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Formulation Development of Dry Powder Injection for Reconstitution of Poorly Water-Soluble Drug, Indomethacin, Using Mixed Solvency Concept and their Evaluations

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ABSTRACT: In this current era of pharmaceutical research, maximum newly invented drugs are found to be very poorly soluble in water. It poses difficulties in various developmental, manufacturing and administrating processes, which lead to the high failure of clinical trials of the drug due to poor pharmacokinetics. Parenteral dosage form could be expected to be an effective tool for avoiding the oral side effects and also achieving maximum bioavailability. Poor solubility of drugs in water is currently biggest challenge and limitation in injectable formulation developments. The prime purpose of any research work should be highly efficient and most effective in the pharmaceutics field to serve the society's needs by developing a formulation after literature survey and market review. The ultimate objective of this present research was to promote the use of mixed solvency concept by formulating the model dry powder injection for reconstitution of the poorly water soluble drug and to decrease the concentration of individual solubilizers required to produce a substantial increase in solubility and thereby resulting in expected synergistic enhancement of solubility of the drug in water. In the present work, poorly water-soluble drug, Indomethacin was selected as a model drug and its dry powder injection for reconstitution was formulated. Indomethacin is a type of medicine called NSAIDS. They are used for their anti-pyretic and anti-inflammatory effects. Due to poor solubility of indomethacin, the products are available in tablet and capsule form. In order to get expected synergistic enhancement of solubility, various blends of solubilizers can be tried thereby reducing the amount of individual solubilizer employed like sodium caprylate, sodium benzoate, poloxamer 407, lysine HCl and sodium citrate to achieve the desired solubility enhancement ratio. Thus, the successful completion of the research work will enable the preparation of stable dry powder injection for reconstitution ofIndomethacin

KEYWORDS: Mixed solvency concept, solubilizers, indomethacin, dry powder injection for reconstitution, solubility.

I. INTRODUCTION

Majority of drugs show the problem of poor solubility, whether in the case of their analytical estimations or in the field of liquid dosage forms in the form of solutions. Commonly used organic solvents for spectrophotometric analysis of water insoluble drugs include methanol, ethanol, chloroform, benzene, dichloromethane, dimethyl formamide, acetonitrile, ethyl acetate, toluene, carbon tetrachloride, acetone, hexane etc. The main drawbacks of organic solvents include high cost, toxicity and pollution. Organic solvents have innumerous adverse effects caused by single exposure like dermatitis, headache, drowsiness, nausea, eye irritation and long term exposure causes serious effects such as neurological disorders, chronic renal failure, liver damage, necrosis, mutagenesis disorder. They should be replaced by other eco-friendly alternative sources. The pollution and toxicity caused by most of the organic solvents is a big challenge. The researchers are doing much work to give eco-friendly solutions for this challenge. Maheshwari[1-6] has given a nice concept, known as mixed- solvency concept. By application of this concept, innumerable solvent systems can be developed. Maheshwari is of the opinion that each substance possesses solubilizing power. He has given several ecofriendly methods in the area of drug estimations and formulations precluding the use of toxic organic solvents. There are very few safe liquids eg. propylene glycol, glycerin, tweens, ethanol, liquid polyethylene glycols (like PEG 200, 300 etc) which are employed by pharmaceutical industries in various dosage forms for making solution type dosage

International Journal of Pharmaceutical Research and Applications
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forms of poorly soluble drugs. Mixed solvency concept, proposed by Maheshwari[7-28] provides a means to develop innumerable solvent systems employing combination of the pharmaceutical excipients in small concentrations. Each substance present on the earth has got solubilizing power. By combining the excipients, additive solvent actions and synergistic solvent actions can be obtained. The problem of toxicity issue due to high concentration of a single solvent can be solved in this manner. The solubility of a large number of poorly soluble drugs have been enhanced by mixed solvency concept. In the present investigation, the poorly water-soluble drug, indomethacin, has been selected as a drug for formulating its dry powder injection for reconstitution by using mixed solvency approach.

II. MATERIALS AND METHODS

Materials

Indomethacin was obtained as gift sample from Elder PharmaceuticalPrivate Limited, Mumbai. All other chemicals and solvents employed were of analyticalgrade.

