



Explore the application of mixed solvency technique in the injection formulation of poorly soluble drugs

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Abstract

In the pharmaceutical industry that on average more than 40% of newly discovered drug candidates are poorly water-soluble. The objective of present research is to explore the application of mixed solvency technique in the injection formulation of poorly soluble drugs and to reduce concentration of individual solubilizers (used for solubility enhancement) to minimize the toxic effects of solubilizers. In the present work poorly soluble drugs Ofloxacin are selected as model drugs. Ofloxacin is a synthetic fluoroquinolone broad spectrum anti-microbial agent used in the treatment of bacterial infections and it is presently available in the market only as tablet dosage form. It is preferred in the treatment of adults with community acquired pneumonia and acute bacterial exacerbations of chronic bronchitis caused by susceptible organism. The present study was undertaken with an intention to develop a stable and effective parenteral formulation, containing the drug Ofloxacin. Ofloxacin is a light sensitive and water soluble drug but unstable at higher temperature in water. So the effects of various co solvents in the solubility of Ofloxacin have been evaluated. Ofloxacin was tried with co solvents such as PEG-200, Span 20 and Glycerin. The drug was made into injection formulation. Various batches of Ofloxacin injection formulation were prepared evaluates for Color, Clarity Test, Leakage Test, Viscosity Determination, pH Determination, Drug content Determination, Stability Study. The formulations were also subjected to accelerated stability test. Out of all trials, formulation containing 45% of PEG- 200 was found to be more stable and passed all tests satisfactorily.

Keywords: ofloxacin; fluoroquinolone; parenteral formulation; mixed solvency; solubilization.

Introduction

Parenteral Formulations are sterile, pyrogen-free, administered by injection through one or more layers of the skin. Parenterals are pyrogen free, sterile dosage forms which are administered through routes other than oral route. The term parenteral derives from the Greek word: para which means outside and enteron which means intestine. Injections act rapidly, with onset of action in 15- 30 seconds for IV, 10-20 minutes for IM, and 15-30 minutes for SC. They also have essentially 100% bioavailability, and can be used for drugs that are poorly absorbed or ineffective when given orally. ^[1] Some medications, such as certain antipsychotics, can be administered as long-acting intramuscular injections. ^[2] IV infusions can be used to deliver continuous medication or fluids. ^[3] Other advantages include Possibility of accurate dosing, minimized first pass effect and can be administered to unconscious patients, infants, elderly persons and patients who cannot take oral medications.

Disadvantages of injections include potential pain or discomfort for the patient, and the requirement of trained staff using aseptic techniques for administration. As the drug is delivered to the site of action rapidly with IV injection, there is a risk of overdose if the dose has been calculated incorrectly, and there is an increased risk of side effects if the drug is administered too rapidly. Similarly drug when administered through wrong route may produce fatal effect and withdrawal of administered drug is not possible in parenteral route.

1.1 Routes of Parenteral Administration

Parenteral routes of administration mainly include three primary routes which are commonly employed: intramuscular,

subcutaneous and intravenous. To a large extent these three routes satisfy the four main reasons for administering parenterals like, for therapy, for prevention, for diagnosis and for temporarily altering tissue function(s) in order to facilitate other forms of therapy. Under special circumstances, other routes are also employed for parenteral administration.

a. Intravenous route

Intravenous route of administration is the route of administration in which injections or infusions are administered directly into the vein. It is one of the most common parenteral routes employed in hospitals today for the purpose of administration of drugs, fluids and/or electrolytes. It is convenient for rapidly infusing large volume of fluids.

b. Intramuscular route

Intramuscular route of administration is the route of administration in which injections are injected directly into the body through a relaxed muscle. It is the most convenient route available for both the administrator and for the patient, especially for children. This route provides a means of sustained release of drugs formulated as aqueous or oily solutions or suspensions. ^[4-7]

c. Intradermal route

Intradermal route is also known as intracutaneous route. The administration is called intradermal when the injection is given into the dermis which is located just beneath and adjacent to the epidermis.

d. Intra-articular route

The route through which infusion or injection is given into the synovial sacs of different accessible joints is known as intra-

articular route. Corticosteroids, lidocaine and antibiotics are mostly administered through this route for infections, inflammations, pain or other problems resulting from inflammatory diseases. [8-10]

e. Subcutaneous route

It is the route through which injection is given into the loose connective and adipose tissue beneath the dermis. Subcutaneous route is mainly preferred if the drug cannot be administered orally due to various reasons like inactivation of the drug by the GIT or lack of absorption or if the patient is unable to ingest medication(s) by mouth or if self-medication of parenterals is desired.

