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## FORMULATION AND DEVELOPMENT OF HIGH CONCENTRATION DICLOFENAC SODIUM INJECTION USING MIXED SOLVENCY CONCEPT AND ITS EVALUATION

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### ABSTRACT

The objective of Present research is explore the application of mixed solvency concept in formulation development of injectable dosage form and to provide single dose aqueous injection formulation (in the form of aqueous solution) of sparingly soluble salt of diclofenac in concentration of 75mg/ml, which cause significantly less pain at site of administration and can be administered by intradeltoid route, in addition to intragluteal and slow IV route. Mixed Solvency concept proposed the every substance present on the earth whether solid, liquid or gas posses solubilising power. Hence for the first time solid solublisers were introduced for formulation development of diclofenac sodium injection (75mg/ml). Present study suggests that diclofenac can be solubilised in maximum concentration of 115 mg/ml in solution of niacinamide and caffeine (10% w/w of each solublisers). It is important to note that caffeine is itself poorly water soluble substance. Niacinamide act as a solvent for caffeine and then both solids solublises diclofenac sodium.

**Keywords:** Diclofenac sodium, Caffeine, Injection, Mixed solvency.

### INTRODUCTION

Diclofenac injections have to be administered deep intramuscularly and are generally administered intragluteally as the injection causes substantial pain at the site of injection and its administration in the deltoid (upper arm) region is generally avoided. Pain at the site of injection is due to relatively large volume of the injection (3ml) and the fact that the injection solution contains relatively high volumes of propylene glycol, which is a known irritant upon parenteral administration and it also increases viscosity of the formulation.

On the other hand intramuscular injection volumes above 2 ml and up to 5 ml must be administered into the gluteal muscle, this is because; the gluteal muscle is larger as compared to the deltoid muscle and hence can accommodate the relatively larger injected volume (3-5ml). On the other hand if this relatively larger volume is injected into the deltoid muscle, which has relatively lesser(i)

muscle mass, the injected solution will cause excessive stretching of the muscle fiber, thereby damaging the local muscle tissue and hence cause pain and discomfort to the patient. The present research attempts to provide diclofenac sodium injection in concentration of 75 mg and reducing the overall volume of injection to 1 ml resulting in the minimization of pain at site of injection using solid solublisers as proposed in mixed solvency concept. In another strategy combination of liquid solublisers such as transcutol hp, PEG 400 and ethanol along with solid solublisers were used to solubilise diclofenac sodium.

### MATERIAL AND METHOD

All the materials and sterile facility for research is provided by M/S Akums drugs and pharmaceuticals limited Ltd Haridwar. Three consecutive batches two different composition of formulation were prepared.

(ii) **Preparation of various blends of solubilizer:** Solid solubilizers were screened on the basis of review of mixed solvency concept such as PVP k-30, lignocaine HCl, niacinamide, sodium benzoate, caffeine, sodium citrate, sodium acetate in concentration of 5% of each solubilizer. To prepare 100 ml blend, 5 gm of each solubiliser was accurately weighed and taken in 100 ml volumetric flask and dissolved in 80 ml de-mineralised by shaking. Volume was made up to the mark with de-mineralised water.

(iii) **Solubility studies:** Solubility of diclofenac sodium was determined using approximate technique. To determine solubility 5 ml of solvent was taken in a clear glass vial and accurately weighed drug (10 mg) was dissolved in the solvent system and the vial was shaken to dissolve the drug. As soon as clear solution is obtained, again 10 mg (accurately weighed) drug was added and the process was repeated till saturation (nearly). Total weighed quantity of drug dissolved in 5 ml solvent was considered to be approximate solubility of diclofenac sodium in respective solvent system.

(iv) **TLC study:** In order to examine the possibility of interaction between drug and solubilisers, thin layer chromatographic studies were performed. A plate of silica gel GF 254 was activated at 110°C for 1 hour and then used. The methanolic solution of diclofenac sodium alone, the aqueous solution of hydrotropic solution as well as solubilized product of diclofenac sodium in blend 7 (5% caffeine + 5% niacinamide) solution were spotted on the base line with the aid of microdropper. Then, the plate was left in air for 10 min to dry and transferred to a solvent jar saturated with solvent system composed of mixture of chloroform, acetone and formic acid solution (90: 5: 5). The solvent system was allowed to run for about 4 cm. Finally, the plate was allowed to air dry for 5 min and observed under UV light for visualization of spots. The respective  $R_F$  values were determined.

