

Investigations on noval method for the formulation of solid dispersions part- I formulation, characterization and selection

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Abstract

The solid dispersions of indomethacin with hydrophilic polymers were prepared by lyophilization. The polymers used in the investigation were HPMC, PVP K30, CBR and PLF 127. The solubility and dissolution of indomethacin from prepared lyophilized solid dispersions were investigated in 0.1 N HCl, purified water and USP-NF dissolution media. Out of fifteen lyophilized formulations from F1 to F15, five formulations F2, F5, F8, F12 and F14 showed highest solubility in purified water. Formulation F2, F8 failed to comply with the USP-NF dissolution test for indomethacin capsules. Formulation F14 showed maximum dissolution in the respective dissolution media within 60 min. Sustained drug release was observed for 6 h with formulations F2 and F8 in USP-NF media. The formulations F2, F5, F8, F12 and F14 were characterized by modulated DSC and FT-IR spectroscopy. Some Formulations on stability testing were found physico-chemically stable at accelerated temperature conditions.

Keywords: lyophilization, indomethacin, Solid dispersions, Dissolution, Stability.

Introduction

The solubility and dissolution of aqueous insoluble drugs has been improved by solid dispersion technique, using hydrophilic polymer carriers in which the insoluble drug is dispersed in amorphous state [1]. The solid dispersion technique is highly accepted in pharmaceutical industry in the formulation of water insoluble drugs for increasing their oral absorption [2-5]. The mechanism involved in the solubility improvement, is the ability of hydrophilic polymer carrier to prevent the drug precipitation in the aqueous environment of GI tract [6-10].

Examples of FDA approved solid dispersions based drugs include Itraconazole, Tacrolimus, lopinavir, Etravirine, Everolimus, Telaprevir, Troglitazone, Nifedipine, verapamil [2-11].

Solvent evaporation and hot melting methods are utilized mainly in the preparation of solid dispersions [2]. Major disadvantages of hot melting method is that the method can only be applied to thermos table, low melting point drugs and carriers; the miscibility and compatibility of polymer-drug physical mixture at high temperature; prolong time required for cooling of the melted physical mixtures results in recrystallization of amorphous drug [2,3]. Lyophilisation is an industrially applicable method alternate to hot melt method; have advantages of being applicable to thermo-sensitive drugs; as the substances are exposed to minimum heating in the process and there is minimum risk of phase separation [12-14]. The major problem associated with amorphous solid dispersions is the thermodynamic instability leading to recrystallization of amorphously dispersed drug. Extensive research has been going on to find the

ways for prevention of recrystallization of amorphous drugs in solid dispersions [15-20]. Polymers such as Polyvinylpyrrolidone, hydroxypropylmethyl cellulose acetate succinate, Eudragit EPO, Polyvinylpyrrolidone-vinyl acetate copolymer prevent the precipitation and crystallization of amorphous drugs in solution [6, 8, 15-20]. The stability of drugs in solid dispersions has been found improved by addition of surface active agents [20].

Surfactants acts by preventing recrystallization of drugs from amorphous state [20]. In the aqueous dissolution media interaction between surfactant and polymer carrier results in extremely stable aqueous dispersions of amorphous colloidal particles [21].

Indomethacin (IMC) a non-steroidal anti-inflammatory drug used in the treatment of arthritis; has been selected because it is water insoluble (0.937mg/L), highly lipophilic (log P value 4.27), low solubility and high permeability; a BCS class II drug (<http://www.drugbank.ca/drugs/DB00328#spectra>).

Indomethacin is readily soluble but very unstable in alkaline solutions with rapid decomposition [22-25]. Several Solid Dispersion systems of water insoluble indomethacin with hydrophilic carriers have been reported in the literature but it has not been studied with system based on carbomer hydrogel, prepared by freeze drying [23-28]. The amorphous solid dispersions with low degree of recrystallization have been reported with 2-hydroxyethyl methacrylate (PHEMA) [29-30].

Carbomers (CBR); the hydrophilic polyacrylic acid derivatives have been employed in the preparation of gels, oral solid dosage forms [31-32], solid dispersions [33,34].

PVPK30 and HPMC 4000cps are widely accepted excipients for solid dosage forms; used in the preparation and stabilization of solid

dispersions [35-39]. Pluronic acid F 127(PLF 127) was investigated as carrier in the preparation of solid dispersions for its surfactant properties [40, 41]

The selection of hydrophilic carrier in the preparation of solid dispersions is based on number of factors such as method of preparation; for example PVP, HPMC and carbomers are not suitable carriers for hot melt method as these polymers are completely burn down at high temperature, hence suitable to be used in solvent evaporation method [42]. The other factor involved is the determination of drug solubility in the aqueous solution of the polymer [43]. Since it is difficult to achieve drug- polymer solubility equilibrium in the highly viscous environment of polymer solution, the exact solubility of drug in polymer solution cannot be calculated [43, 44].

The present study has been done with objectives; preparation and characterization of amorphous indomethacin solid dispersions (LSDs) with carbomer 940P, Polyvinylpyrrolidone K30, Hydroxypropylmethyl cellulose 4000cps and Pluronic F127 as hydrophilic carriers by lyophilisation using hydro-alcoholic vehicle. Selection of LSDs formulations to be reformulated in non- alcoholic aqueous vehicle for further investigations.

Materials and Methods

Indomethacin [IMC] was purchased from Alfa Aesar, GmbH & Co KG, Germany. Hydroxypropylmethyl cellulose 4000cps (HPMC), Polyvinylpyrrolidone K30(PVP) and carbomer 940P(CBR), lactose were purchased from UFC Biotechnology, Amherst, USA. Pluronic F127 (PLF 127), Indomethacin RS, Potassium phosphate monobasic and ethanol (99.9% HPLC grade) were purchased from sigma aldrich USA. All other chemicals used in the experimental study were of analytical grade.