Methods

UV Spectrophotometric analysis of indomethacin

About 50 milligrams of indomethacin was accurately weighed and transferred in a 50 ml volumetric flask and 20 ml of 30% sodium benzoate solution was added. Then the flask was shaken to dissolve the drug completely. After that, the volume was made with Milli-Q water up to 50 ml to obtain the stock solution of 1000 µg/ml concentration. The stock solution (1 ml) taken and diluted up to 50 mlwith Milli-Q water to obtain dilution of 20 µg/ml concentration. The resulting solution was scanned between 300-400 nm on Shimadzu-1700 UV spectrophotometer against Milli-Q water. The spectra as recordedin figure1.

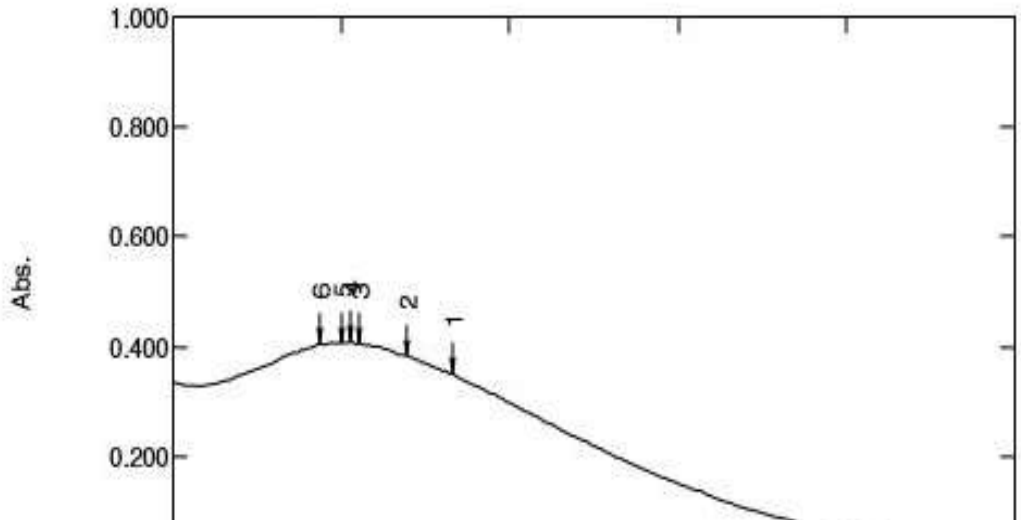

Fig. 1: UV spectra of indomethacin in Milli-Q water

DSC of Drug Sample

The DSC study was carried out on a Perkin Almer Differential Scanning Calorimeter with thermal analyser. The drug sample (2.5 mg) was placed in an aluminium pan. The pan was placed on the heating cell after sealing. Heating at a rate of 20°C/min with a continuous purgeof nitrogen (45 CC/min) was done with recording of energy changes in the sample with respect to an empty aluminium pan as reference in the temperature range of 50-210°C. Obtained DSC thermogram (melting isotherm) is shown in fig. 2.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 2 Mar-Apr 2021, pp: 314-326 www.ijprajournal.com ISSN: 2249-7781