(v) **Optimization of solubiliser concentration for development of aqueous injection.** Strategy I: Caffeine and niacinamide were proposed as novel solubilisers for diclofenac sodium and their concentrations to be used to formulate solution which is stable in freeze thaw study is determined on basis of trial and error. (F1 to F7) Strategy II: Transcutol HP, PEG 400 and glycofurol were used as solubilisers. (F8 to F12). Strategy III: Combination of solid and liquid solubilisers were studied for formulation development of aqueous injections. (F13 to F22)

(vi) **Freeze thaw study of various trial formulations:** Freeze thaw study was selected as a primary screening procedure for optimization of concentration of various solubilisers. This method was designed to simulate storage and temperature conditions and to induce any anticipated precipitation and check it in a much shorter time. The vials were kept alternately at  $40 \pm 1^\circ\text{C}$  and  $4 \pm 1^\circ\text{C}$  for 24 hour

each, and shaken everyday for 5 minutes on a touch type vortex mixer. Two vials of formulation were taken, one of which was kept at  $40 \pm 1^\circ\text{C}$  and the other at  $4 \pm 1^\circ\text{C}$  for first day, followed by subsequent temperature cycling and shaking as described. After 7-7 such cycles at  $4 \pm 1^\circ\text{C}$  and  $40 \pm 1^\circ\text{C}$  (alternately), the vials were observed to check turbidity and precipitation, if any.

(vii) **Viscosity study of optimized trials.**

Viscosity parameter is selected as a secondary screening procedure for optimized formulation of suitable solubiliser concentration. Viscosity was determined on Brookfield viscometer DV 2+ pro using spindle no.00 Viscosity at maximum torque was recorded.

(viii) **pH study of optimized trial**

pH stability of developed formulations was determined using digital pH meter (Cyber scan 510), previously calibrated using standard buffer solution.

(ix) **Optimized formula**

The injection formulae which were found satisfactory in freeze thaw, pH and viscosity study (trial no. F7 and F22) was considered as optimized formula for further study.

**Formulation of aqueous injection**

Three Pilot batches (Batch size 2.0 litre) of optimized aqueous injection formula was prepared in Grade C area at the temperature NMT  $25^\circ\text{C}$  and RH 45%  $\pm 5\%$  and positive pressure maintained at processing area. Protective secondary gowning and safety goggles were used properly. All the utensils used were washed with WFI followed by 70 % IPA and dried at  $121^\circ\text{C}$  for 30 min. Type I glass, clear ampoules were used for filling. Filling was carried out under sodium vapour lamp with continuous nitrogen purging.

(x) **Analysis of bulk solution:** The pH (using digital pH meter, Eutech instruments), Density (using RD bottle), assay (using HPLC method) and description test of bulk solution was done

(xi) **Accelerated stability studies:** As soon as product is developed, it is subjected to ageing. Its physical properties, chemical composition and even biological availability may change. The prepared formulations were subjected to  $40^\circ\text{C}$  75% RH to observe stability of drug on proposed formulation. Samples were withdrawn at 1 month 3 months, and 6 months and analysed using Shimadzu HPLC (Model LC20A system.). Percent drug residual at definite time interval were recorded using HPLC method for diclofenac sodium injection as per IP 2014.

(xii) **Physical stability testing of formulated injections:** The vials samples of formulations (20 sample of each batch) were kept at room temperature (RT),  $40^\circ\text{C}/75\%$  RH and  $2-4^\circ\text{C}$ . For physical stability studies, the samples were

observed at definite time intervals for colour change and clarity (to observe any turbidity or precipitation).

(xiii) **pH stability study of formulation:** Injection formulations were subjected to pH stability study for period of 3 months. pH was measured using digital pH meter (Eutech instruments), which was calibrated using standard buffer solution at each time interval.

(xiv) **Osmolarity:** Osmolarity of formulation F7, F22 and marketed product Dynapar AQ was determined using freezing point based osmometer, Advance instruments (Model 33201).

## RESULTS AND DISCUSSION

**Solubility study:** Highest solubility observed in blend of caffeine and niacinamide.

(i) **TLC study:** The results of TLC study revealed that there is no considerable change in  $R_F$  values of diclofenac sodium solubilized in methanol and diclofenac sodium solubilized in solubliser blend solution. From the results of TLC study, it can be concluded that there is no salt formation or complexation of drug and solubliser molecule.

(ii) **Freeze thaw study :** Trial F7, F11, F12 and F22 were found to be stable during entire freeze throw study. No precipitation and turbidity was found in all four formulations.

(iii) **Viscosity:** Viscosities of formulation F7 and F22 were found satisfactory, hence both formulations were considered as optimized formulations.

(iv) **pH study:** pH of all 4 formulation found in range of 8 to 9 as given by IP monograph.