Preparation of Indomethacin- Polymer aqueous solution

IMC-polymer aqueous solution in the ratio of 1:1(1part IMC and 1Part PVP) was prepared as follows. 1g of polymer was dispersed in 50 ml of purified water (RO water) over the period of 15 minutes with constant stirring using magnetic stirrer. Solution of IMC in ethanol (1g/10ml) was prepared and added slowly drop wise in to the solution of PVP maintained under constant stirring conditions over a period of 15 minutes. Similarly drug polymer mixtures in different ratios have been prepared with CBR, PVP K30, HPMC 4000cps and PLF 127.

Lyophilization

The IMC-Polymer aqueous solutions prepared were transferred in to open clear glass bottles of 60ml, frozen at -30°C for 24h. Solvent was removed by two stage lyophilisation (Freeze drier Christ Beta 2-8 LD Plus, Martin Christ Germany).first stage the main drying was

done at condenser temperature -20°C, vacuum 1 mbar for 12 hr. At second stage which followed first stage automatically, the final drying was done at condenser temperature -31°C, vacuum 0.34 mbar for 12hr. The LSDs were further kept in vacuum desiccator for 12 h and were stored in screw capped clear glass bottles sealed with paraffin film.

Drug content determination

Accurately weighed LSDs equivalent to 50mg of IMC was dispersed in 10ml of purified water and it is gently shaken for 15 minutes. 50 ml methyl alcohol was added and the solution was shaken well. Sufficient methanol was added to produce 100ml. filter the solution, to the 5ml of filtrate, a mixture of equal volume of methanol and phosphate buffer pH 7.2 was added to produce 100ml (0.025mg/ml). The optical density (A_T) of the solution was determined at 320nm by using Evolution 60S UV-visible spectrophotometer[45].The absorbance (A_S) of indomethacin RS standard solution (0.025mg/ml) prepared with same procedure as described was measured. The content of IMC in LSDs was calculated with following equation.

$$Content_{LSD} = \frac{A_T}{A_S} \times C_{std}$$

C_{std} = Standard content of IMC in mg(50mg)

Solubility profile of lyophilized solid dispersions

Solubility of LSDs was determined in purified water and simulated gastric fluid without enzymes (solution of 0.2%w/v NaCl and 0.7% HCl in purified water). An excess amount of LSDs was added to 25 ml of purified water in glass bottles (screw capped capacity 50 ml). The dispersion was equilibrated by shaking in a warm bath at $37^\circ\text{C} \pm 0.5^\circ\text{C}$ for 48 h. After 48h, the mixture was centrifuged and the supernatant was diluted to 100ml with the respective media and absorbance was measured at 320nm spectrophotometrically [45]. The concentration of drug was determined from standard calibration curve of standard indomethacin; prepared with concentration range 10µg/ml to 50µg/ml. A phase diagram of indomethacin solubility (mcg/ml) vs polymer (%w/w) was constructed; compared with the solubility of pure crystalline IMC RS.

In-vitro Dissolution Testing

Dissolution investigations were performed on filled capsules containing the LSDs equivalent to 50mg of IMC. The testing was done with USP basket apparatus Type I; Erweka Germany. The dissolution media used was 750ml of USP30-NF25 media for IMC capsules (pH7.2), paddle rotation speed 50rpm; maintained at $37^\circ\text{C} \pm 0.5$. The test was performed for 1 h; 10ml sample was withdrawn, substituted with pre-warmed media, at 20minutes time interval, filtered, diluted to 50 ml with the dissolution media and the

absorbance of the solution was measured at 320nm. The percentage drug dissolved was calculated from Specific absorbance ($A_{1cm}^{1\%}$) of indomethacin RS (45). The dissolution testing was also done in 0.1N HCl and purified water as dissolution media. The test was done in duplicate and average value of the two was recorded.

Differential scanning Calorimetry (DSC)

Thermal behavior of IMC, LSDs were recorded by differential scanning calorimeter, Modulated DSC VI.1A was used with an argon purge at 45cc/min in order to determine the melting endotherm on set temperature and heat of fusion(ΔH). Samples were heated at 10°C/min under nitrogen atmosphere in the 70-250°C. The instrument was calibrated for temperature and enthalpy with indium.

The ΔH of the pure crystalline drug, in LSDs was determined. The percent crystallinity of the drug in the LSDs was calculated using the following equation from heat of fusion [42, 43]:

$$\text{Percentage crystallinity} = 100 \times \left(\frac{\Delta H_s}{\Delta H_c \times C} \right)$$

ΔH_s , ΔH_c are the enthalpy of LSDs and pure crystalline drug respectively.

C is the amount of drug (weight fraction) in the LSDs.

The pure drug was assumed as 100% crystalline.

Fourier Transform Infrared Spectroscopic studies (FTIR)

Spectrum of IMC, LSDs and hydrophilic polymers was recorded on Cary 630 FTIR spectrophotometer, Agilent Technologies. The IR determinations were carried out in the scanning range of 4000-650 cm^{-1} [44-45].

Stability evaluation

LSDs in sealed screw capped clear glass bottles were placed at 45°C for 90 days in HERATHERM Incubator (Thermo scientific). At the interval of 30days, samples were evaluated for appearance, drug contents and dissolution rate.

Results and Discussion

Drug content Uniformity

A UV spectrum of IMC prepared in Phosphate buffer pH 7.2 was presented in figure 1; indicated the λ_{max} at 321nm. A standard calibration curve for IMC was prepared with concentration of drug 10 $\mu\text{g}/\text{ml}$ to 70 $\mu\text{g}/\text{ml}$ in phosphate buffer pH 7.2, was represented in figure 1.1. The curve was found linear and the $R^2 = 0.997$.

