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Formulation development and evaluation of diclofenac sodium injection using benzyl alcohol (co-solvent), mixed solvency concept

Yasir Mehmood

ABSTRACT

Introduction: Mixed solvency is a concept of solubilization of the material. For producing new formulation, especially in the form of injection it is essential to solubilize the active pharmaceutical ingredients (API) in the solvent and that must be stable throughout the shelf life. Aqueous solubility of raw materials is important for injection formulation, but in some cases if the drug is not soluble in water, oil can be used for drug solubility. In this present investigation, mixed-solvency approach has been applied for the enhancement of aqueous solubility of poorly water-soluble drugs, diclofenac sodium (selected as a model drug). Those drugs that poorly soluble in aqueous media are required fractioned oil to enhance its solubility. In most of the cases to make raw materials soluble in water, solubilizing agent in high concentration (co-solvent and surfactant) are use for drug solubility. But due to high concentration of co-solvent and use of oil can make more painful to inject. In the present study, we formulated the diclofenac sodium injection without using high concentrations of propylene glycol as co-solvent which is used in conventional formulation. Benzyl alcohol is used as preservative in conventional formulation and in this formulation benzyl alcohol uses as co-solvent for diclofenac sodium in aqueous medium and due to this, injection is less painful then propylene glycol based injection. At the end, we studied the stability, toxicity, pyrogenicity and isotonicity of the formulated injection. Conclusion: From the various formulation studied, it was found that benzyl alcohol (6–7% v/v) is good and save solubilizing agent for preparation of injection dosage form of diclofenac sodium. This mixed solvency shall prove definitely a boon for pharmaceutical industries for the development of dosage form of poorly water soluble drugs.

Keywords: Mixed solvency, Diclofenac Sodium, Benzyl alcohol

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INTRODUCTION

Formulation has numerous benefits in drug discovery and development. It enables efficacy, toxicity, and pharmacokinetic (PK) studies. Formulation can improve oral bioavailability, shorten onset of a therapeutic effect, enhance stability of drugs, and reduce dosing frequency. More consistent dosing can be achieved by reducing food effect through formulation [1]. A drug molecule has to be water soluble to be readily delivered to the cellular

membrane while retaining its hydrophobic properties and water insolubility can postpone or completely derail–important new drug formulation [2]. So, there is a much needed reformulation of currently marketed products and can be significantly affected by these type of issues. Maheshwari R. K. gives the concept of mixed solvency [3]. According to his opinion that all the substances solids, liquids and gases possess solubilizing ability and hence aqueous solutions, containing different dissolved substances can also enhance the solubility of poorly water-soluble drugs [4]. An intramuscular (IM) medication is given by needle into the muscle. It can be a solution, oil, or suspension. Drugs in aqueous solution are rapidly absorbed. However, very slow constant absorption can be obtained if the drug is administered in oil or suspended in other repository vehicles. Solubility may also be enhanced by altering the pH and using co-solvents but excess amount of these agents may have adverse effects. The vehicle should contain a minimum amount and low concentration of the co-solvent to reduce viscosity and toxicity effects. Polyethylene glycol 600, polyethylene glycol 800, and polyethylene glycol 400 used as co-solvent. Mixed solvency is the phenomenon to increase the solubility of poorly soluble drugs, using blends of solubilizing agents [5]. This technique gives the idea that additive or synergistic enhancement effect on solubility of poorly soluble drugs. By using this method in the formulation of different dosage forms made of insoluble drugs soluble and can reduce the concentration of solubilizing agents that are use in the formulation for its solubility in different solvent and minimize the side effects. In most of the conventional formulation of injection of diclofenac sodium propylene glycol is use as solubilizing agent [6]. The concentration of propylene glycol is used 25–30% [7] Urea (M.P. 130–135°C) dissolves diclofenac sodium (M.P. 283°C). This shows that melted urea act as solvent for diclofenac sodium. In supercritical fluid technology liquefied carbon dioxide acts as solvent for many insoluble substances [8]. These indicate that all substances possess some solvent character. All weaker solvents can be made strong solvent by proper selection of co-solvent. Mixed hydrotropy is another type of co-solvency [3]. Hydrotropic agents also increase the solubility of poorly water-soluble drugs [9]. Hydrotropy or mixed hydrotropy also used to enhance the aqueous solubility of poorly soluble drugs [10]. The present research is to explore the application of mixed solvency technique in the injection formulation of poorly water-soluble drug [11]. The formulation was also studied for physical and chemical stability. Diclofenac sodium is pain killer and indicated for the treatment of relative humidity rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, tendinitis, bursitis and acute gout. It is also indicated in the relief of mild to moderate pain and the treatment of primary dysmenorrhea [12].

