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## Original Research Paper

### A FACILE APPROACH TO ENHANCE SOLUBILITY AND DISSOLUTION RATE OF NORFLOXACIN BY NANOPLEX

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#### ABSTRACT

Nanoplex means drug nanoparticle forms a complex with oppositely charged polyelectrolyte. In this technique both cationic and anionic drugs forms a complex with its oppositely charged polyelectrolyte. In present work norfloxacin a class IV drug and polyanionic dextran sulfate was used as polyelectrolyte. In preparation of nanoplex norfloxacin was ionized with acidic solution gives cationic charges on drug it forms a complex with anionic dextran sulfate. In this process due to charge neutralization on drug it precipitates out in nanosize and strong electrostatic interaction between drug and polyelectrolyte prevents drug molecule to revert in its crystalline form. Hence process has capability of giving amorphous and nanosize formulation. Pluronic F 68 used as stabilizer and sodium chloride for its charge shielding effect. Nanoplex shows a particle size 346 nm, complexation efficiency 90%, drug loading 60% and stability for one month with 20 fold enhancement in solubility and dissolution rate.

**Keywords:** Nanoplex, Polyelectrolyte, Solubility enhancement, Norfloxacin, Complexation efficiency.

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#### INTRODUCTION

The most of new promising drug candidate exhibits low saturation solubility in aqueous phase there for development of new promising method is the need of research era to make the drug more soluble drugs having low aqueous solubility shows low oral bioavailability so requires high and frequent dosing causing pill burden and high finance to patients (Ando *et al.* 2005). The salt formation of weak organic acidic and basic drug is easiest way to increase saturation solubility of acidic and basic drug (Rabinow *et al.* 2004). The NanoAPI formulation depends on particle size reduction to nanosize which follows Ostwald-Freundlich solubility theory. Ostwald-Freundlich equation states that the saturation solubility enhancement by nanoionization is significant only for size  $\ll 100$  nm (Grant *et al.* 1995). NanoAPI

with sizes of  $\sim 150$ - $200$  nm has been found to exhibit only 15% increase in saturation solubility than microscale counterparts. Amorphous API dissolution results in a highly supersaturated solution producing apparent solubility that is significantly greater than the saturation solubility of crystalline counterparts. The high supersaturation level consequently enhances drug absorption across the gastrointestinal lumen, results in enhanced bioavailability. The significant thing about amorphous form is that the generation of high supersaturation level has been shown to translate to enhance bioavailability *in vivo* (Yang *et al.* 2010, Tam *et al.* 2008). Amorphous API is typically prepared in the form of microscale solid dispersion of the drug which is stabilized by using high transition temperature polymer (e.g.,

hydroxypropylmethylcellulose (HPMC), poly (ethylene glycol) by cogrinding, hot melt extrusion, or antisolvent precipitation techniques (Yamada *et al.* 1999, Verreck *et al.* 2003). A number of nanoscale amorphous API (or amorphous nanoAPIs) have been successfully prepared by a wide range of techniques (e.g., antisolvent precipitation and sonoprecipitation) with drug loading up to 90%(w/w) but having a number of drawbacks Chen *et al.* 2010, Matteucci *et al.* 2006, Dhumal *et al.* 2008). Nanoplex means drug nanoparticle complex with oppositely charged polyelectrolyte. In this technique cationic or anionic drug is reacted with oppositely charged polyelectrolyte to form complex. The water insoluble drug is first dissolved in acidic or basic medium to form anionic or cationic drug solute. Afterward the ionized drug solution is mixed with an oppositely charged polyelectrolyte solution which initiates drug-polyelectrolyte electrostatic interaction and the simultaneous charge neutralization as shown in figure 1. The drug solute is transformed back to its sparingly soluble form upon charge neutralization, leading to a loss of solubility and hence rapid precipitation and formation of nanoscale drug-polyelectrolyte complex. The combination of rapid precipitation and strong electrostatic interactions between the drug and polyelectrolyte avoids the drug molecules from assembling into ordered crystalline structures. As a result, amorphous drug-polyelectrolyte nanoparticle complex is formed (Cheow *et al.* 2012). In present work norfloxacin is used as model drug of BCS class IV having low solubility and permeability belongs to fluoroquinolone class of antibiotics (Wang *et al.* 2012). For the norfloxacin solubility enhancement various techniques were tried like solid lipid nanoparticle,  $\beta$ -cyclodextrin complexation, crystal modification but in the present work a novel nanoplex approach is used (Dua *et al.* 2007, Yadav *et al.* 2005).