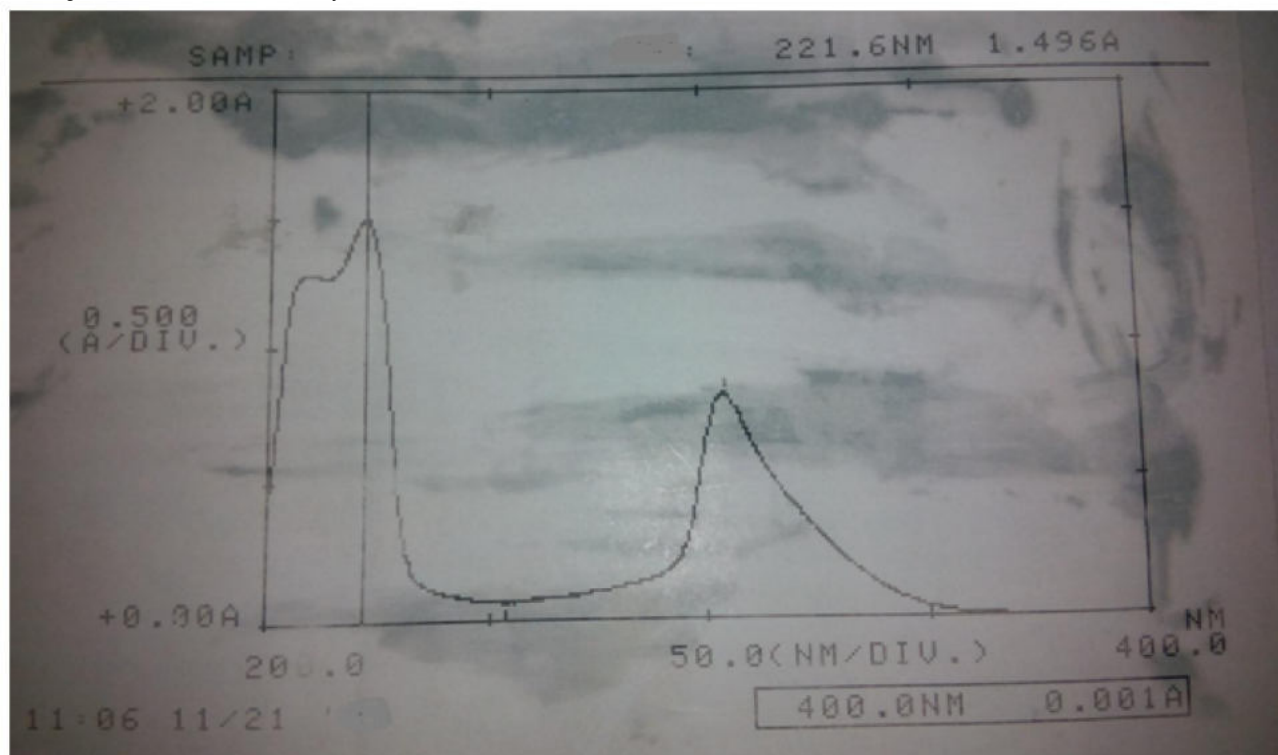


Figure1: UV-Spectra of IMC in Phosphate Buffer pH 7.2

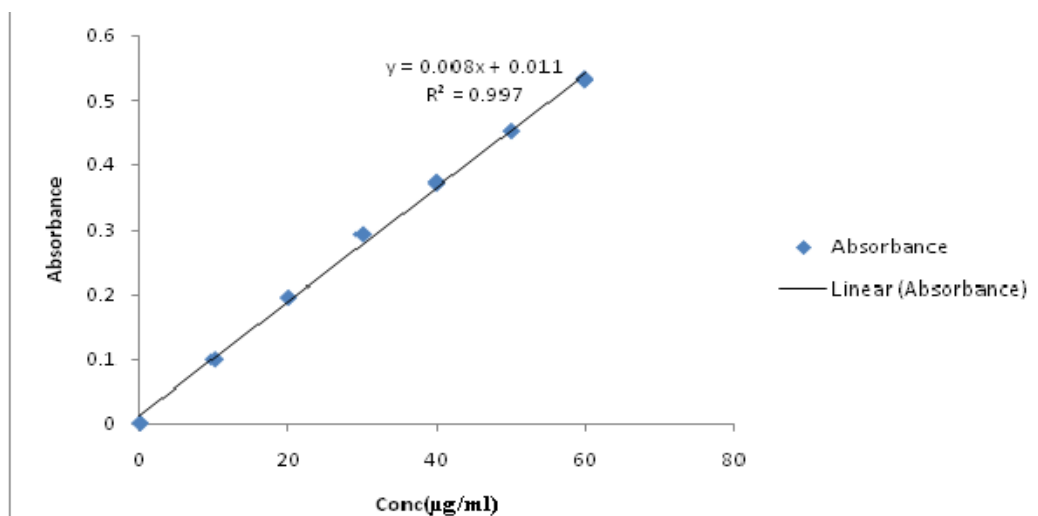


Figure 1.1: Standard calibration curve of indomethacin

Fifteen LSD formulations of IMC with HPMC, PVP, CBR and PLF 127 in different ratios were prepared and coded F1 to F15 (Table 1). The IMC content in all the formulations was found in the range of

98% to 99%. All the formulations complied for USP-NF test for content uniformity.

Table 1: LSDs formulations of Indomethacin with different polymers

Code	Formulation	Drug content (%± SD)
F1	IMC: HPMC	1:1 99.21±0.37
F2		1:1.5 99.30±0.23
F3		1:2 98.41±0.45
F4	IMC: PVPK30	1:1 98.40±0.35
F5		1:1.5 98.45±0.39
F6		1:2 99.30±0.42
F7	IMC: CBR	1:1 98.87±0.28
F8		1:1.5 98.92±0.32
F9		1:2 99.21±0.29
F10	IMC:HPMC:PLF127	1:1:0.2 98.55±0.39
F11		1:1:0.4 98.78±0.19
F12		1:1:0.6 99.21±0.22
F13	IMC:PVP:PLF127	1:1:0.2 98.46±0.29
F14		1:1:0.4 99.50±0.34
F15		1:1:0.6 98.76±0.28

Solubility of LSDs

Figure 1(a) represents the solubility profile of LSDs in purified water. The concentration of IMC 29.13 mcg/ml was found with LSDs prepared with HPMC, formulation F1. 30.31 mcg/ml concentration of IMC was found with F2. The concentration of IMC 15.84 mcg/ml was found with LSD containing PVPK30 in drug to polymer ratio 1:1(F4), followed by F5, 16.89 mcg/ml and F6, 15.57 mcg/ml respectively. Lowest concentration of IMC 1.63mcg/ml was found in LSDs prepared with CBR (F7).

