate supersaturation of INDO. In PVP family, it is observed that supersaturation was directly proportional to the concentration of PVP in solution. As we increase the concentration of polymers, the ability to generate and maintain INDO in supersaturated state is increased. However, in HPMC family the ability to generate and maintain INDO in supersaturated state is not concentration dependent. The solvent casting study shows that PVP K29 shows the fastest release rate as compared to PVP 12 and PVP K90; and HPMC E5 has a higher release rate as compared to HPMC E15 and E50. PVP K90 and HPMC E5 solvent cast have better stability when compared to the other grades in respective family. Spray dried solid dispersion of a binary system of INDO-Polymer were prepared at 75%, 50% and 25% drug loading using the same parameters except the feed concentration. PVP K29 and HPMC E5 showed higher yields than respective members of their family. At the higher drug loading, PVP K29 has higher yield as compared to HPMC E5. However, at low drug loading the yield of both polymers are same.

MDSC analysis revealed that PVP forms amorphous dispersion at all drug loading whereas HPMC forms amorphous dispersions above 50% drug loading. However, when these dispersions were subjected to elevated temperature and humidity HPMC SD at 50% drug loading and below were affected most, followed by PVP SD at 75% drug loading. PVP K90 SD shows miscibility even after storage at accelerated conditions. Dissolution profile suggests that PVPK29 and HPMC E5 show the highest amount of drug releasein non-sink media. The drug release increases as we increase the polymer content in SD for lower molecular weight polymer and as the molecular weight of the polymer increases the drug

release is dictated by dissolution of the polymer. At the higher drug loading, higher molecular weight polymers like PVP K90 and HPMC E50 are more effective as compared to other polymers in respective family.

FTIR revealed that there is stretching of the carbonyl bond of amide and acid, indicating breakage of hydrogen bonds between crystalline INDO and formation of bond between INDO and the polymer. The hydrogen bond is a non-covalent interaction and it was qualitatively estimated by FTIR. However, there is further need to quantify and differentiate such interaction using the advanced analytical tools.

TABLE 10: MEAN PARTICLE SIZE OF INDO-SD

Polymer	75% Drug Loading		50% Drug Loading		25% Drug Loading	
	% yield	Stdev	% yield	Stdev	% yield	Stdev
PVP K12	69	3.46	65	1.59	67	1.02
PVP K29	75	1.26	72	1.17	78	1.30
PVP K90	43	0.88	49	1.13	49	1.11
HPMC E5	62	1.75	64	1.07	79	0.91
HPMC E15	49	0.80	50	0.47	60	0.47
HPMC E50	50	0.87	50	1.26	46	1.52

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