## MATERIALS AND METHODS

### Materials

Norfloxacin was obtained as gift sample from Haffkins Ajantha Pharmaceuticals, Jalgaon. Dextran sulfate sodium salt (5000 Daltons) and

Pluronic F 68 was purchased from Himedia laboratories Ltd, Mumbai. Sodium chloride and glacial acetic acid was purchased from RFCL chemicals, Mumbai.

### Method of Preparation of Nanoplex

Norfloxacin drug solution in glacial acetic acid (GAA) of pH 3 (10 mg/ml) was added to equal volume of dextran solution (10 mg/ml) in micro centrifuge tube in presence of sodium chloride salt (0.1M, 1ml). Non ionic surfactant pluronic F 68 (0.2%w/v, 1ml) was added to both drug and dextran sulfate solution to ensure colloidal stabilization of nanoplex. White precipitates of drug were observed upon immediate addition of drug solution to dextran sulfate solution. Suspension was left for 3hrs at ambient temperature condition to allow the complexation to equilibrate. To remove excess drug and dextran sulfate nanoplex suspension was washed three times with 0.2% w/v pluronic F 68 solutions in water by centrifugation. Final solution was freeze dried to obtain dry powder.

### Evaluation of Nanoplex

#### Complexation Efficiency

It is defined as mass of drug that forms complex with polyelectrolyte relative to initially added drug and calculated by measuring optical density of supernatant after first centrifugation of nanoplex suspension (Thorsteinn *et al.* 2012).

#### Production Yield

It is ratio of weight of initially added drug and polyelectrolyte to dry nanoplex formulation formed after freeze drying (Cheow *et al.* 2012).

$$\text{Production yield} = \frac{\text{Wt of nanoplex}}{\text{Wt of drug} + \text{Wt of polyelectrolyte}} \times 100$$

#### Drug loading

It is actual amount of drug present in nanoplex powder. It was calculated by dissolving 5 mg of nanoplex powder in 20 ml ethanol and measuring absorbance of solution after centrifugation and filtration (Anitha *et al.* 2011).

#### Infrared Spectroscopy

The samples of 2 mg were accurately weighed to this 100 mg of KBr powder was added then

mixture was gently grinded in mortar pestle. 50-100 mg of sample mixtures were placed in polished surface of bolt inside barrel then second bolt was placed and rotated with 5 turns, this gives more translucent pellet. The pellet is then placed in sample holder. At last FT-IR instrument was runned and bands were assigned in  $\text{cm}^{-1}$  (Bonoiu *et al.* 2009).

#### *Particle Size Analysis*

Particle size of nanoplex was analyzed by photon correlation spectroscopy on particle size analyzer (Nano ZS 90, Malvern, UK) using water as dispersion medium and quartz cuvette as sample holder. The sample was scanned 100 times for determination of particle size (Thomas *et al.* 2010).

#### *Zeta Potential*

Zeta potential of nanoplex was determined by using photon zetasizer (Nano ZS 90, Malvern, UK). The sample was diluted 10 times with solvent before analysis and fibre curette was used as sample holder (Thomas *et al.* 2010).