CBR formulations showed slightly enhanced solubility of IMC in purified water. Formulations based on HPMC and PVP showed an increase in the solubility of IMC, 10 times and 5 times respectively in comparison to the CBR formulations. Maximum solubility of IMC was found with the formulations containing 150%w/w polymer. There is no further increase in solubility of IMC observed with further increase in the polymer weight in the formulations prepared with HPMC, PVP and CBR.

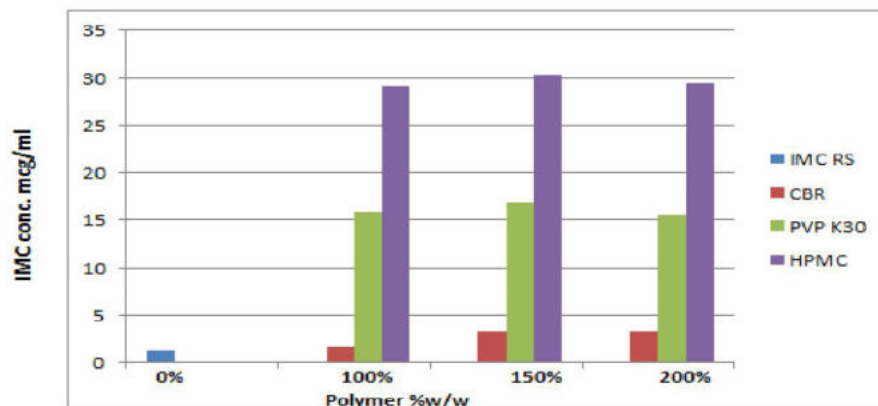


Figure 1(a): solubility of LSDs in purified water

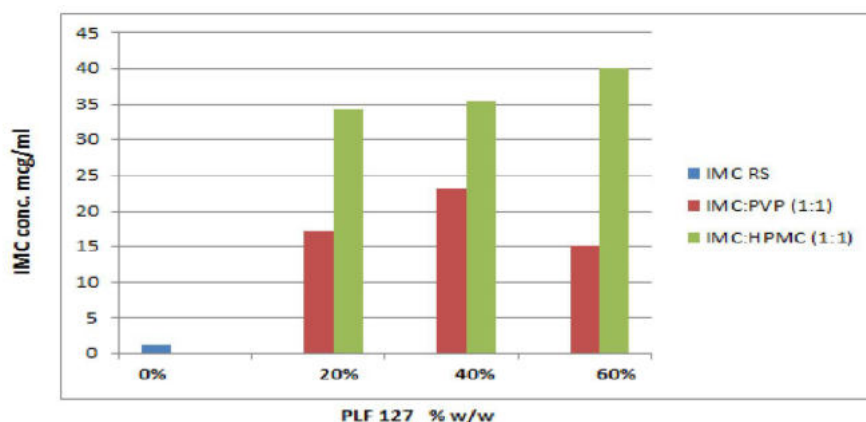


Figure 1(b): influence of plf 127 on solubility of LSDs in purified water

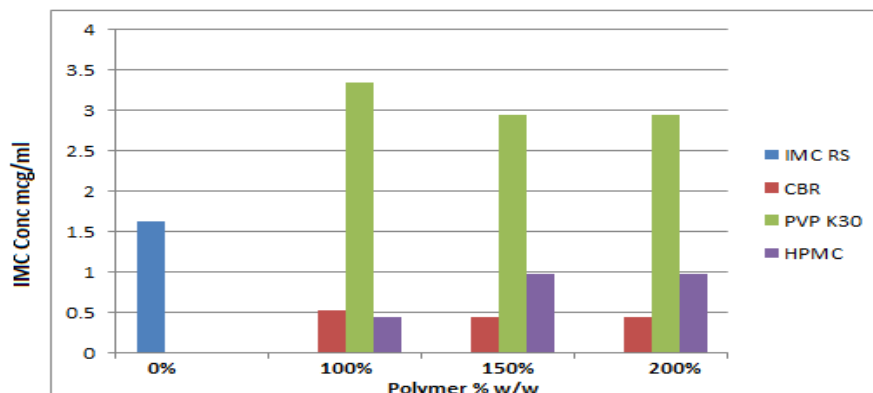


Figure 1(c): solubility of LSDs in simulated gastric fluid

HPMC, PVP based LSD formulations were prepared with PLF 127 ranging from 20%w/w to 60% w/w coded from F10 to F15. The figure 1(b) represented the effect of addition PLF 127 on solubility of IMC from Formulation F1 to F6. The concentration of IMC in solution; 40.05mcg/ml and 23.21mcg/ml was found with formulation F12 and

F14 respectively. Addition of PLF 127 to the PVP K30 based formulation F4 results in the 50% increase in concentration of IMC in formulation F14. The solubility determinations carried out in SGF were represented in figure 1(c). The maximum concentration of IMC 0.973mcg/ml, 3.34mcg/ml, 0.449, 5.97mcg/ml and 2.55mcg/ml was



found in SGF for formulation F2, F5, F8, F11 and F15. These results indicated that concentration of IMC in solution from LSDs depended on the type of polymer used in the formulation. The highest drug concentration was observed with HPMC based formulations followed by PVPK30. There was least effect of CBR on the concentration of IMC. Drug solubility of IMC in purified water was found increased with the addition of PLF 127 in HPMC and PVPK30 formulations(F10 to F15) and was found depended on the amount of PLF127 in the formulation(figure 1b). F2, F5, F8, F12 and F14 formulations based on HPMC, PVPK30, CBR and PLF127 showed maximum solubility of IMC within each group in purified water and were selected for further investigations.