MATERIALS AND METHODS

The gift sample of diclofenac sodium was provided by Ameer pharmaceuticals Pvt. Limited, Lahore, Pakistan. Benzyl alcohol, sodium hydroxide and sodium metabisulphite were purchased from local market. All other chemicals and solvents used were of analytical grade. Other material and instruments include Spectrophotometer (UV-1800, Shimadzu, Japan), FTIR (Agilent 4500 Series Portable FTIR Spectrometer), limulus amebocyte lysate reagent, sterility media, NaOH, glass ampoules, rabbit, pyrogen meter (panomax PX/PTA-461 china), stability chamber (Darwin Chambers - PH030), HPLC (DYNAMIC UV1) and pH meter (Hanna pH meter model HI 9025C).

Solubility studies

Solubility studies of diclofenac sodium were performed in aqueous with different concentration of benzyl alcohol; solution containing different concentration of solubilizing agent (benzyl alcohol). Various concentration of mixed blends were prepared for solubilization of diclofenac sodium (Table 1). Solubility of diclofenac sodium in water using different concentration of benzyl alcohol was determined by stirrer mixing method. For adjusting the required pH SMS and NaOH were added. Different solution were prepared and observed by naked eye for its solubility. Filter all the good solution with 0.2 micron filter paper and about 3 ml of each solution was taken in a ampoule separately. Ampoules were properly sealed by the machine. They were kept in orbital flask shaker maintained at 25°C for 12 hr. The solution was then allowed to equilibrate for 24 hr (undisturbed). After this, the ampoules were kept in stability chamber at 40°C and relative humidity 70% for six weeks. The supernatant was suitably diluted with ethanol and analyzed using UV/Visible spectrophotometer (Shimadzu) at 277 nm against respective reagent blanks.

Procedure for preparation of solution

Add water for injection about 70% of the batch size having 60°C temperature in a glass beaker and kept glass beaker on the magnetic stirrier device. Provide continuous nitrogen purging for about 10 minutes. Processing continues under nitrogen purging. Now add gradually weighed quantity of diclofenac sodium to the WFI and mixing was allowed for several minutes. The solution was then filtered with 0.45 µ filter paper and made up to 100% volume with WFI. This solution allows cooling at room temperature. Now start to add benzyl alcohol in the solution until the clear of the solution obtain. After clarity of the solution add SMS and NaOH in the solution for adjusting the pH. The pH was then adjusted near to 8.0. Stir the solution at room temperature. Now start to add benzyl alcohol in the solution until the clear solution is obtain. After clarity of the solution add SMS and NaOH in the solution for adjusting the pH. The solution was stirred

until all the SMS and NaOH was dissolved. The pH was then adjusted near to 8.0. The resultant diclofenac sodium solutions were sterilized by filtration with 0.22 μm filters or sterilized by the autoclave 121°C for 15 minutes now fill and sealed it in transparent glass ampoules. The prepared solution was evaluated for various physical and chemical parameters. For each parameter, average values of two samples were considered until all the SMS and NaOH was dissolved (Tables 2, 3).

Evaluation of formulation batches

Physical appearance: Prepared solution of Diclofenac sodium injection was visually observed with naked eye for their physical appearance or its solubility at initially and after 6 weeks of time interval.

pH measurement: The pH of the prepared formulations was measured using pH meter at 25±1°C.

Particulate matter: The particulate matter in the formulation can be determined by the visual inspection by naked eye under direct light beam.

Assay content for diclofenac sodium

Analysis method for diclofenic sodium injection

Each ampoule (3 ml) contains diclofenac sodium 75 mg.

Sample Preparation: Transfer 2 ml of solution equivalent to 50 mg of diclofenac sodium to a 100 ml volumetric flask. Dilute it to volume with the methanol. Dilute 1 ml of solution to 50 ml with the methanol.

Standard Preparation: Transfer 50 mg of diclofenac sodium to a 100 ml volumetric flask. Dilute it to volume with the methanol. Dilute 1 ml of solution to 50 ml with the methanol. Measure the absorbance of both sample and standard solution at ultraviolet-visible spectrophotometer at 277 nm.

Calculations

Observations

(a) Absorbance of sample solution = A
(b) Absorbance of standard solution = B
(c) Record the reading.