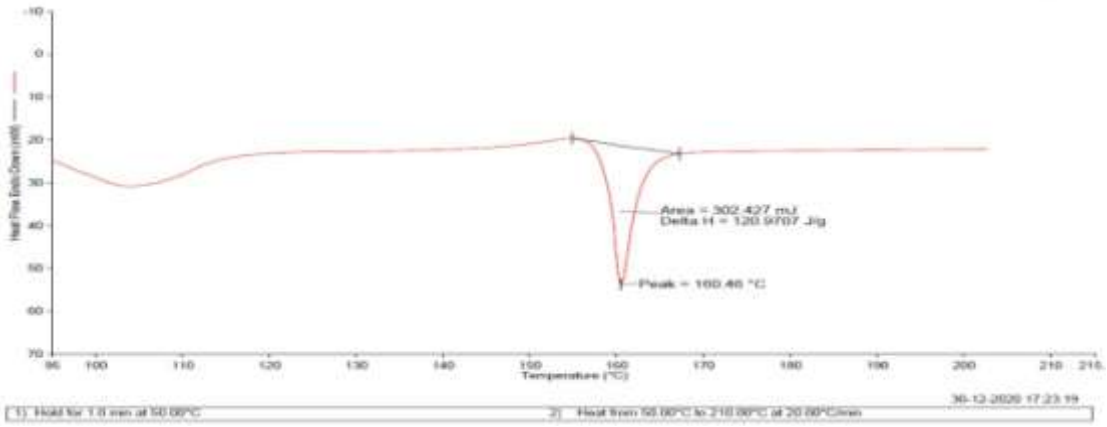

Figure 2: DSC spectrum of Indomethacin drug sample

Melting point determination of indomethacin

Drug sample was packed in a capillary tube and melting point was determined by analog melting point testing apparatus. The melting point of indomethacin drug sample was found to be 158-160 ºC which is comparable to the value reported in the literature.

Preparation of calibration curve of indomethacin in Milli-Qwater

About50 milligramindomethacinwasaccuratelyweighedand transferred to a 50 ml volumetric flask. The drug was dissolved by addition of 20 ml of 30% w/v sodium benzoate solution and the volume was made up to 50ml with Milli-Q water, so as to obtain a solution of 1000 µg/ml. Above solution (0.5 ml) was taken and diluted up to 50 ml with Milli-Q water to obtain the dilution of 10 µg/ml concentration. Likewise, 1.0 ml, 1.5 ml, 2.0 ml, 2.5 ml solutions were taken and diluted up to 50 ml to obtain dilutions of 20, 30, 40 and 50 µg/ml concentrations, respectively. Absorbances of prepared dilutions (10, 20, 30, 40, 50 µg /ml) were measured at 320 nm against the respective reagent blanks on Shimadzu-1700 UV spectrophotometer. The obtained data was recorded in table 1 and graphically represented in figure 3.

Table 1: Absorbance data for calibration curve of indomethacin in Milli-Q water at 320 nm (n=3)

S.No.	Concentration (µg/ml)	Absorbance (mean ± S.D.)
1.	0	0.000±0.00
2.	10	0.196 ± 0.0091
3.	20	0.399±0.0127
4.	30	0.612± 0.0021
5.	40	0.794±0.0091
6.	50	1.020±0.0011

International Journal of Pharmaceutical Research and Applications
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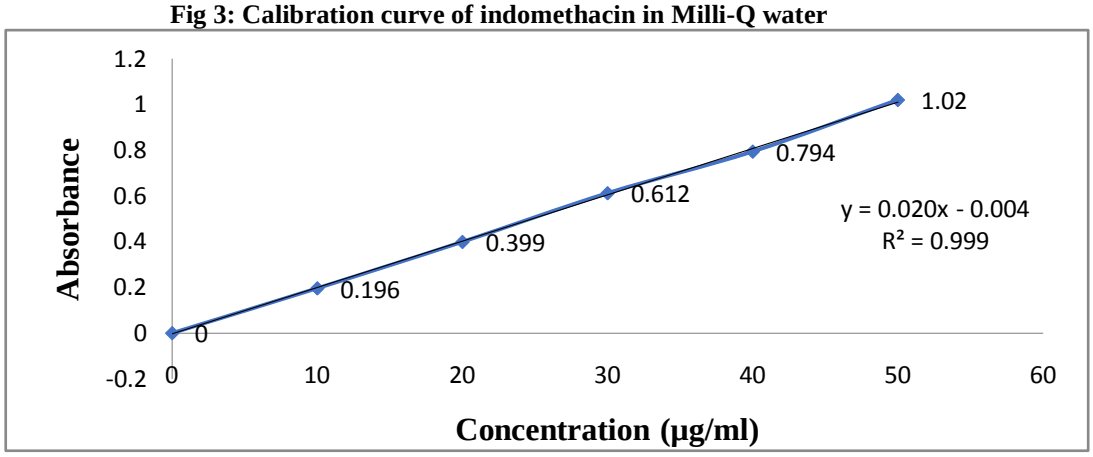
Fig 3: Calibration curve of indomethacin in Milli-Q water



2.2.5 Approximate solubility determination of indomethacin in various aqueous solutions of solid solubilizers (mixedblends)

One ml of the blend was taken in a 10 ml volumetric flask and accurately weighed 5 mg of indomethacin drug was transferred to this flask and vigorous shaking was done for 15-20 minutes. If the drug dissolves completely to give clear solution then another 5 mg of indomethacin drug was added to the flask. Again, vigorous shaking was done. The same process was repeated until a turbid solution is obtained even after shaking for 20 minutes. The same procedure was repeated for all blends to get approximate solubility of indomethacin in various blends. Amount dissolved per ml of a solvent system was determined. Table 2 gives the results of the approximate solubilitystudies.