In-vitro Dissolution Testing

Dissolution of Indomethacin RS

The specific absorbance ($A_{1cm}^{1\%}$) of indomethacin solution (10mg/ml) at 320nm was reported 193(41). Mathematically the absorbance of 0.0133mg/ml solution of indomethacin (A_m) was calculated as follows:

$$\left(\frac{10}{193} = \frac{0.0133}{A_m}\right); A_m = 0.256$$

Experimentally; 50mg of indomethacin RS was accurately weighed and was dissolved in freshly prepared 750ml dissolution media as per USP30-NF25, composed of 1 part phosphate buffer pH 7.2 and 4 part purified water. The media was stirred at 100rpm using magnetic stirrer. The temperature of the medium was maintained at 37°C.

10 ml of sample was withdrawn from the solution after 60 minutes and replaced with fresh dissolution medium maintained at same temperature, made up to 50ml with dissolution medium in a 50ml volumetric flask (0.0133mg/ml). The absorbance of the resulting solution was measured spectrophotometrically at 320nm. The experiment was carried out in triplicate and the average standard absorbance (A_s) was found 0.258. A_s was used to calculate the percentage drug dissolved at different time intervals in the dissolution experiments of LSDs as follows;

$$\% \text{ IMC dissolved} = \frac{A_t}{A_s} \times 100$$

Where ' A_t ': absorbance of the test sample

Dissolution of LSDs in USP-NF Media

Figure 2(a) represents the dissolution profile of LSDs in USP-NF dissolution media. The percentage dissolved IMC at 20 minutes interval was found 27.73, 83.2, 12.0, 76.95, and 100.1 % for F2, F5, F8, F12 and F14 respectively. At 40 minutes time interval the percentage IMC dissolved was found 32.03, 98.43, 14.84, 85.54, and 100% for F2, F5, F8, F12 and F14 respectively. At 60 minutes time interval the percentage IMC dissolved was found 39.84, 99.21, 15.23, 92.96, and 100.7% for F2, F5, F8, F12 and F14 respectively. The formulations were arranged in the increasing order for percentage dissolved at 60 minutes as F8<F2<F12<F5<F14. The USP-NF dissolution tolerance limit for indomethacin capsules stated as; not less than 80% of the labeled amount dissolved in 20 minutes. Formulation F5, F12 and F14 complied at the USP-NF dissolution test tolerance limit for indomethacin capsules.

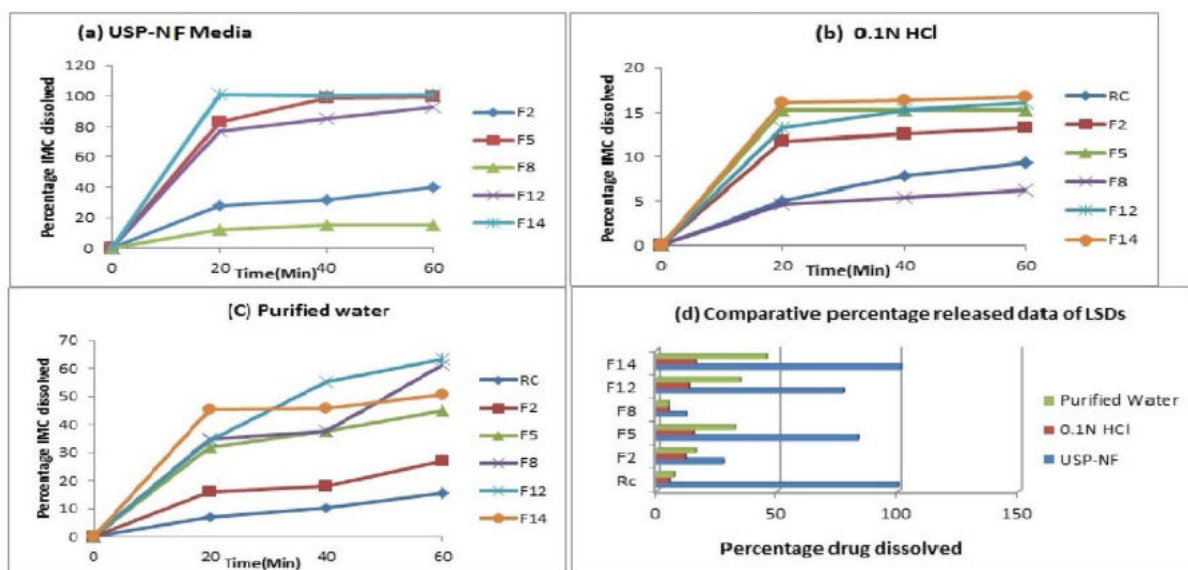


Figure 2: In vitro dissolution profile of LSDs

Dissolution of LSDs in 0.1N HCl

Figure 2(b) represents the dissolution profile of LSDs in 0.1N HCl. Dissolution of IMC capsule containing physical mixture of IMC and lactose equivalent to 50 mg of IMC was carried out that serve as reference capsule (RC) for comparison with LSDs. At 60 minutes time interval the percentage IMC dissolved was found 9.37, 13.28, 14.84, 6.25, 16.01, and 16.79% for RC, F2, F5, F8, F12 and F14 respectively. The formulations were arranged in the increasing order of percentage IMC dissolved as F8<RC<F2<F5<F12<F14 at 60 minutes.

Dissolution of LSDs in Purified water

Figure 2(C) represents the dissolution profile of LSDs in purified water. Dissolution of 50mg of IMC capsule containing pure IMC was carried out that serve as reference (RC) for comparison with LSDs. Reference capsule contained 50mg of pure IMC mixed with 100mg of lactose. At 60 minutes time interval the percentage IMC dissolved was found 15.62, 26.95, 44.92, 18.28, 50.78, and 63.51% for RC, F2, F5, F8, F12 and F14 respectively. The formulations were arranged in the increasing order of percentage IMC dissolved as RC<F8<F2<F5<F12<F14 at 60 minutes.