Calculations

$$\frac{A}{B} \times 100 = c$$

Limit: 90–110%

RESULTS AND DISCUSSION

Physical appearance

Physical appearance (transparency, color, precipitation, etc.) of prepared formulations or solution was studied. Batch D3 and D4 appeared colorless and clear initially as well as after six week of interval at 25°C/60% relative humidity and 40°C/75% relative humidity (Table 4).

pH Measurement

The pH of all the formulations was set initially in the range of 7.5–8.1. The pH of the prepared solution initially and after six weeks of interval was measured which are given in Table 5.

Accelerated Stability Studies

When the product is developed, it was subjected to getting a result, because after some time its physical properties, chemical proprieties and even its biological availability may be changed. The prepared formulations were subjected to 2–8 C, 25C, 40C and 55C with 70% relative humidity to observe the stability of medicament in developed formulations Table 6. Samples were withdrawn after 7, 14, 21 and 28 days and analyzed spectrophotometrically at 277 nm after suitable dilution with ethanol to determine content of drug. The initial composition in the formulation was taken as 100% (Tables 7, 8).

Effect of sunlight on drug degradation

One set of colorless vials containing the formulations were exposed to sunlight to estimate the effect of light on the stability of formulations. Other set of colorless vials containing formulation were wrapped with aluminium foil (controlled) and stored in dark. Both sets of vials were stored at room temperature. One vial of each formulation and each set was withdrawn every seventh day up to 28 days, suitably diluted with ethanol and observes at 277 nm under ultraviolet/visible spectrophotometer (Shimadzu) to determine the drug remained. The initial drug content of formulations was taken as 100% for the study (Figure 1, 2).

Effect of atmospheric oxygen on stability

To assess the effect of oxygen, the injection (3 ml) was filled in 5 ml and 20 ml vials. The air in 20 ml capacity ampoules was not displaced before sealing, whereas the air present in the 5 ml capacity vials was replaced by flushing with nitrogen and sealed. Samples from both sets of vials were withdrawn periodically at seventh-day intervals and the drug content was estimated

CONCLUSION

From the various formulation studied, it was found that benzyl alcohol(6–7% v/v) is good and save solubilizing agent for preparation of injection dosage form of diclofenac sodium. In conclusion, the results of this study suggest that a stable aqueous injection of diclofenac sodium can be successfully developed using

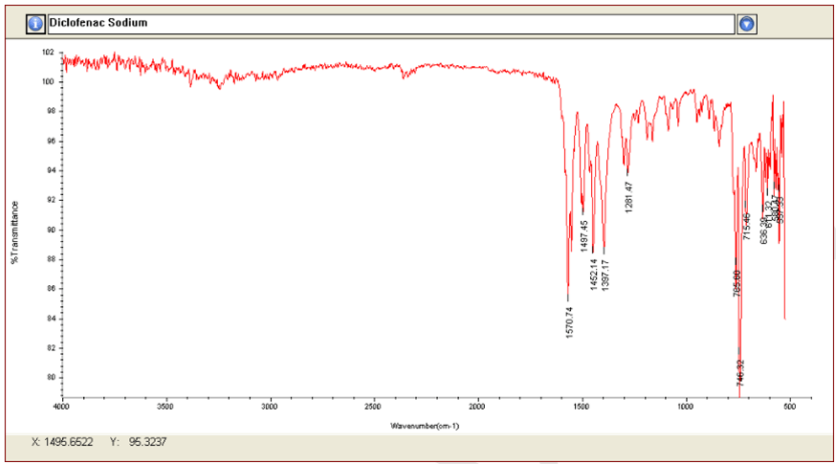

Figure 1: FTIR of raw material diclofenac sodium.