Table 2: Results of approximate solubility studies of indomethacin in various aqueous solutions of solubilizers.

S. No.	Blends	The composition of blends (w/v)	Approximate solubility
1.	B-1	Sodium Caprylate- 15 % Sodium Benzoate - 5 % Sodium Citrate - 5 % Lysine HCl -2.5%	75 mg/ml
2.	B-2	Sodium Caprylate - 10% Sodium Benzoate - 2.5 % Sodium Citrate - 2.5 % Lysine HCl - 2.5% □-Cyclodextrin -2.5%	40 mg/ml
3.	B-3	Sodium Caprylate - 5 % □-Cyclodextrin -5 % Sodium Citrate -5 % Arginine -10% Benzoic Acid - 5%	50 mg/ml

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 2 Mar-Apr 2021, pp: 314-326 www.ijprajournal.com ISSN: 2249-7781

S. No.	Blends	The composition of blends (w/v)	Approximate solubility
4.	**B-4**	Sodium Caprylate - 5 % Sodium Benzoate - 5 % Vanillin -. 5 % Sodium Citrate - 2.5 % Benzoic Acid -5% Poloxamer 407 -5% Niacinamide -2.5% Arginine - 10%	40 mg/ml
5.	**B-5**	Sodium Caprylate -10 % Sodium Benzoate -5 % Sodium Citrate - 5 % Lysine HCl - 2.5 %	45 mg/ml
6.	**B-6**	Sodium Caprylate - 5 % Arginine - 5 % Lysine HCl - 5 %	70 mg/ml
7.	**B-7**	Sodium Caprylate -5 % Arginine - 5 % Lysine HCl -10 % Benzoic acid - 3%	45 mg/ml
8.	**B-8**	Sodium Caprylate - 5% Sodium Benzoate -5 % Sodium Citrate - 5 % Lysine HCl- 5% Poloxamer 407- 5%	35 mg/ml
9.	**B-9**	Sodium Caprylate - 5 % Sodium Benzoate - 5 % Poloxamer 407 - 5 % Lysine HCl - 5%	30 mg/ml
10.	**B-10**	Sodium Caprylate - 10 % Sodium Benzoate - 2.5% Sodium Citrate - 2.5% Lysine HCl -5% Poloxamer 407 -5% Niacinamide - 2.5%	65 mg/ml
11.	**B-11**	Sodium Caprylate - 5 % Poloxamer 407 - 10 % Lysine HCl - 5 %	20 mg/ml
12.	**B-12**	Sodium Caprylate - 10 % Sodium Benzoate -2.5 % Lysine HCl - 5 % Niacinamide -2.5 %	50 mg/ml

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 2 Mar-Apr 2021, pp: 314-326 www.ijprajournal.com ISSN: 2249-7781

S. No.	Blends	The composition of blends (w/v)	Approximate solubility
13.	B-13	Sodium Caprylate -10 % Poloxamer 407 -5 % Niacinamide -2.5 % Lysine HCl -2.5%	35 mg/ml
14.	B-14	Sodium Caprylate -10 % Sodium Benzoate -5 % Lysine HCl - 5%	40 mg/ml
15.	B-15	Sodium Caprylate - 10 % Lysine HCl - 5 % Niacinamide - 5 %	45 mg/ml
16.	B-16	Sodium Caprylate - 10 % Lysine HCl - 5 % Poloxamer 407 - 5 %	40 mg/ml
17.	B-17	Sodium Caprylate -10 % Lysine HCl - 5 % Sodium Citrate -5 %	45 mg/ml
18.	B-18	Sodium Caprylate - 10 % Lysine HCl - 5 % □-Cyclodextrin 5 %	30 mg/ml
19.	B-19	Sodium Caprylate -10 % Lysine HCl - 5 % Sodium Acetate - 5 %	40 mg/ml
20.	B-20	Sodium Caprylate -5 % Arginine - 5 % Lysine HCl -15 % Benzoic acid - 3%	30 g/ml