#### *Powder X-Ray Diffraction*

Powder X-ray diffraction patterns of samples was determining using Powder X-ray diffractometer (Bruker, D-08 advance, Germany) at a scan rate of  $10 \text{ min}^{-1}$ . Having  $2\theta$  range from 10 to 80. This gives idea about nature of the sample.<sup>16</sup>

#### *Scanning Electron Microscopy*

The surface morphology of the sample was observed by using scanning electron microscope (Hitachi S-4800 Type II). The samples were fixed on a brass stub using double sided tape and made electrically conductive by coating with a thin layer of gold by sputter coater palaron E 5100 (Cheow *et al.* 2012).

#### *Dissolution Study*

Dissolution testing of nanoplex was carried out by dialysis bag method to determine drug release. The dissolution medium was 6.8, rpm 50 rpm and temperature  $37^\circ\text{C}$ . Sampling interval was kept 15 min. The same procedure was followed for drug as well as nanoplex. The absorbances were taken by UV-Visible spectroscopy (Cheow *et al.* 2012).

#### *Saturation Solubility Study*

Solubility of both drug and formulation was calculated by using orbital flask shaker method. The excess of nanoplex and drug were dissolved in distilled water and phosphate buffer pH 6.8 in conical flask. These flasks were then placed in orbital flask shaker for 24 hr. After incubation flasks were allowed to equilibrate then they were subjected for centrifugation and filtration. The concentrations of drug were determined by taking absorbance using spectrophotometric analysis (Baka *et al.* 2008)

#### *Stability study*

Stability testing of nanoplex was carried out by placing 50 mg of nanoplex powder in environmental stability chamber at 55% RH and  $25^\circ\text{C}$  temperature for 1 month and tested for its drug content (Cheow *et al.* 2012).

## **RESULTS**

### **Complexation Efficiency, % Yield and Drug Loading**

Complexation efficiency, % yield and drug loading of norfloxacin nanoplex having drug: polyelectrolyte ratio found higher for 1:1 as compare to other drug: polyelectrolyte ratio i.e. 1:0.5 and 1:1.5 as shown in table no. 1. Hence we can definitely say that nanoplex shows good results for complexation efficiency, % yield and drug loading when drug and polyelectrolyte were in same concentration as shown in figure 2.

### **Particle Size Analysis**

Particle size of norfloxacin nanoplex was found to be 346 nm as shown in figure 3. Polydispersibility index gives degree of particle size distribution. Higher value of polydispersibility index indicates broad particle size distribution and narrow size distribution is essential to prevent particle growth due to Ostwald ripening and maintaining stability of nanoplex. Batches with lower polydispersity values showed long-term stability. Polydispersibility index was found to be 0.5 which indicates the particles were in monodisperse form.

### **Zeta Potential Analysis**

Zeta potential analysis was performed to investigate the surface properties of nanoplex.

Zeta potential is an important parameter for prediction of stability of nanoplex. Zeta potential of norfloxacin nanoplex was observed -32.5 as shown in figure 4 which indicates moderate stability of nanoplex.

#### FT-IR of Study

In figure no. 5 (A) Represents FT-IR spectra of norfloxacin drug which shows C=O stretch at  $1700\text{ cm}^{-1}$ , NH stretch at  $3446\text{ cm}^{-1}$ , NH bending vibration at  $904\text{ cm}^{-1}$ , CF bending at  $1034\text{ cm}^{-1}$ . (B) Represents a FT-IR spectra of dextran sulfate which shows S=O vibration at  $1239$  and  $986\text{ cm}^{-1}$ , O-S-O vibration at  $818$  and  $575\text{ cm}^{-1}$ . (C) Represents FT-IR of mixture of norfloxacin and dextran sulfate showing peaks of both drug and polyelectrolyte which reveals that they are compatible with each other. (D) Represents FT-IR of nanoplex shows peaks of both norfloxacin and dextran sulfate which indicates presence of both norfloxacin and dextran sulfate in it.

#### FE-SEM Analysis

FE-SEM images shown in figure no. 6 of norfloxacin revealed that the plex structure is formed. Nanoplex of norfloxacin are clearly observed in the images.