Figure 2(d) represents the comparative dissolution data of IMC formulations in USP-NF media, 0.1N HCl and purified water at t=20minutes. Formulation F2 showed 27.73% IMC released in USP-NF, 16.01% in purified water, 11.71% in 0.1N HCl. In purified water, the drug released from F2 was 2 times higher than RC. Formulation F5 showed 83.2% IMC released in USP-NF media, 32.03% in purified water, and 15.23% in 0.1N HCl. In purified water the drug released was 4.5 times higher than RC. Formulation F8 showed 12.1% IMC released in USP-NF media, 4.68% in purified water, and 4.68% in 0.1N HCl. In purified water the drug released was similar to the RC. Formulation F12 showed 76.95% IMC released in USP-NF, 34.37% in purified water, 13.28% in 0.1N HCl. In purified water, the IMC released from F12 was 5 times higher than RC. Formulation F14 showed 100% IMC released in USP-NF, 45.37% in purified water and 16.01% in 0.1N HCl. In purified water, the drug released was 7 times higher than RC.

IMC, a weak acidic drug pKa 4.5, readily dissolved in USP-NF dissolution media pH7.2. The dissolution rate of IMC varied with the type of polymers. Maximum release of drug in all the three type of dissolution media that is USP-NF, 0.1 N HCl and purified water was found with F14 and F12 formulations based PLF 127 with PVP K30 and HPMC followed by PVPK30 based F5 within 60 minutes. Very

slow release of IMC was found with LSDs based on HPMC (F2) and CBR (F8).

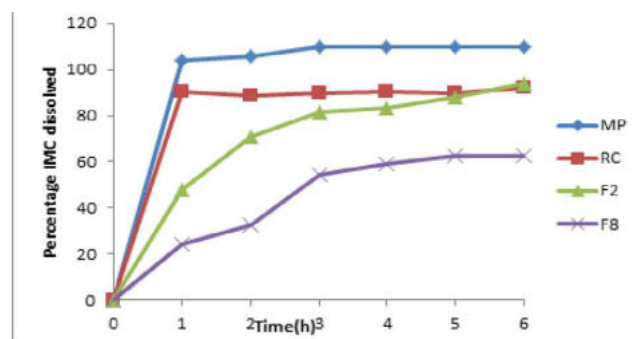


Figure 2(e): Sustained dissolution of F2&F8 in USP-NF

The dissolution experiment for formulation F2 and F8 was conducted for 6 h in USP-NF dissolution media (figure 2e). The release of IMC from F2 and F8 was compared with marketed product (MP) as external standard and reference capsule containing 50 mg of IMC as internal standard. At the end of 6h; 84% and 62% drug released was found with formulation F2 and F8 respectively. Sustained slow release of IMC in case of F2 and F8 formulations is due to the fact that the release of drug from hydrophilic matrixes of HPMC and CBR depended on the swelling behavior (gelation) which in turn influenced by the pH and temperature in case of CBR [49] and ionic strength of the dissolution media in case of HPMC [50]. The gel barrier is the major determining factor in the drug dissolution profile related to the time. The thicker and faster gel formation led to the slow release of drug (50).

At the end of 60 minute dissolution test in USP-NF media for formulations F2, F5, F8, F12 and F14, the baskets of dissolution test apparatus were removed and pattern of gel formed was assessed by visual evaluation of bulkiness of the gel Figure 2F. In USP-NF dissolution media, gel formation with maximum bulkiness was observed in CBR based formulation F8 followed by HPMC based F2.

The formulation F5, F12 and F14 had almost similar release profile indicated the inhibitory effect of PLF 127 on gel formation of HPMC in F12. PLF 127; a nonionic surfactant HLB value 29, improve the wettability and prevent the thickening of hydrogel in HPMC based F12. The PVPK30 based formulation F5 and F14 showed no sign of gel formation during dissolution process, complete dissolution was observed with few traces of residue was found in the dissolution basket after 60 minutes.

The pattern of gel formation by LSDs in 0.1N HCl was found physically similar with that in purified water.



Figure 2:(f): Pattern of gel formation in dissolution media

Differential scanning Calorimetry (DSC)

IMC has demonstrated very much characterized endothermic pinnacle (T_m) at 161.03°C relating to the dissolving purpose of crystalline drug. There was complete absence of endothermic peak of INH was observed in all five formulations F2, F5, F8, F12 and F14. Wretchedness of melting point is not the same as IMC and individual polymer in this way affirming the arrangement of new stage. Bringing down of melting temperature focuses was because of the breaking of bonds, cluttered and non randomized structure of particle. It prompts bring down initiation vitality to achieve the dissolving focuses. The expansive, less sharp crests with lessening in dissolving purpose of IMC in strong scatterings indicates diminish in the slow disintegration of the medication in the polymer amid the DSC warming slope. The percentage crystallinity of IMC in each formulation was found 22.71, 19.06, 26.45, 11.75 and 18.42% respectively, endorsed the co-relation between the percentage crystallinity of IMC and the dissolution pattern of IMC from each formulation. State of amorphousness of IMC demonstrated that it was molecularly scattered inside the carrier.

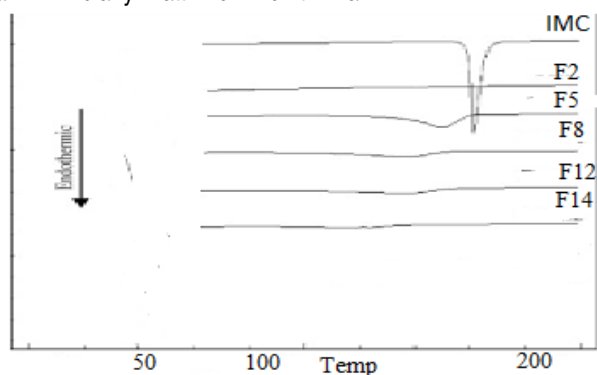


Figure 3: DSC thermogram of IMC Solid Dispersions

Fourier Transform Infrared Spectroscopic studies

The structure of IMC was depicted in fig 3a. Figure 3b and 3c represented the FTIR spectrum of pure indomethacin, LSDs and Hydrophilic carriers respectively. Characteristic absorption peaks were appeared at frequencies 2967cm^{-1} , 2928cm^{-1} , 1713cm^{-1} , 1689cm^{-1} , 1590cm^{-1} , 1480cm^{-1} and 1307cm^{-1} . Absorption peaks at 2967cm^{-1} and 2928cm^{-1} were due to C-H stretching of methyl groups and aromatic rings. Peaks at 1713cm^{-1} and 1689cm^{-1} were due to the C=O stretching of two carbonyl groups pertaining to benzoyl and acidic group. Peaks due to C=C stretching of aromatic rings were found at 1590cm^{-1} and 1480cm^{-1} . Strong absorption peak at 1307cm^{-1} was observed due C-N stretching. No extra peaks was appeared in the spectra of prepared LSD formulations indicated no interactions between drug indomethacin and hydrophilic carrier.