2.2.6 Determination of equilibrium solubility of drug indomethacin in Milli-Q water

In Milli-Q water, the equilibrium solubility determination for the drug indomethacin was carried out. Ten ml of water contained in a 20 ml glass vial was added to the excess amount of the drug and the vial was capped. The vial was shaken for 24 hours on the mechanical bath shaker and then permitted for twenty-four hours to equilibrate and filtered through Whatman filter no. 41. Aliquot filtrate was sufficiently diluted with Milli-Q water. The UV-Visible spectrophotometer was used to analyse water and dilution (Shimadzu 1700). The result is presented in Table 3.

Table 3: Equilibrium solubility of drug indomethacin, in Milli-Q water

S.No.	Solvent	Solubility (mg/L)
1.	Milli-Q water	0.937

2.2.7 Equilibrium solubility determination of indomethacin in selected blends (B-2, B-12, B-13)

In order to carry out the equilibrium solubility study of indomethacin in various selected blends (table 2), 4ml of each blend was taken in the appropriate vials and then some excess amount of drug was added into each vial. Then, vials were subjected to continuous shaking in water bath incubator shaker for 24 hrs. Vials were found to

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 2 Mar-Apr 2021, pp: 314-326 www.ijprajournal.com ISSN: 2249-7781

contain undissolved drug. Then, vials were kept undisturbed for 12 hrs. After filtration through Whatman filter paper no. 41, the filtrates were suitably diluted with Milli Q water and absorbances were measured at 320 nm against reagent blanks. Then, equilibrium solubility of drug in each blend was calculated by using the calibration curve.Results of equilibrium solubility studies are shown in table 4.

Table 4: Results of equilibrium solubility studies of indomethacin in selected blends

S.No	Blend	Blend composition	Solubility(mg/ml)
1.	**Blend-2**	Sodium Caprylate - 10% Sodium Benzoate - 2.5 % Sodium Citrate - 2.5 % Lysine HCl - 2.5% □-Cyclodextrin -2.5%	37.5 mg/ml
2.	**Blend-12**	Sodium Caprylate - 10 % Sodium Benzoate -2.5 % Lysine HCl - 5 % Niacinamide -2.5 %	43.2 mg/ml
3.	**Blend-13**	Sodium Caprylate -10 % Poloxamer 407 -5 % Niacinamide -2.5 % Lysine HCl -2.5%	42.8 mg/ml

Optimization of blend for preparation of dry powder forinjection

On the basis of results obtained from solubility studies, the mixed blends (three) in which solubility of indomethacin was more than 25 mg/ml were selected. Such selected mixed blends were B-2, B- 12, and B-13. To develop 1 ml of indomethacin injection, the amount of solubilizers and drug that will be administered through each mixed blend was determined. Injection formulations were developed based on the solubility of indomethacin in blends. The proposed formulations are shown in table 5, 6 and 7.

Table 5: Formulation DPF1

S. No.	Ingredients	Formula for 25 mg / 1 ml	Formula for50 ml batch
1	Indomethacin	25 mg	1.25 g
2	Sodium Caprylate	100 mg	5.0 g
3	Sodium Benzoate	25 mg	1.25 g
4	Sodium Citrate	25 mg	1.25g
5	Lysine HCl	25 mg	1.25g
6	β-cyclodextrin	25 mg	1.25g

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 2 Mar-Apr 2021, pp: 314-326 www.ijprajournal.com ISSN: 2249-7781

Table 6: FormulationDPF2

S. No.	Ingredients	Formula for 25 mg / 1 ml	Formula for 50 ml batch
1	Indomethacin	25 mg	1.25 g
2	Sodium Caprylate	100 mg	5.0 g
3	Sodium Benzoate	25 mg	1.25g
4	Niacinamide	25 mg	1.25g
5	Lysine HCl	50 mg	2.5g

Table 7: FormulationDPF3

S. No.	Ingredients	Formula for 25 mg / 1 ml	Formula for 50 ml batch
1	Indomethacin	25 mg	1.25g
2	Sodium Caprylate	100 mg	5.0g
3	Poloxamer 407	50 mg	2.5g
4	Niacinamide	25 mg	1.25 g
5	Lysine HCl	25 mg	1.25g