#### XRD Analysis

Figure no. 7 shows a XRD of norfloxacin which shows maximum intensity up to 400 indicates crystalline nature of drug and figure no. 8 shows XRD of nanoplex which shows maximum intensity up to 400 indicates amorphous nature of it.

#### Saturation Solubility Study

Saturation solubility study for pure drug and nanoplex was carried out in distilled water, pH 6.8 buffer and pH 1.2 solutions. The table no. 2 and figure no. 9 show that there was nearby 20 folds increment in drug solubility compared to raw drug crystal and that was significant.

#### Dissolution Study

Dissolution of pure drug and nanoplex was carried out in pH 6.8 buffer. Drug and nanoplex shows complete dissolution as shown in table no. 3 and in figure no. 10 at the end of 240 and 150 min respectively from these we can conclude that due

to increase in solubility of drug in nanoplex formulation dissolution rate was increased.

#### Drug Release Kinetics

As shown in table no.4 the  $r^2$  value of Koresmeyers Pappas model is higher than that of other models hence nanoplex follows Koresmeyers Pappas model for drug release.

#### Stability Study

Stability of optimal nanoplex formulation was carried out at RH 55% and temp  $25^{\circ}\text{C}$ . After one month and 15 days storage drug content found was 62.97% and 62.56% respectively as shown in table no 5. From these we can definitely say that nanoplex was stable for at least one month.

## DISCUSSION

In nanoplex formation simultaneous amorphization and nanonization of poorly water soluble drug improves the solubility and dissolution rate it ultimately enhance bioavailability of that drug. We have demonstrated the stable amorphous nanoplex of norfloxacin drug by using highly efficient drug-polyelectrolyte complexation process. This method of nanoplex preparation requires only mixing of two solutions at ambient conditions and also solvent free, fast, low energy, produces uniform size nanoparticles with retention of antimicrobial activity of norfloxacin. The drug and polyelectrolyte forms a complex by electrostatic and hydrophobic interaction between NOR-DXT and NOR-NOR respectively. The role of salt in nanoplex formation is its charge shielding effect. In absence of salt there is repulsion between like charge of DXT chain and it inhibits spatial interaction between them. Consequently, in absence of salt there is no formation of precipitate. The majority of orally administered drugs are amphiphilic in nature and soluble in weak acid or base they can be transformed into amorphous nanoplex by simple complexation method. The complexation efficiency, % yield and drug loading are depends on drug: polyelectrolyte ratio ( $R_{\text{Drug/PE}}$ ). In this regards,  $R_{\text{Drug/PE}} > 1$  denotes the presence of more drug than PE available for complexation resulting in low CE. However  $R_{\text{Drug/PE}} < 1$  denotes excess of



PE which ensures high CE but low % yield. There for  $R_{Drug/PE}$  value equal to unity shows optimal formulation with high CE (~90%) and % yield (~60%). The nanoplex shows high drug loading (i.e. ~56%) as compared to other nano-crystalline drug prepared by conventional technique which needs a use of surfactant stabilizer to suppress crystal growth and minimize agglomeration. The particle size of nanoplex is about 346 nm with 0.5 polydispersibility index showing monodisperse particles that leads to significant difference in surface area to volume ratio in drug and nanoplex. The zeta potential analysis reveals that nanoplex is moderately stable. The FT-IR study indicates that complex is formed in between drug and polyelectrolyte as it shows peaks of both drug and polyelectrolyte. The XRD analysis gives idea about amorphous nature of nanoplex. The SEM image indicates structure of nanoplex. Saturation solubility and dissolution study of nanoplex shows increment in solubility by 20 folds and enhancement in dissolution rate than that of drug which ultimately enhances bioavailability of norfloxacin drug. The prepared nanoplex is

evaluated for 1 month stability by calculating its drug content it shows 1 month stability.