f. Intraperitoneal route

The route of administration in which the injection or infusion is given directly into the peritoneal cavity via a needle or indwelling catheter or directly into an abdominal organ, such as the kidney, liver or bladder is known as intraperitoneal route. This route is mostly employed to treat local or wide spread intra-abdominal disease due to tumor or injection; to dialyze and remove different toxic substances from the body.

g. Intra-arterial route

Injection or infusion given into an artery which leads directly to the target organ is known as intra-arterial route of administration. This route is employed generally for the purpose of injecting radiopaque substances for roentgen graphic studies of the vascular supply of various organs or tissues. [11, 12]

h. Intracardiac route

Injections given directly into the chambers of heart is called intracardiac route of administration. When better routes of delivery are required this route is preferred. Under unusual circumstances and during certain emergency conditions, such as cardiac arrest, in which the drugs have to reach the myocardium rapidly, intracardiac injections may be used. [13, 14]

i. Intracisternal route

Injections when given directly into the cisternal space surrounding the base of the brain is called intracisternal route of administration. This route is mainly used for diagnostic purpose. It is mostly used in case of elevated intracranial pressures and the risk of herniation of the brain exists, if fluid is removed from the lumbar sac. [15, 16]

j. Intralesional route

Injection given directly into or around a lesion, usually located in or on the skin or soft tissues, to achieve a therapeutic effect. This is effective in case of a potential local effect. It is useful in neutralizing various toxins, like tetanus. [17, 18]

Materials and Methods

Drug Profile

Selected Drug

Ofloxacin

Ofloxacin is a broad spectrum antibiotic that is active against both gram positive and gram negative.

IUPAC Name

(±)-9-fluoro-2, 3-dihydro-3-methyl-10- (4-methyl-1-piperazinyl)-7-oxo-7 H-pyrido [1, 2, 3- de]-1,4-benzoxazine-6-carboxylic acid

Empirical formula

C₁₈H₂₀FN₃O₄

Molecular weight

361.3

Melting point

250-257 °C

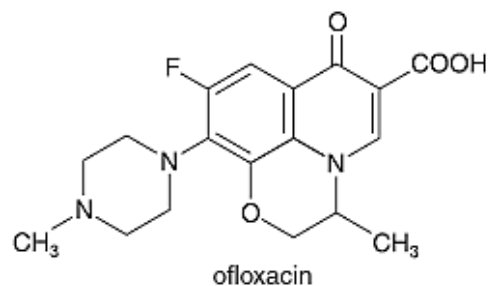


Fig 1: Structure

Materials

Ofloxacin, Nicotinamide, Glycerine, Methanol, Ethanol, Tween 80, Dichloromethane, Potassium dihydrogen phosphate, Hydrochloric acid, Ascorbic acid, Sodium hydrogen phthalate, Mannitol, Hydroxy Propyl Cellulose, Colloidal silicon dioxide Crospovidone, Magnesium stearate, Sodium bicarbonate, Iron oxide red, Sodium bicarbonate, Trisodium phosphate, Magnesium hydroxide. All the chemicals and materials were purchased from S D Fine chemical Ltd, Mumbai.

Methods

Preformulation study

The basic purpose of the preformulation activity are to provide a rational basis for the formulation approaches, to maximize the chances of success in formulating an acceptable product and to ultimately provide a basis for optimizing drug product quality and performance.

Description

It is the initial evaluation during preformulation studies which assess the colour, odor and taste of the substance.

Melting point determination

Melting point of Ofloxacin was determined by Open capillary method.

Determination of λ_{max}

A solution of Ofloxacin containing the concentration 10 μ g/ ml was prepared in DM water. The solution was scanned in the range of 200 – 400 nm UV spectrum using Systronic double beam spectrophotometer.

Solubility

Aqueous solubility is an important physicochemical property of drug substance, which determines its systemic absorption and in turn its therapeutic efficacy.

Excess of drug was added to different solvents in 10 ml stoppered volumetric flasks. Then Drug was made to dissolve in the solvent by placing the volumetric flask in the shaker bath at 25° C for 6 hours. The volumetric flasks were then placed at room temperature for 24 hours.

The solutions were filtered and appropriate dilutions were made to measure absorbance at 286.7 nm using UV visible spectrophotometer, and water as blank. Solubility of drug in other blends was also determined.