(v) **Analysis of bulk solution:**

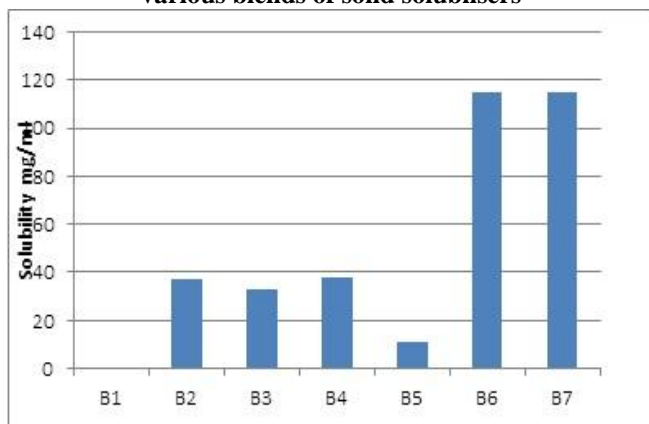
(vi) **Accelerated stability studies using HPLC:**

(vii) **Physical stability study:** Both the injection formulations were found to be unaffected in respect of colour stability at all taken temperature conditions for period of 30 days. No visual colour change or precipitate was observed in the developed formulations.

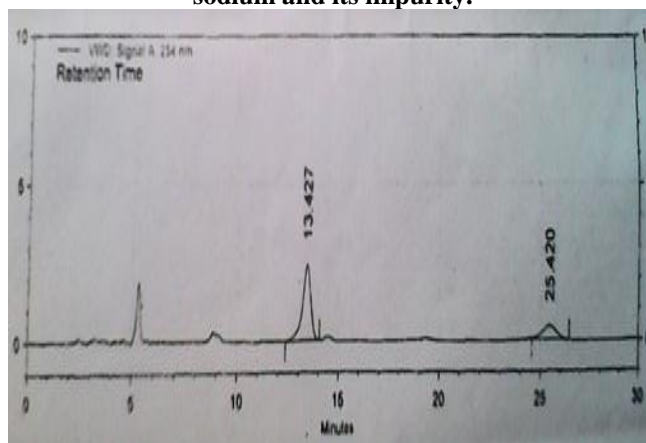
(viii) **pH stability study of formulation:** The pH values of all three batches of formulation F7 were found to be in range as provided in I.P 2014 monograph i.e 8.0 to 9.0 but pH values of formulation F22 was found out of the range.

(ix) **Osmolarity:** Osmolarity of proposed formulations F7 and F22 were found to be less as compared to osmolarity of reference product Dynapar AQ.

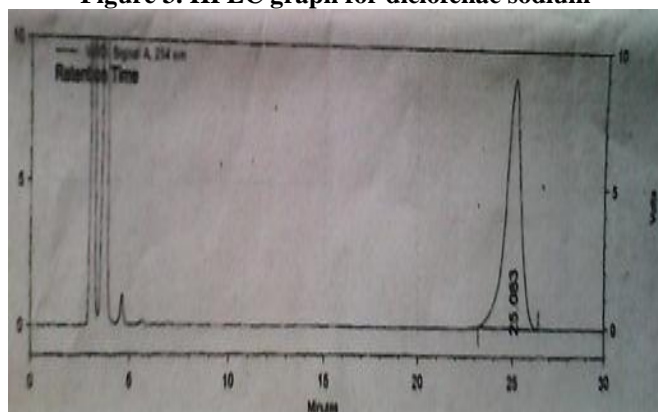
**Figure 1. Solubility profile of diclofenac sodium in various blends of solid solublisers**



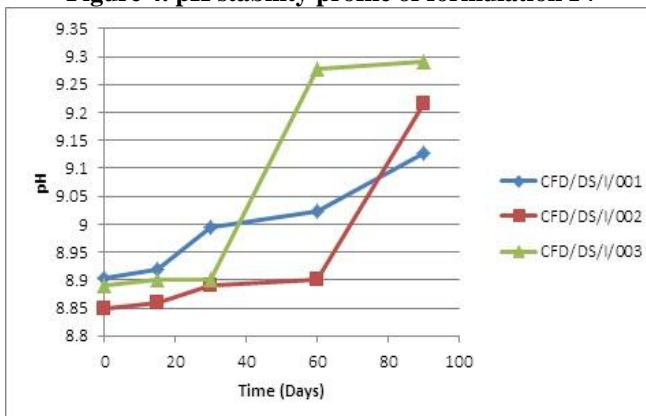
**Figure 2. HPLC graph for resolution between diclofenac sodium and its impurity.**