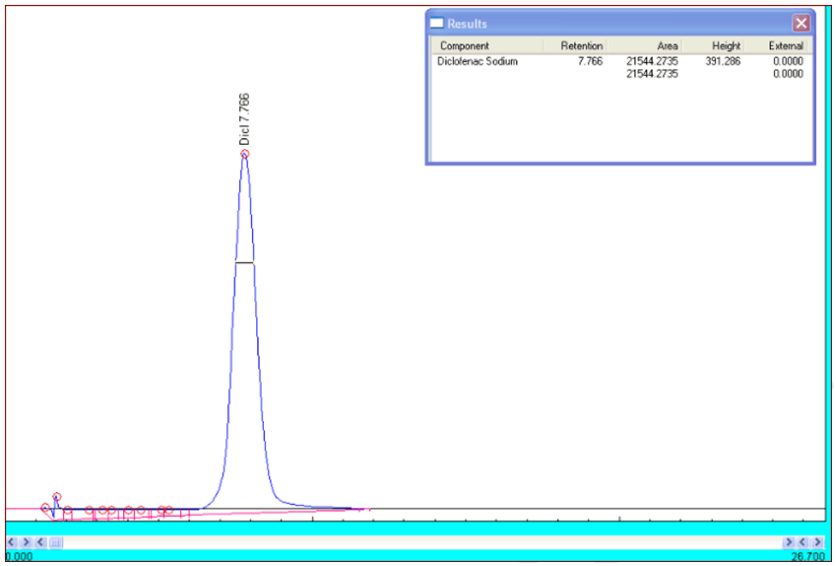

Figure 2: Chromatogram of diclofenac sodium injection.

Table 1: Different formulations of diclofenac sodium solution

Formulation code	Diclofenac Benzyl alcohol for solubility	Sodium 75 mg/3ml with different % of			For pH adjusting	pH of solution
	Diclofenac sodium	WFI	Benzyl alcohol (ml)	SMS (mg)	NaoH(mg)	
D1	375 mg	15 ml	0.99 ml	10 mg	5 mg	6.7
D2	375 mg	15 ml	1.01 ml	20 mg	10 mg	7.2
D3	375 mg	15 ml	1.02 ml	30 mg	15 mg	7.5
D4	375 mg	15 ml	1.03 ml	40 mg	20 mg	8.0
D5	375 mg	15 ml	1.04 ml	50 mg	25 mg	8.3
D6	375 mg	15 ml	1.05 ml	60 mg	30 mg	8.5
D7	375 mg	15 ml	1.06 ml	70 mg	35 mg	8.8
D8	375 mg	15 ml	1.07 ml	80 mg	40 mg	9.0
D9	375 mg	15 ml	1.08 ml	90 mg	45 mg	9.3
D10	375 mg	15 ml	1.09 ml	100 mg	50 mg	9.5

Table 2 : Formulation of injection

Raw Material	Unit	Quantity
Diclofenac Sodium	mg	75.00
Benzyl Alcohol	ml	0.2
Sodium Metabisulphite	mg	9.08
Sodium Hydroxide	mg	3.80
Water for Injection q.s to make 3 ml		

Table 3: Observation for physical appearance

		Storage condition	
Formulation code	Time Point	25°C	40°C
D1	Initial	Discoloration	Discoloration
D2	Initial	Discoloration	Discoloration
D3	Initial	Clear,	Clear,
D4	Initial	Clear solution	Clear solution
D5	Initial	Clear	Clear
D6	Initial	Discoloration	Discoloration
D7	Initial	Discoloration	Discoloration
D8	Initial	Discoloration	Discoloration
D9	Initial	Discoloration	Discoloration
D10	Initial	Discoloration	Discoloration

Table 4: Observation for physical appearance

		Storage condition	
Formulation code	Time Point	25°C	40°C
D1	6 weeks	Discoloration	Discoloration
D2	6 weeks	Discoloration	Discoloration
D3	6 weeks	Clear,	Clear,
D4	6 weeks	Clear solution	Clear solution
D5	6 weeks	Discoloration	Discoloration
D6	6 weeks	Discoloration	Discoloration
D7	6 weeks	Discoloration	Discoloration
D8	6 weeks	Discoloration	Discoloration
D9	6 weeks	Discoloration	Discoloration
D10	6 weeks	Discoloration	Discoloration

Table 5: Results of pH measurement

Formulation code	Time Point	Storage condition	
		25°C	40°C
D1	6 weeks	7.45	7.56
D2	6 weeks	7.56	7.56
D3	6 weeks	7.59	7.86
D4	6 weeks	8.16	8.26
D5	6 weeks	7.56	8.56
D6	6 weeks	7.96	7.50
D7	6 weeks	8.56	7.56
D8	6 weeks	7.06	7.86
D9	6 weeks	8.16	7.86
D10	6 weeks	8.56	8.06

Table 6: Results of particle matter

Formulation code	Time Point	Storage condition	
		25°C	40°C
	Initial	-	-
D1	6 week	++	++
	Initial	-	-
D2	6 week	++	+++
	Initial	-	-
D3	6 week	--	--
	Initial	-	-
D4	6 week	+	+
	Initial	-	-
D5	6 week	--	--
	Initial	-	-
D6	6 week	+	+
	Initial	-	-
D7	6 week	+++	+++
	Initial	-	-
D8	6 week	++	+++
	Initial	-	-
D9	6 week	+	++
	Initial	-	-
D10	6 week	++	++

Key: (-) = Absent (+) = Very few colloidal particulates, fibers or filling artifacts
(++) = Evidence of physical instability under light
(+++) = Physical instability readily observable with the naked eye.