Determination of partition coefficient

50 mg of drug was taken in three separating funnels. The separating funnels were shaken for 2hrs in a wrist action shaker for equilibration. Two phases were separated and the amount of the drug in aqueous phase was analyzed spectrophotometrically. The partition coefficient of the drug in phases was calculated by using formula:

$K_{PC} = \frac{\text{Concentration of Drug in Oil Phase}}{\text{Concentration of Drug in Water Phase}}$

Drug - Excipient Interaction Studies

Compatibility was performed by preparing compatibility blends at different ratio of different excipients with API, based on the tentative average weight. The blends were stored at accelerated condition of 40°C ±2°C/ 75% ±5% RH for 30 days. The samples were compared with initial samples data after the 2nd and 4th week of the study.

FTIR Study

FTIR spectra matching approach was used check the purity of received drug sample. About 10mg of the drug was triturated with KBr and compressed to form a transparent pellet using a hydraulic press at 10 tones pressure.

It was scanned from 4000 to 150 cm⁻¹ in a shimadzu FTIR spectrophotometer. The FTIR spectrum of pure drug and excipients and matching was done to detect any appearance or disappearance of peaks.

Table 1: Drug - Excipient Interaction Studies

S. No.	Composition	Ratio (Drug : Excipient)
1.	Ofloxacin	1:1
2.	Ofloxacin+ PEG 200	1:1
3.	Ofloxacin+ Resorcinol	1:1
4.	Ofloxacin+ Glycerin	1:1

Differential Scanning Calorimetry (DSC)

The physical state of drug was analyzed by DSC. The thermogram of drug was obtained at a scanning rate of 10°C/min conducted over a temperature range of 25-350°C.

Preparation of standard calibration curve

100 mg of Ofloxacin was accurately weighted into 100 ml volumetric flask, dissolved in DM water and volume was made up with DM water. Pipette 1ml of this solution into another 10 ml volumetric flask and the volume was made with DM water and marked as Stock. From this Ofloxacin standard stock solution (1000µg/ml), 1ml solution was diluted to 10 ml using DM water solution to get concentrations of 100 µg/ml. from this solution, aliquots of, 0.5 ml, 1.0 ml, 1.5 ml, 2.0 ml, 2.5 ml, 3.0 ml from standard drug solution were diluted to 10 ml with DM water. The absorbance of these solutions was measured at 286.7 nm against DM water as a blank.

Optimization of Formulation Blends

Attempts were made to develop a stable parenteral formulation using cosolvent/s along with other excipients. On the basis of result obtained from solubility studies, mixed blends in which solubility of Ofloxacin was higher. To develop Ofloxacin injection, amount of solubilize and drug that will be administered through each mixed blend was determined.

Formulation Development of Injection

- Preparation of Blend:** Every ingredient for each blend were accurately weighed & transferred in 25 ml volumetric flask. 20 ml of water for injection was added to flask was shaken to dissolve the content. Then volume was made up to 25 ml.
- Preparation of Aqueous solution of Ofloxacin:** For preparation of aqueous solution of Ofloxacin about 20 ml of Hydrotropic Blend solution was taken in 25 ml volumetric flask. Weighed amount of Ofloxacin was transferred in to volumetric flask & flask was shaken until complete Dissolution of drug and finally volume made up to 25 ml.
- Treatment of packaging material:** Vials were first washed three times with distilled water. All these vials were dried in an oven and sterilized by dry heating in an oven at 160 °C for 2 hrs in inverted position. Rubber closures and aluminum seals used for plugging the vials were first washed several times with distilled water and then autoclaved at 15 lbs pressure (121 °C) for 20 minutes and finally dried in oven.
- Preparation of aseptic area:** The walls and floor of aseptic room were thoroughly washed with filtered tap water followed by 5% phenol solution. The room was fumigated using a mixture of formaldehyde and potassium permanganate.
- Aseptic filtration:** The Aqueous solution of Ofloxacin was prepared as above & sterilized by filtration under the Membrane filter 0.22 µm (Millipore) was used for the filtration.

Evaluation of Formulation

Appearance and color of formulation

Appearance and color of formulation was performed by visually inspecting the externally clean vial under a good light, baffled against reflection into the eyes, and viewed against black and white background, with the content set in swirling motion.

Drug content

0.1 ml of the formulation was pipette out and transferred to 10 ml volumetric flask. The volume in the second flask was made up to the mark with distilled water. This final diluted solution was estimated UV spectrophotometrically at 286.7 nm.

Determination of pH

The pH of prepared formulations was determined using digital pH meter. The pH so obtain were recorded.

Clarity testing

Clarity test of product was performed by visually inspecting the externally clean vial under a good light, baffled against reflection

into the eyes, and viewed against black and white background, with the content set in swirling motion.