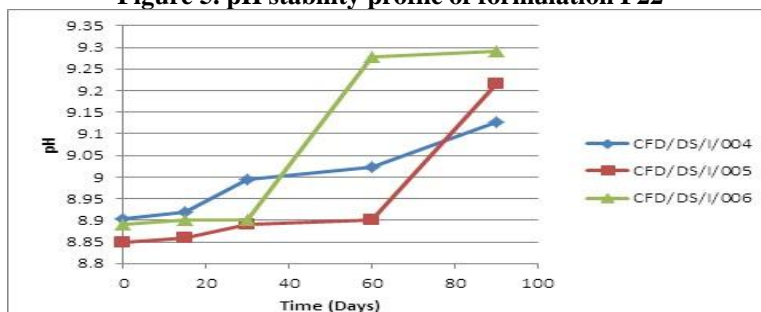


**Figure 3. HPLC graph for diclofenac sodium**



**Figure 4. pH stability profile of formulation F7**



**Figure 5. pH stability profile of formulation F22****Table 1. Composition of various aqueous solutions containing blends of solid solubilisers.**

S.NO	Blend	5% each solubiliser
1.	B1	PVP k-30 + lignocaine + niacinamide + Sodium benzoate
2.	B2	PVP k-30 + niacinamide + sodium benzoate
3.	B3	PVP k-30 + sodium citrate + niacinamide + sodium benzoate
4.	B4	PVP k-30 + niacinamide + sodium benzoate(10%)
5.	B5	PVP k-30 + sodium citrate + sodium acetate
6.	B6	PVP k-30 + caffeine + niacinamide + sodium benzoate
7.	B7	caffeine + niacinamide

**Table 2. Composition of formulations (Trial F1 to F7)**

S.No	Ingredient	Quantity (% w/v)						
		F1	F2	F3	F4	F5	F6	F7
1.	Diclofenac sodium	7.5	7.5	7.5	7.5	7.5	7.5	7.5
2.	Niacinamide	5	5	7.5	7.5	7.5	10	10
3.	Caffein	5	7.5	5	7.5	10	7.5	10
4.	Sodium sulfite	0.1	0.1	0.1	0.1	0.1	0.1	0.1
5.	Benzyl alcohol	2	2	2	2	2	2	2
6.	Water for injection	qs	qs	Qs	qs	qs	qs	Qs

**Table 3. Composition of formulations (Trial F8 to F12)**

S.No	Ingredient	Composition (%w/v)				
		F8	F9	F10	F11	F12
1.	Diclofenac sodium	7.5	7.5	7.5	7.5	7.5
2.	Transcutol HP	5	10	15	20	30
4.	PEG 400	-	3	5	7	15
5.	Benzyl alcohol	4	4	4	4	4
6.	Sodium sulfite	0.1	0.1	0.1	0.1	0.1
7.	Water for injection	qs	Qs	qs	qs	Qs

**Table 4. Composition of formulations (Trial F13 to F22)**

S.No	Ingredient	Composition (%w/v)									
		F13	F14	F15	F16	F17	F18	F19	F20	F21	F22
1.	Diclofenac sodium	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
2.	Niacinamide	2.5	2.5	2.5	5	10	10	10	10	10	2.5
3.	Caffein	2	2	2	5	5	5	5	5	5	5
4.	PEG 400	5	-	-	5	-	5	-	-	-	5
5.	Transcutol HP	5	-	10	5	5	5	-	-	10	10
7.	Ethanol	-	-	-	-	-	-	-	10	10	10
8.	Sodium sulfite	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
9.	Benzyl alcohol	2	2	2	2	2	2	2	2	2	2
10.	Water for injection	qs	qs	qs	qs	qs	qs	qs	qs	qs	Qs

**Table 5. BOM for formulation F7 (BatchDS/I/ 001, 002, 003)**

S.NO	Ingredient	Std.	Qt/ml	Qt for 2.0 litre	Category
1.	Diclofenac Sodium	I.P	75 mg	152.47 gm	Active
2.	Caffeine	I.P	100 mg	200 gm	Solubliser
3.	Niacinamide	I.P	100 mg	200 gm	Solubliser and stabilizer
4.	Sodium sulfite	I.P	1 mg	2 gm	Antioxidant
5.	Benzyl alcohol	I.P	0.02 ml	40 ml	Preservative
6.	Water for injection	I.P	1 ml (qs)	2.0 litre (qs)	Vehicle