2.2.9. Formulation of dry powder injection for reconstitution

The dry powder injections for reconstitution were formulated according to the formulation detail given in above tables, the procedure is given below. To individually minimize the particle size, all the solubilizers were passed through sieve no 80. The required amounts of all excipients and drugs were then weighed and mixed by geometric dilution method with the help of mortar andpestle." The mixed blend was again passed through sieve no 80 and mixed manually in a plastic bag of suitable size. The prepared formulation was then transferred to vials in required amount for stability study and vials were capped and sealed immediately. [Formulation DPF1-225 mg per vial, formulation DPF2-225 mg per vial and formulation DPF3-225 mg pervial.]. Each vial was having 25 mg indomethacin.

2.2.10 Evaluation of dry powder injection for reconstitution

The prepared formulations were subjected for various evaluation parameters

a) Determination of pH of reconstitutedinjection

The developed formulations were reconstituted by use of MillI-Q water and 10 ml volume was taken to determine the pH by using digital pH meter (Cyber Scan 510, Eutech Instruments, Singapore). The results are shown in table 8.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 2 Mar-Apr 2021, pp: 314-326 www.ijprajournal.com ISSN: 2249-7781

Table 8: pH values of reconstituted injection formulations

Formulationcode	pH
DPF1	6.4
DPF2	6.3
DPF3	6.5

b) Determination of reconstitution time

To determine the reconstitution time, Milli-Q water (1 ml) was used to dissolve the dry injection formulation (by manual shaking) for all the batches and time were noted to obtain a clear solution. The reconstitution times obtained were recorded in table 9.

Table 9: Reconstitution times of various formulations

Formulation code	Reconstitution time
DPF1	1 min 40 sec
DPF2	1 min 45 sec
DPF3	1min 30 sec

c) Clarity testing of reconstituted injection

Clarity test of reconstituted product was performed by visually inspecting the externally clean vial viewed against black and white background under good light.

Results of the clarity testing of the reconstituted developed injection formulation are shown in table 10.

Table 10: Clarity of various reconstituted injections

Formulation code	Clarity
DPF1	Clear
DPF2	Clear
DPF3	Clear

2.2.11 Dilution study of reconstitutedinjection

Series of dilutions were done by diluting reconstituted injection of indomethacin (formulation DPF_1, DPF_2, and DPF_3) with different diluents, normal saline (0.9% NaCl) and 5% dextrose solution. The diluted products were observed for any precipitation up to 24 hours. The observations were recorded in Table 11, 12 and13.

Table 11: Dilution profile of reconstituted solution of formulation DPF1

Dilution	Time (hrs.)											
	Normal saline solution						5% Dextrose solution					
	1	2	4	6	8	24	1	2	4	6	8	24
1:1	-	-	-	-	-	-	-	-	-	-	-	-

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 2 Mar-Apr 2021, pp: 314-326 www.ijprajournal.com ISSN: 2249-7781

1:5	-	-	-	-	-	-	-	-	-	-	-	-
1:10	-	-	-	-	-	-	-	-	-	-	-	-
1:20	-	-	-	-	-	-	-	-	-	-	-	-
1:30	-	-	-	-	-	-	-	-	-	-	-	-
1:40	-	-	-	-	-	-	-	-	-	-	-	-
1:50	-	-	-	-	-	-	-	-	-	-	-	-
1:100	-	-	-	-	-	-	-	-	-	-	-	-
1:500	-	-	-	-	-	-	-	-	-	-	-	-

(-) No precipitation, (+) Precipitation

Table12 : Dilution profile of reconstituted solution of formulation DPF2

Dilution	**Time (hrs.)**											
	Normal saline solution						**5% Dextrose solution**					
	1	**2**	**4**	**6**	**8**	**24**	**1**	**2**	**4**	**6**	**8**	**24**
1:1	-	-	-	-	-	-	-	-	-	-	-	-
1:5	-	-	-	-	-	-	-	-	-	-	-	-
1:10	-	-	-	-	-	-	-	-	-	-	-	-
1:20	-	-	-	-	-	-	-	-	-	-	-	-
1:30	-	-	-	-	-	-	-	-	-	-	-	-
1:40	-	-	-	-	-	-	-	-	-	-	-	-
1:50	-	-	-	-	-	-	-	-	-	-	-	-
1:100	-	-	-	-	-	-	-	-	-	-	-	-
1:500	-	-	-	-	-	-	-	-	-	-	-	-