Leakage test

The methylene blue solution was prepared 1% then all vials emerged in solution for few min. then check leakage test for formulation.

Viscosity

The Brookfield Viscometer/Rheometer was used to determine the viscosity of all formulations.

Result and Discussion

Preformulation Studies

Colour and Appearance

The drug (Ofloxacin) colour is “Off-white” as same as the reported reference.

Melting Point

The Melting point of Ofloxacin was found to be 256.15 ± 0.12 . The reported melting.

Point of Ofloxacin is 250-257 °C. Hence, observed values are complies with USP.

Table 2: Description of Ofloxacin

S. No.	Tests	Results
1	Colour	Off-White
2	Melting Point	$256.15 \pm 0.12^{\circ}\text{C}$

Determination of λ_{max} and Preparation of Standard Calibration Curve

Solution was scanned under UV-Vis Spectrophotometer and λ_{max} was determined. It was found to be as per the monograph. The UV visible of Ofloxacin showed peak at 287.6 nm, which is

same as reported in literature shown in figure & absorbance recorded in table. From the calibration curve equation is given as $y = 0.0709x - 0.0089$. The value of R² is 0.9997. On the basis of obtained result it was concluded that Ofloxacin, Obeyed Beers Lambert's law in the range of 2 µg/ml to 10 µg/ml.