**Table 6. BOM for formulation F22 (Batch DS/I/004,005,006)**

S.NO	Ingredient	Std.	Qt/ml	Qt for 2.0 litre	Category
1.	Diclofenac Sodium	I.P	75 mg	152.47 gm	Active
2.	Caffeine	I.P	100 mg	200 gm	Solubliser
3.	Niacinamide	I.P	100 mg	200 gm	Solubliser and stabilizer
4.	PEG 400	-	0.05 ml	100 ml	Solubliser
5.	Tansculol HP	-	0.1 ml	200 ml	Solubliser
6.	Ethanol	I.P	0.1 ml	200 ml	Solubliser
7.	Sodium sulfite	I.P	1 mg	2 gm	Antioxidant
8.	Benzyl alcohol	I.P	0.02 ml	40 ml	Preservative
9.	Water for injection	I.P	1 ml (qs)	2.0 litre (qs)	Vehicle

**Table 7. Solubility results in various blends**

S.NO	Blend	Solubility (mg/5ml)	Solubility (mg/ml)
1.	B1	Precipitation is observed	Precipitation is observed
2.	B2	185	37
3.	B3	165	33
4.	B4	190	38
5.	B5	55	11
6.	B6	575	115
7.	B7	575	115

**Table 8. R<sub>F</sub> values of diclofenac sodium and solubilized product**

S. No.	System	R <sub>F</sub>
1.	Drug in methanol	0.69
2.	Drug in blend 7	0.70

**Table 9. Viscosity result formulations**

S.No	Formulation	Viscosity	RPM	Torque	Temperature
1	F7	2.56 CPS	80	90.5 %	27.6 °C
2	F11	7.98 CPS	120	98.1 %	28 °C
3	F12	8.77 CPS	60	79.8 %	28 °C
4	F22	3.13 CPS	160	83.6 %	26.3 °C

**Table 10. PH result of various optimized formulations.**

Formulation	pH
F7	8.51
F11	8.77
F12	8.80
F22	8.74

**Table 11. Result of analysis**

B.No	Description	Wt/ml	pH	Assay
DS/I/001	Slightly faint colour	1.08 gm/ml	8.515	100.35%
DS/I/002	Slightly faint colour	1.08 gm/ml	8.490	103.93%
DS/I/003	Slightly faint colour	1.09 gm/ml	8.508	101.03%

DS/I/004	Very slightly yellow colour	1.079 gm/ml	8.903	98.34%
DS/I/005	Very slightly yellow colour	1.072 gm/ml	8.859	96.16%
DS/I/006	Very slightly yellow colour	1.077 gm/ml	8.890	99.12%

**Table 12. Chemical stability data of diclofenac sodium in formulation F7 and F22**

Batch No.	Time	% drug remaining (40°C and 75% RH)
DS/I/001	Initial	100.35 %
	1 month	99.29 %
	2 month	99.23
	3 month	98.15 %
DS/I/002	Initial	103.93 %
	1 month	100.00 %
	2 month	99.54 %
	3 month	98.94 %
DS/I/003	Initial	101.03 %
	1 month	99.78 %
	2 month	99.32 %
	3 month	99.16 %
DS/I/004	Initial	98.34 %
	1 month	98.16 %
	2 month	96.29 %
	3 month	96.16 %
DS/I/005	Initial	97.85 %
	1 month	96.01%
	2 month	95.47%
	3 month	95.30 %
DS/I/006	Initial	99.12%
	1 month	98.58 %
	2 month	97.49
	3 month	96.43 %

**Table 13. pH stability data of diclofenac sodium injection formulation**

Batch No.	pH				
	Initial	15 days	30 days	60 days	90 days
CFD/DS/I/001	8.515	8.517	8.523	8.600	8.675
CFD/DS/I/002	8.490	8.499	8.500	8.521	8.679
CFD/DS/I/003	8.508	8.654	8.658	8.891	8.990
CFD/DS/I/004	8.903	8.919	8.994	9.023	9.127
CFD/DS/I/005	8.849	8.859	8.890	8.900	9.216
CFD/DS/I/006	8.890	8.900	8.900	9.279	9.290

**Table 14. Osmolarity result of various marketed and prepared formulation**

S.No	Formulation	Osmolarity
1.	Dynapar AQ	1559 mosm/kg
2.	Voveran	Sample do not freeze.
3.	F7	421 mosm/kg
4.	F22	1256 mosm/kg

## CONCLUSION

The objective of the present research is to explore the application of mixed solvency technique in the formulation of injection dosage form of water- insoluble drug diclofenac sodium and to reduce concentration of

individual solubliser to minimize the side effects. Every substance has solublising power and hence various solid solublisers can be screened for their use in various pharmaceutical formulations.

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