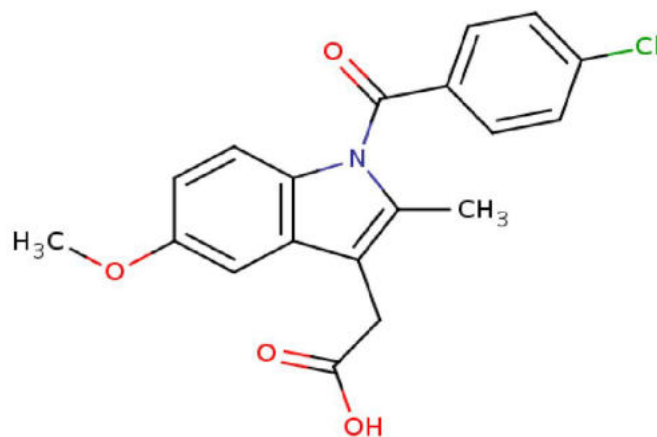


Figure 3(a): Structure of indomethacin

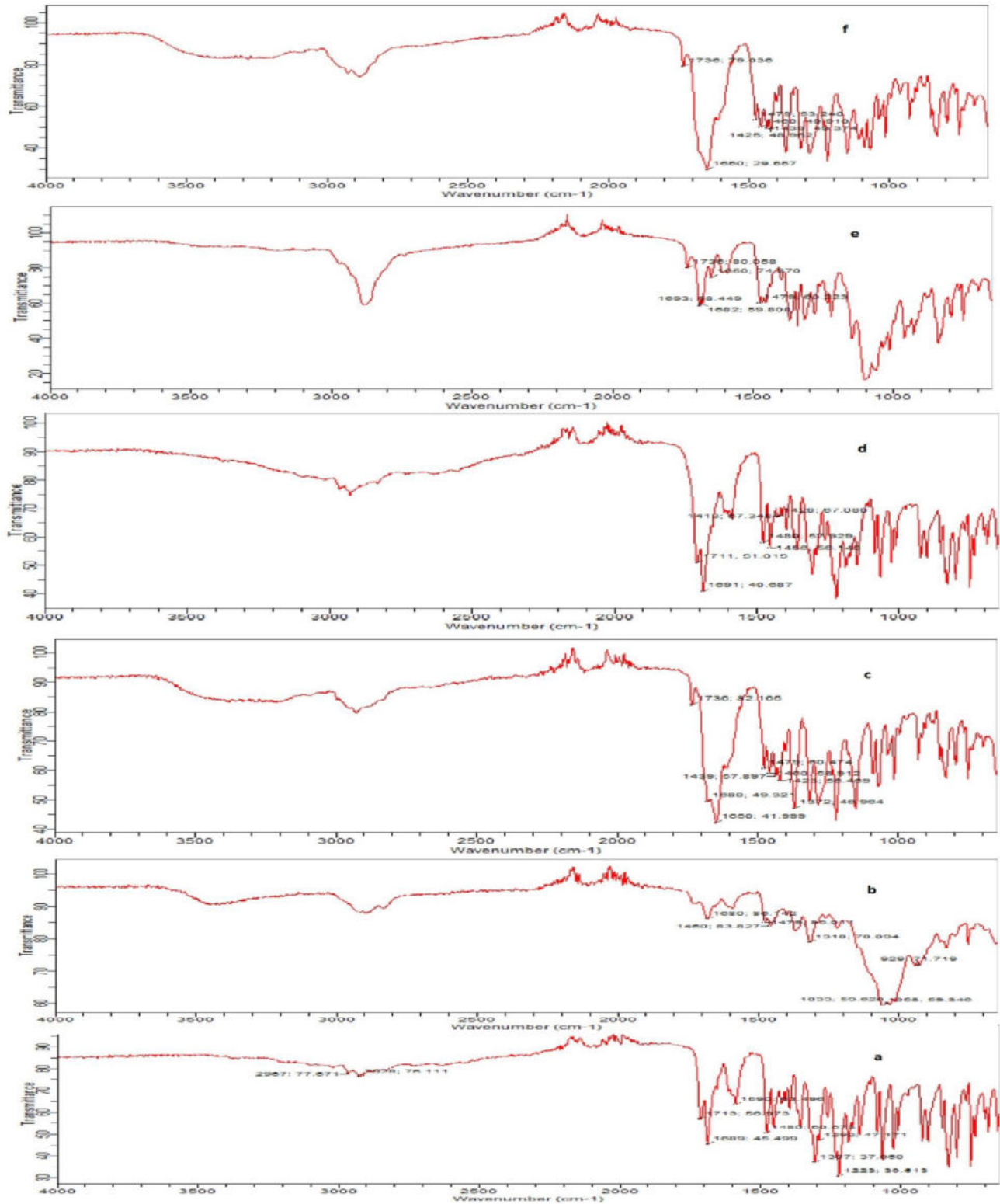


Figure 3b: FTIR spectrum of LSDs. a) IMC, b) F2, c) F5, d) F8 e) F12, f) F14

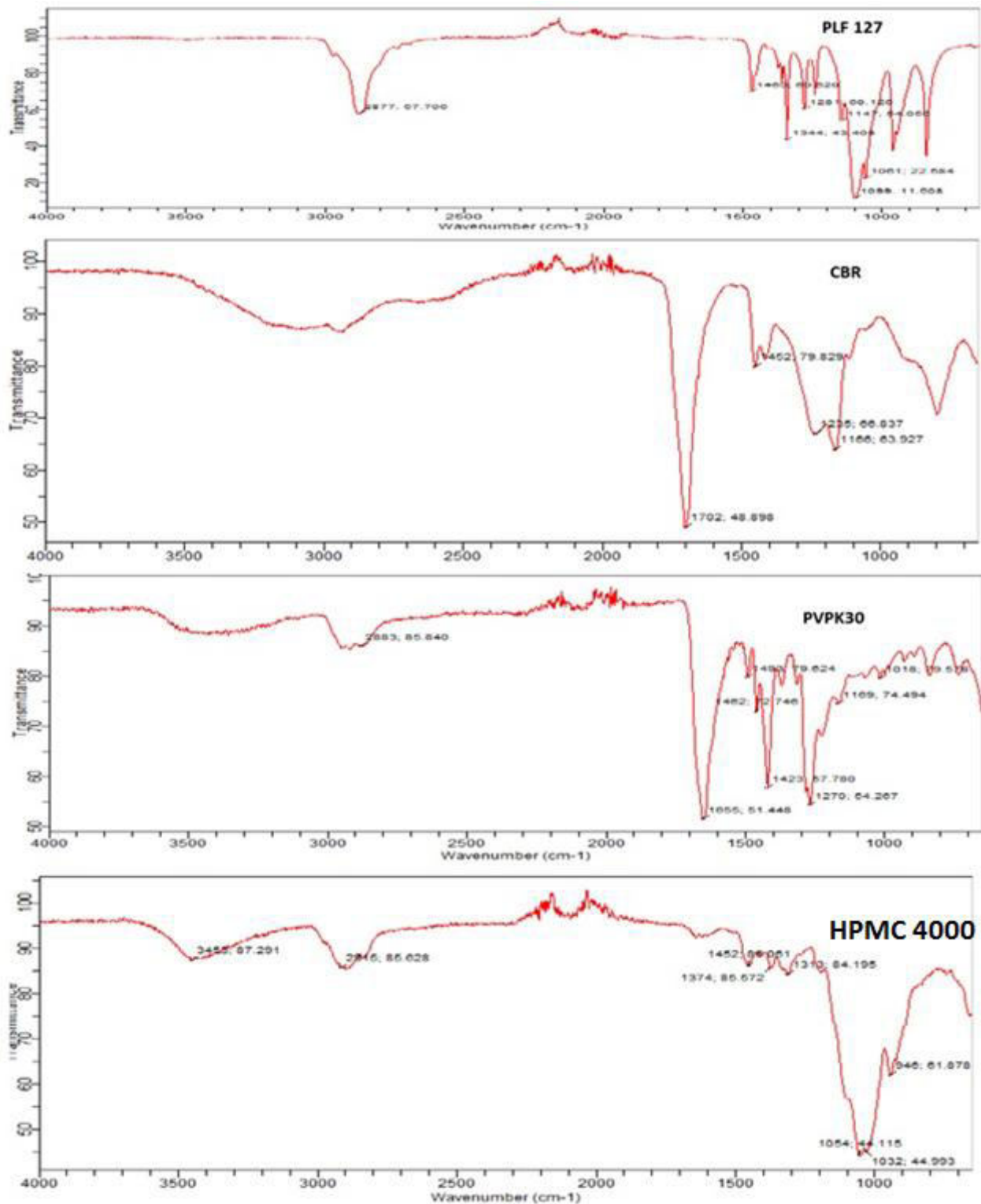


Figure 3c: FTIR Spectrum Of Hydrophilic Polymers

Stability Evaluation

Formulation F5, F12 and F14 complied with the USP30-NF25 monograph dissolution test requirements for indomethacin capsules, were selected for stability studies for 3 month period. All the three formulations were free flowing powder. The stability data for LSDs was presented in Table 2. The appearance of the test formulations was compared with the formulations kept at laboratory temperature. There was no sign of any discoloration found in the formulations during the entire stability studies period. Slightly melted mass formation was observed in formulation F12 and F14

which resulted in formulation deposition (stickiness) at bottom of the bottle after one month of storage. This was due to the low melting point (56°C) of PLF 127.

The amount of non-degraded drug present (% drug content) in LSDs was determined as per assay method described earlier. The formulations were found chemically stable with % drug content was not less than 98.37 in F5, 99.22 in F12 and 99.41 in F14 after 90 days.

The dissolution experiments was done in duplicate (n=2) as per USP-NF method described earlier. The amount of drug released after 20 minutes was determined

Table 2: Stability Evaluation Data of LSDs