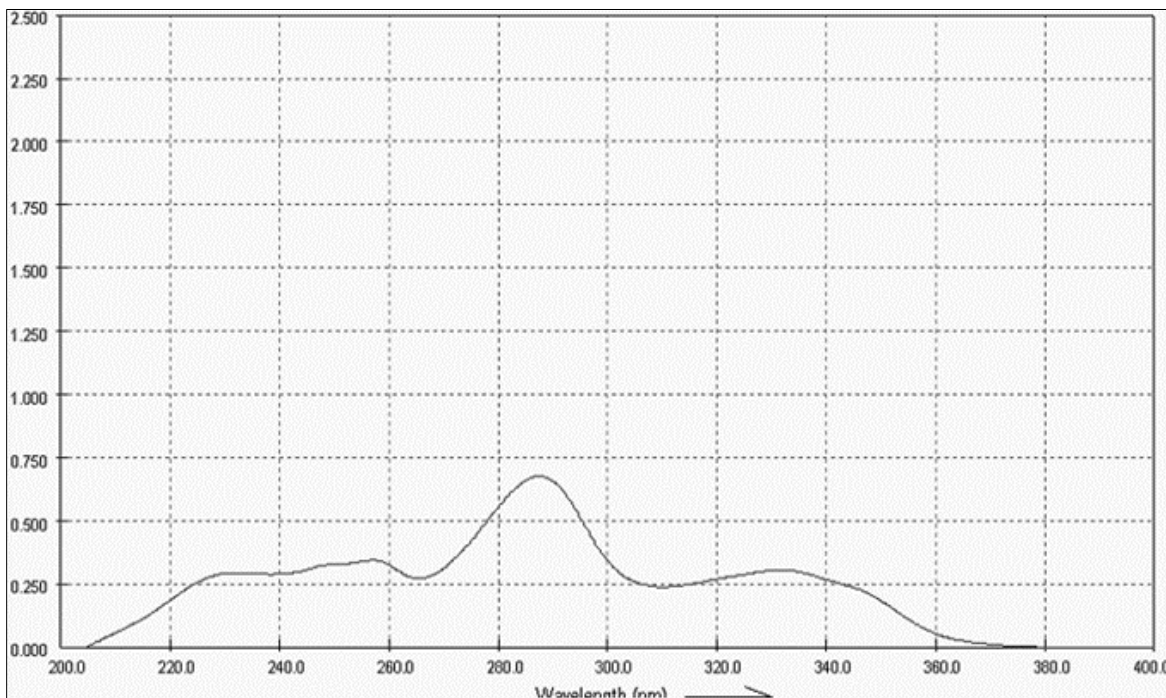


Fig 2: UV spectra of Ofloxacin in DM water

Table 3: Wavelength of maximum absorption of Ofloxacin in DM Water

S. No.	Solvent	λ_{max}
1	DM Water	286.7 nm

Table 4: Standard calibration data of Ofloxacin in DM Water

S. No	Concentration (µg/ml)	Absorbance at λ_{max} 286.7 nm
1	0	0
2	2	0.129
3	4	0.268
4	6	0.411
5	8	0.561

6	10	0.705
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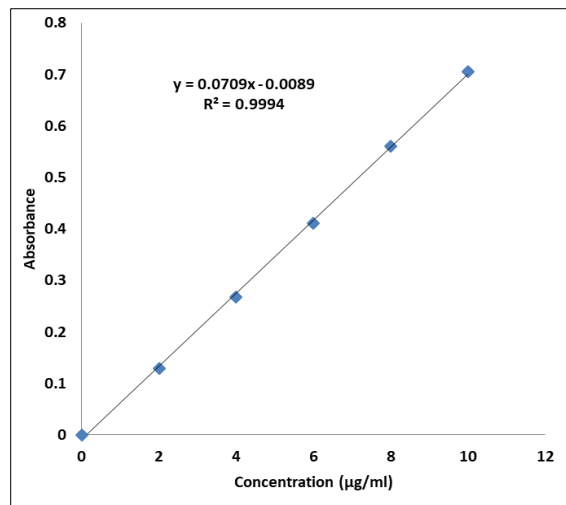


Fig 3: Standard calibration curve of Ofloxacin in DM Water

FTIR Study

The infrared spectrum of Ofloxacin was concordant with the reference spectrum of Ofloxacin and shows all the major peaks

As shown in Figure the procured sample is pure and can be used for further studies.

FTIR Spectra shown in Figure 6.3.

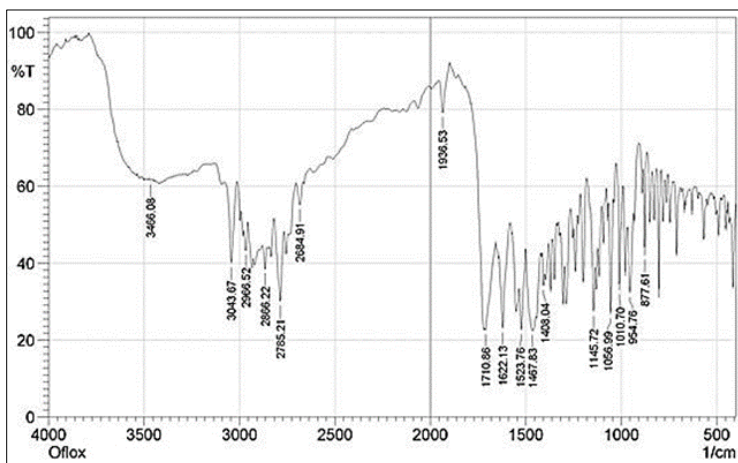


Fig 4: FTIR spectra of Ofloxacin

Table 5: Partition coefficient of Ofloxacin

S. No.	Solvent	Partition coefficient
1	n-octanol/ pH 7.4 Buffer	1.16

Drug Excipients Compatibility Study

From the drug excipients compatibility study, it was observed that there was no change between drug and excipients.

Thus it was concluded that the excipients selected for the formulation were compatible with Ofloxacin and reported in Table 6

Table 6: Drug Excipients Compatibility Study

S. No.	Composition	Ratio (Drug: Excipient)	I Week	II Week	III Week	IV Week
5.	Ofloxacin	1:1	No Change	No Change	No Change	No Change
6.	Ofloxacin + PEG-200	1:1	No Change	No Change	No Change	No Change
7.	Ofloxacin + Resorcinol	1:1	No Change	No Change	No Change	No Change
8.	Ofloxacin + Glycerin	1:1	No Change	No Change	No Change	No Change

DSC Thermogram

The thermogram of Ofloxacin showed peak indicating.

The melting point of the drug is 268.75°C which is identically near to the melting point mentioned in standards. Figure 4.