(-) No precipitation, (+) Precipitation

Table 13: Dilution profile of reconstitution solution of formulation DPF3

Dilution	**Time (hrs.)**											
	Normal saline solution						**5% Dextrose solution**					
	1	**2**	**4**	**6**	**8**	**24**	**1**	**2**	**4**	**6**	**8**	**24**
1:1	-	-	-	-	-	-	-	-	-	-	-	-

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 2 Mar-Apr 2021, pp: 314-326 www.ijprajournal.com ISSN: 2249-7781

1:5	-	-	-	-	-	-	-	-	-	-	-	-
1:10	-	-	-	-	-	-	-	-	-	-	-	-
1:20	-	-	-	-	-	-	-	-	-	-	-	-
1:30	-	-	-	-	-	-	-	-	-	-	-	-
1:40	-	-	-	-	-	-	-	-	-	-	-	-
1:50	-	-	-	-	-	-	-	-	-	-	-	-
1:100	-	-	-	-	-	-	-	-	-	-	-	-
1:500	-	-	-	-	-	-	-	-	-	-	-	-

(-) No precipitation, (+) Precipitation

2.2.12. Thin layer chromatographicstudies

In order to examine the possibility of interaction between drug and solubilizers, thin layer chromatographic studies were performed. A plate of silica gel GF 254 was activated at 110℃ for 1 hour and then used. The solution of indomethacin in ethanol alone and the aqueous solution solubilizers containing indomethacin in B-2, B-12, B-13 were spotted with the aid of microdropper on the base line. Then, the plate was left in air for sufficient time to dry and transferred to a solvent jar saturated with the solventsystem.

The solvent system was allowed to run for about 4 cm. Finally, the plate was allowed to air dry for sufficient time and was observed for visualization of spots under iodine chamber. The results of TLC study revealed that there is no significant change in R_f values of indomethacin solubilized in blend solutions. From the results of TLC study, it can be concluded that there is no reaction of drug(indomethacin) with solubilizers. The respective R_f values were determined and recorded in table 14.

Table 14: R_f values of indomethacin in TLC study

Solvent system	**Adsorbent**	**R_f value**			
		Drug	**DPF1**	**DPF2**	**DPF3**
Sodium caprylate (20% w/v)	Silica Gel GF 254	0.40	0.41	0.40	0.42

III. RESULTS AND DISCUSSION

The UV visible spectroscopy of indomethacin showed peak at 320nm, which is same as reported in literature (fig. 01). The DSC spectrum of indomethacin was same as reported in literature and principal peak was obtained at 160.46^{o}C. DSC curve was shown in figure 2. The melting point of indomethacin was found to be 158 ^{o}C. From the calibration curve, equation is given as $y = 0.0203x - 0.0041$. The value of R^2 is 0.9995. On the basis of obtained result, it was concluded that indomethacin, obeyed Beers Lamberts law in the range of 10 mcg/ml to 50 mcg/ml. Hence, it was inferred that the procured drug sample was pure indomethacin and hence used for further studies. Desired solubility was observed in three blends which are Blend-2, Blend-12, Blend-13. These blends were selected for the batch formation and were examinedfor different parameters. Solubilities were recorded in table 2. Dilution studies indicated that the formulations (DPF_1, DPF_2, and DPF_3) were stable (up to 24 hours) against precipitate formation in normal saline solution and 5% dextrose solution. In the case of batch formulation DPF_1, DPF_2, and DPF_3, no precipitations were found in any dilution ratio and results are shown in table 11,12 and13.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 2 Mar-Apr 2021, pp: 314-326 www.ijprajournal.com ISSN: 2249-7781

IV. CONCLUSION

Mixed solvency concept has nicely been applied to formulate dry powder injection for reconstitution ofindomethacin. The problem of instability of drug in readymade injections can be solved by making dry powder injection for reconstitution of several poorly water soluble drugs using solid solubilizers (mixed solvency concept).

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