Time(Days)	Appearance			% Drug content ⁽ⁿ⁾			Dissolution (t=20min) (% IMC Released) Media USP-NF*		
	F5	F12	F14	F5	F12	F14	F5	F12	F14
30	+	+	+	98.42	99.23	99.45	82.31	81.62	97.8
60	+	+	+	98.36	99.21	99.43	83.72	82.17	94.57
90	+	+	+	98.37	99.22	99.41	82.12	81.93	96.78

+ ; no sign of discoloration

n; an average of two determinations.

Conclusion

The solid dispersions of indomethacin prepared by lyophilization method showed enhancement in solubility and dissolution of indomethacin in purified water. Improvement in solubility and dissolution depended on the type, ratio and combination of hydrophilic polymer(s) used in the formulation. There was no improvement in dissolution observed with CBR based F8 formulation. Formulation F2, F5, F12 and F14 were found with enhanced dissolution by 2, 4.5, 5 and 7 times respectively than the pure drug indomethacin in purified water. Formulation F5, F12 and

F14 comply the USP-NF dissolution test for indomethacin capsules. PLF 127 inhibited the gel formation of HPMC in USP-NF dissolution media. DSC confirmed the amorphous state of IMC in solid dispersions. There was no drug-polymer physico-chemical interaction found with FT-IR spectroscopic analysis. Stability testing for three months indicated that the test formulations F12 and F14 were physically unstable at accelerated temperature storage conditions. The formulations F2 and F5 were selected for further experimental studies

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