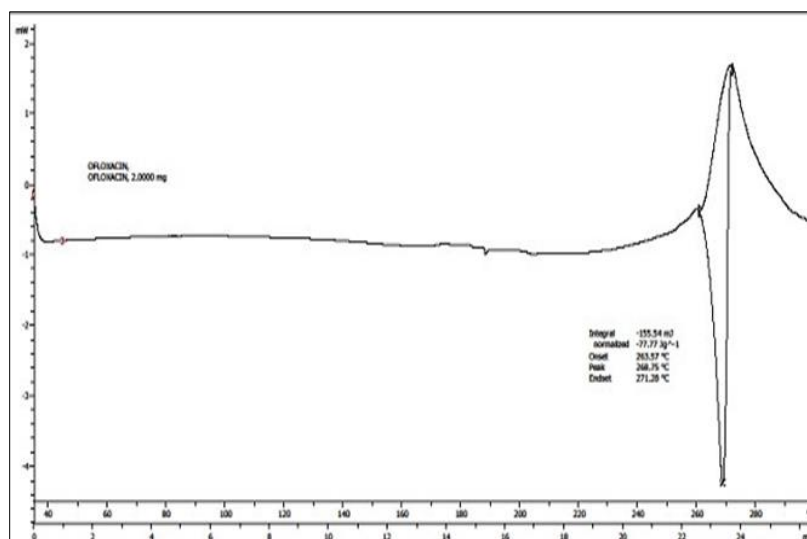


Fig 5: DSC Thermogram of Ofloxacin

Solubility studies, Blend Optimization and Formulation Development

Ofloxacin was found to be very soluble in water and methanol, freely soluble in ethanol, chloroform and ethyl acetate and in soluble in ether and n-hexane. Ofloxacin solubility in different cosolvents was also performed and reported in table. The solubility of Ofloxacin was increased by use of various solubilizers. It is clear that solubilizers may increase or decrease the solubility of drugs. Solubility recorded in table and Solubility profile shown in figure. All 14 blend solubility was determined in mg/ml. In Blend MB11 shows low solubility & Blend no. MB 3 shows high solubility. Solubility recorded and reported. A stable parenteral formulation of Ofloxacin was formulated after performing trials with various solvents. On the basis of solubility profile of blend, Blend MB 2, 3, 8 and 13 were selected for formulation. Table 7, 8, 9, 10, 11 and Figure 5.

Table 7: Solubility Study of Ofloxacin in different common Solvents

S. No.	Solvent	Solubility
1.	Water	+++
2.	Methanol	+++
3.	Ethanol	++
4.	Ethylacetate	++
5.	Chloroform	++
6.	Ether	-
7.	N-hexane	-

Table 8: Solubility Study of Ofloxacin in different Solvents and Cosolvent

S. No.	Solvent	Absorbance	Concentration (mg/ml)
1.	0.1NaoH	2.15	34.35
2.	Ascorbic acid	1.98	31.65
3.	Nicotinamide	0.31	4.94
4.	20% PEG400	2.17	34.71
5.	Resorcinol	2.49	39.76
6.	Tween 80	0.90	14.47
7.	Span 80	1.68	26.82
8.	Glycerine	2.26	36.24
9.	Ethanol	0.81	12.94

Table 9: Different Blends of Ofloxacin Parenteral Formulation

Mix Blend	Ingredients of Mix Blend (%) in grams					
	PEG-200	Resorcinol	Glycerin	Benzyl alcohol	Methyl Paraben	Propyl Paraben
MB1	45	-	-	1.5	0.2	0.02
MB2	45	4	-	1.5	0.2	0.02
MB3	45	4	5	1.5	0.2	0.02
MB4	-	4	5	1.5	0.2	0.02
MB5	-	-	5	1.5	0.2	0.02
MB6	30	-	-	1.5	0.2	0.02
MB7	30	5	-	1.5	0.2	0.02
MB8	30	5	5	1.5	0.2	0.02
MB9	-	5	5	1.5	0.2	0.02
MB10	-	-	5	1.5	0.2	0.02
MB11	25	-	-	1.5	0.2	0.02
MB12	25	4	-	1.5	0.2	0.02
MB13	25	4	5	1.5	0.2	0.02
MB14	-	4	5	1.5	0.2	0.02

Table 10: Solubility Enhancement Ratio of Different Formulation Blends

S. No.	Mix Blend	Solubility Enhancement Ratio
1.	MB1	21.58
2.	MB2	37.00
3.	MB3	43.94
4.	MB4	20.67
5.	MB5	18.15
6.	MB6	17.58
7.	MB7	14.89
8.	MB8	13.15
9.	MB9	14.43
10.	MB10	10.67
11.	MB11	13.61
12.	MB12	14.45
13.	MB13	13.52
14.	MB14	10.67