Table 7: Results of assay content of diclofenac sodium

Formulation	Time	Storage condition	
		Temp 25°C	Temp 40°C
D1	Initial	101%	100.2%
	6 week	99.3%	99.3%
	Initial	102%	102%
D2	6 week	101%	101%
	Initial	99,6%	99.6%
D3	6 week	99.2%	99.0%
	Initial	99.5%	99.5%
D4	6 week	99.1%	99.1%
	Initial	101%	100.3%
D5	6 week	99.9%	99.9%
	Initial	100.1%	100.1%
D6	6 week	99.3%	99.3%
	Initial	102%	102%
D7	6 week	101.3%	101%
	Initial	99.0%	99.0%
D8	6 week	98.7%	98.5%
	Initial	101%	100%
D9	6 week	100.5%	99.5%
	Initial	101%	100.2%
D10	6 week	99.3%	99.3%

Table 8: Result of microbiology testing of only successful formulations

Formulation	Sterility result	Endotoxin limit	Pyrogen (BP2013)
D3	No growth	3.45 EU/ML	Complies
D4	No growth	3.82 EU/ML	Complies

the concept of mixed-solvency approach. The amount of individual solubilizer required to increase the measurable solubility shall be very high which sometimes shows the toxicity. Therefore, the use of benzyl alcohol which is physiologically compatible often acts synergistically to improve the solubility and reduce the risk of toxicity.

Thus it can be concluded that, with the carefully designed experimental technique, solubility of poorly water-soluble drug can be improved by using the "mixed solvency" approach. The application of the mixed solvency approach in the development of formulations shall prove to be a boon for pharmaceutical industries because the quantity of water soluble solubilizers can be selected at safe level (well below their toxic levels) for a modest increase in solubility of a water-insoluble drug.

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Author Contributions

Yasir Mehmood – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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REFERENCES

1. Desai NP. Compositions and methods of delivery of pharmacological agents. US Patent US 9012518 B2. 2013. [Availabel at: https://www.google.com/patents/US9012518]
2. Torchilin VP. Targeted polymeric micelles for delivery of poorly soluble drugs. Cell Mol Life Sci 2004 Oct;61(19-20):2549–59.
3. Maheshwari RK. Mixed-Solvency - A novel concept for solubilization of poorly water soluble drugs. Delving Journal 2009;50(1):39–43.
4. Maheshwari RK. “Mixed-solvency approach” - Boon for solubilization of poorly water-soluble drugs. Asian Journal of Pharmaceutics 2010;4(1):60–3.
5. Maheshwari R. Shilpkar R. Formulation development and evaluation of injection of poorly soluble drug using mixed solvency concept. International Journal of Pharma and Biosciences 2012;3:179–89.
6. Yalkowsky SH, Rubino JT. Solubilization by cosolvents I: organic solutes in propylene glycol-water mixtures. J Pharm Sci 1985 Apr;74(4):416–21.
7. Strickley RG. Solubilizing excipients in oral and injectable formulations. Pharm Res 2004 Feb;21(2):201–30.
8. Woods HM. Materials processing in supercritical carbon dioxide: surfactants, polymers and biomaterials. Journal of Materials Chemistry 2004;14(11):1663–78.
9. Chen H, Khemtong C, Yang X, Chang X, Gao J. Nanonization strategies for poorly water-soluble drugs. Drug Discov Today 2011 Apr;16(7-8):354–60.
10. Jain P. Solubility enhancement techniques with special emphasis on hydrotrophy. International Journal of Pharma Proffessional’s Research 2010;1:34–45.
11. Agrawal A, Maheshwari RK. Formulation development and evaluation of in situ nasal gel of poorly water soluble drug using mixed solvency concept. Asian Journal of Pharmaceutics. 2011;5(3)131–40.
12. Mehmood Y. Combination of Allopurinol’and Sustained Release Diclofenac Sodium for Treatment of Gout. International Journal of Science and Research (IJSR) 2014;3(5).