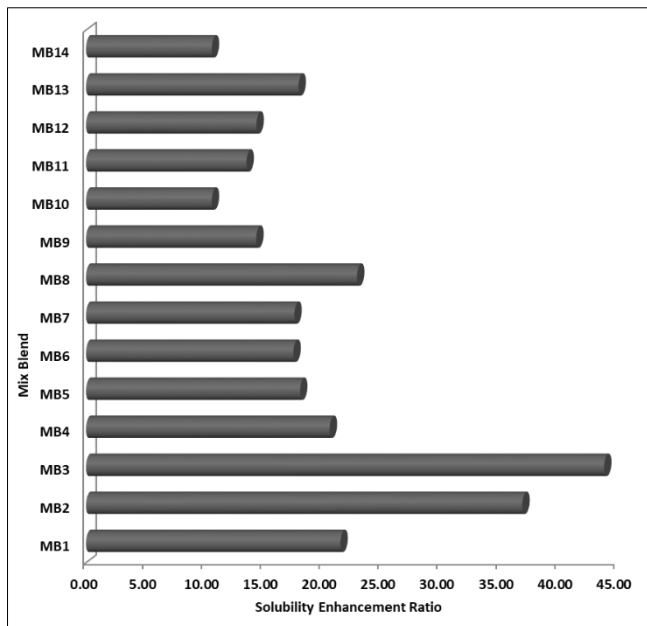


Fig 6: Solubility Enhancement Ratio of Different Formulation Blends

Table 11: Optimized Selected Parenteral Formulations of Ofloxacin

Ingredients	Formulation (%) in grams			
	F1	F2	F3	F4
Ofloxacin	25	25	25	25
PEG-200	45	45	30	25
Resorcinol	4	4	4	4
Glycerin	-	5	5	5
Benzyl alcohol	1.5	1.5	1.5	1.5
Methyl Paraben	0.2	0.1	0.2	0.1
Propyl Paraben	0.02	0.02	0.02	0.02

Evaluation of Formulation

- Appearance of prepared parenteral formulation of Ofloxacin recorded in table 12. All formulations showed clear and transparent. Table 12.
- The Clarity test of given parenteral formulation of Ofloxacin was found to be clear. Shown in Table 12.
- The leakage test for given parenteral formulation of Ofloxacin was found to be Passes & result shown in Table 12.
- The prepared formulations were assayed for % drug content. All formulation was showed good results. Table 13 and Figure 6.
- The pH of all developed formulation of parenteral formulation was measured and found satisfactory and recorded in Table 13 and Figure 7.
- The viscosity of all parenteral formulation was found to be satisfactory and the result show in Table 13 and Figure 8.

Table 12: Appearance, Clarity Test and Leakage Test of Different Parenteral Formulation

S. No.	Formulation Code	Appearance	Clarity Test	Leakage Test
1.	F1	Transparent	Clear	Passed
2.	F2	Transparent	Clear	Passed
3.	F3	Transparent	Clear	Passed
4.	F4	Transparent	Clear	Passed

Table 13: % Drug Content, pH and Viscosity Test of Different Parenteral Formulation

S. No.	Formulation Code	% Drug Content	pH	Viscosity (cp)
1.	F1	100.45	5.4	1.55
2.	F2	100.12	6.2	1.61
3.	F3	100.34	5.3	1.45
4.	F4	100.28	5.2	1.42

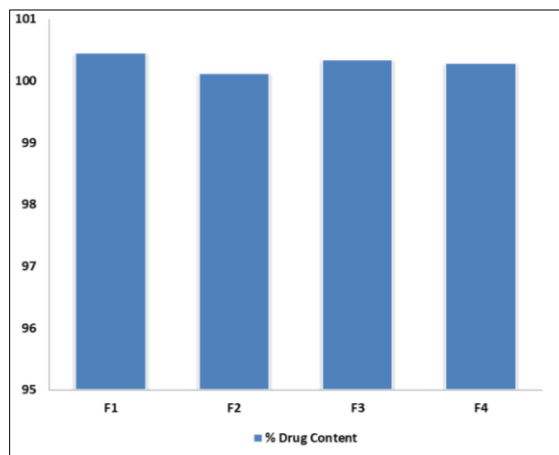


Fig 7: % Drug Content study of Different Formulation

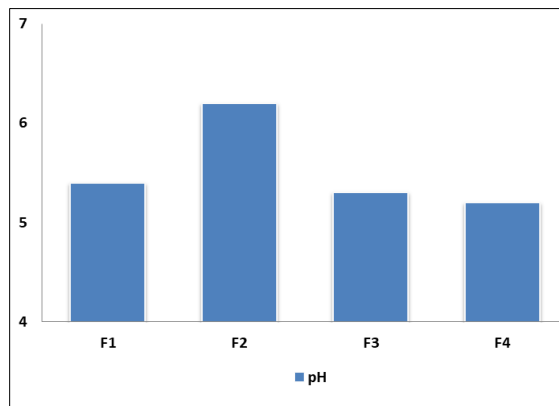


Fig 8: pH study of Different Formulation

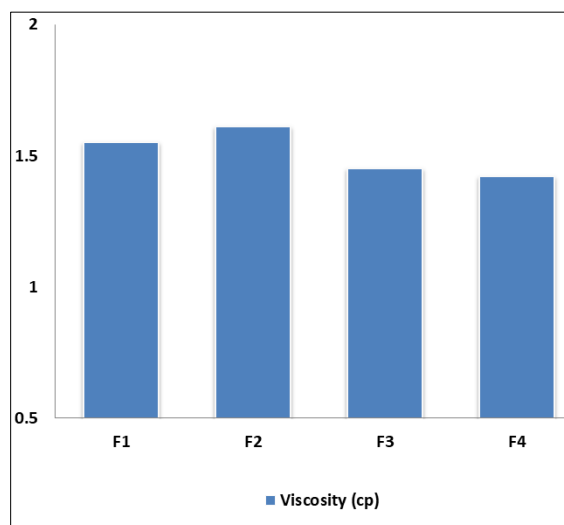


Fig 9: % Viscosity Measurement of Different Formulation

In most of the methods of Solubilization, high concentration of an additive (hydrotropic agent/cosolvents/surfactants/etc.) is required to produce an appreciable increase in solubility of a poorly soluble drug. In this case, the solubilizing agent employed to give a desirable solubility for the poorly soluble drug may produce its own toxicity. In the present study, Ofloxacin were selected as model drugs. These drugs were tried to solubilize by employing the combination of physiologically compatible solubilizers in attempt to prepare their parenteral formulations (aqueous injection of Ofloxacin).

The objective of present work was to explore

- To design the parenteral formulation of poorly soluble drugs
- The novel application of mixed solvency technique in the injection formulation
- To reduce concentration of individual solubilizers (used for solubility enhancement)
- To minimize the toxic effects of solubilizers.

In the present work, the procured Ofloxacin drug samples were characterized by various tests. Melting point was determined by open capillary method and found concordant with standard. Spectrophotometric method was used to analyze the drugs; Ofloxacin showed peak at 287.6 nm was selected for analysis. FTIR spectroscopy was performed for further characterization of drugs, prior to use in the formulation. The procured samples of drugs were found to be in confirmation with the reported literature and were thus, used for further studies.

In preformulation studies, calibration curves of drug were prepared in various media; the correlation coefficients obtained were very close to one which confirmed that the Beer-Lamberts law was obeyed in concentration range of 2-10 µg/ml and solubilizer range 10-50 µg/ml for drug solutions in all media for both Ofloxacin. The UV interference studies (in aqueous media for Ofloxacin) showed that none of the selected solubilizers interfere in UV estimation of drugs. Solubility studies of Ofloxacin were performed in various media, viz., distilled water, 25% aqueous solution containing individual solubilizers. The Ofloxacin was found to be practically insoluble in water having solubility 0.11mg/ml. There was appreciable enhancement in solubility of Ofloxacin in aqueous solutions containing individual solubilizers and combination of solubilizers. These results showed synergistic enhancement in solubility when the solubilizers were used in mixed blends. To check the influence of pH on the Solubility of Ofloxacin solubility of Ofloxacin were determined in different pH solution. Ofloxacin solubility slightly decreases with increase in pH. From the results of solubility studies, mixed blends in which solubility of Ofloxacin was more than 4 mg/ml were selected to develop the injections, such mixed blends were MB3, MB4, MB7 and MB13. The injection formulations of various strengths were developed based on solubility of Ofloxacin in individual mixed blends. Prepared formulations were sterilized by membrane filtration method flushed with nitrogen and filled in glass vials. The formulations when subjected to accelerated stability studies showed good stability at lower temperature. From the results of stability studies and literatures it was concluded that Ofloxacin is sufficiently stable in aqueous media. The clarity and leakage test were passes

found as per IP Standard. Viscosity was measure by Brookfield viscometer all blends showed satisfactory results. And Sterility was passes & No fungi or bacteria presence of due to unhygienic condition at small scale production of aqueous injection of Ofloxacin.

Conclusion

Thus, above findings supports that by using novel technique of mixed solvency the required solubility can be achieved, solubilizers can be selected in safer range and dosage forms can be developed which are expected to show good stability also. The above research findings showed that, a stable aqueous injectable formulation containing Ofloxacin were successfully developed. There is good scope for other poorly water-soluble drugs to develop their aqueous formulation by the use of combination of suitable solubilizers are known to safe hence, toxicities/safety related issues may not rise, suggesting the adoptability for large scale manufacturing. The proposed techniques would be economical convenient and safe. Thus, the study opens the chances of preparing such aqueous formulation of poorly-water soluble drugs.

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