## CONCLUSION

Stable nanoplex of norfloxacin have been successfully prepared by self-assembly drug-polyelectrolyte complexation process in presence of salt. Nanoplex formulation of norfloxacin shows 20 fold enhancements in solubility of norfloxacin with faster dissolution rate as compared to raw drug. The complexation process involves simple mixing of drug and polyelectrolyte solution, is entirely aqueous based, is a fast and with high complexation efficiency, drug loading & production yield. The nanoplex after freeze drying remain amorphous after 1 month storage.

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**Table 1:** Drug: polyelectrolyte optimization of nanoplex

Sr. No.	D:PE ratio	CE (%)	% Yield	Drug loading (%)
1.	1:0.5	48.98	40.56	30.77
2.	1:1	90.87	60.64	56.32
3.	1:1.5	80.05	30.55	22.61

**Table 2:** Saturation solubility study in different medium

Sr. No.	Medium	Conc.(mg/ml) in drug	Conc. (mg/ml) in nanoplex	Enhancement ratio
1.	Distilled water	0.66	13.47	20.40
2.	pH 1.2 Solution	0.9241	14.99	22.71
3.	Phosphate buffer of pH 7.4	0.8317	-	-
4.	Methanol	1.5131	-	-
5.	Phosphate buffer of pH 6.8	0.777	14.11	21.37

**Table 3:** % Drug release study of drug and nanoplex

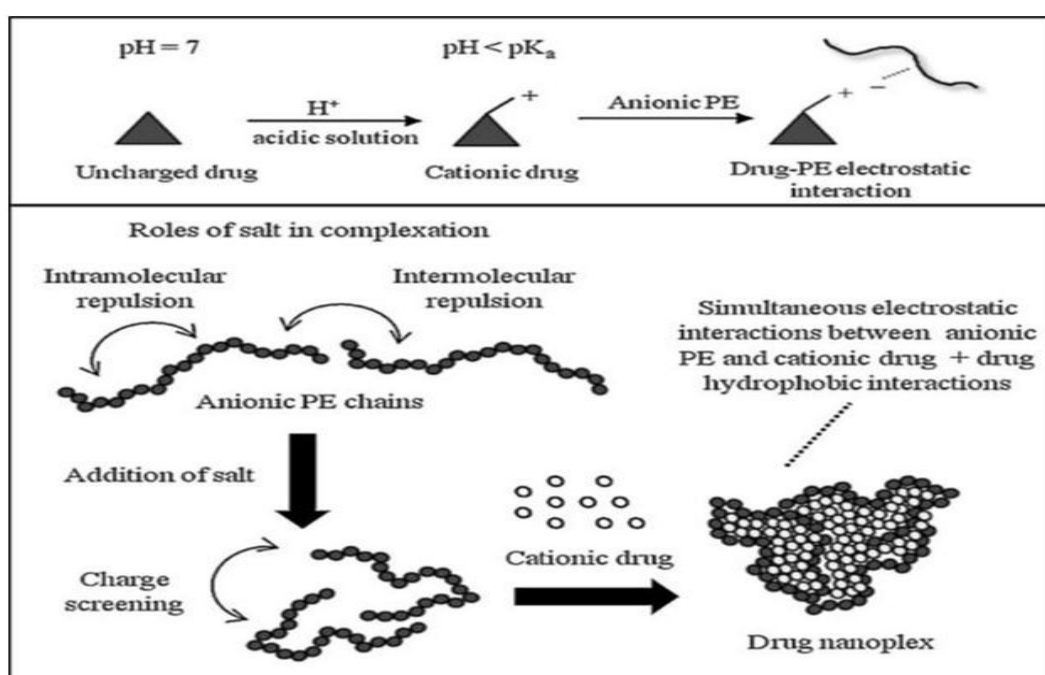
Sr. No.	Time	% CDR	
		Drug	Nanoplex
1.	0	0	0
2.	15	6.21	19.34
3.	30	15.45	37.23
4.	45	26.76	52.78
5.	60	37.12	67.90
6.	90	42.37	79.73
7.	120	50.98	86.24
8.	150	67.03	93.21
9.	180	73.24	
10.	210	81.01	

**Table 4:** Drug release kinetics of nanoplex

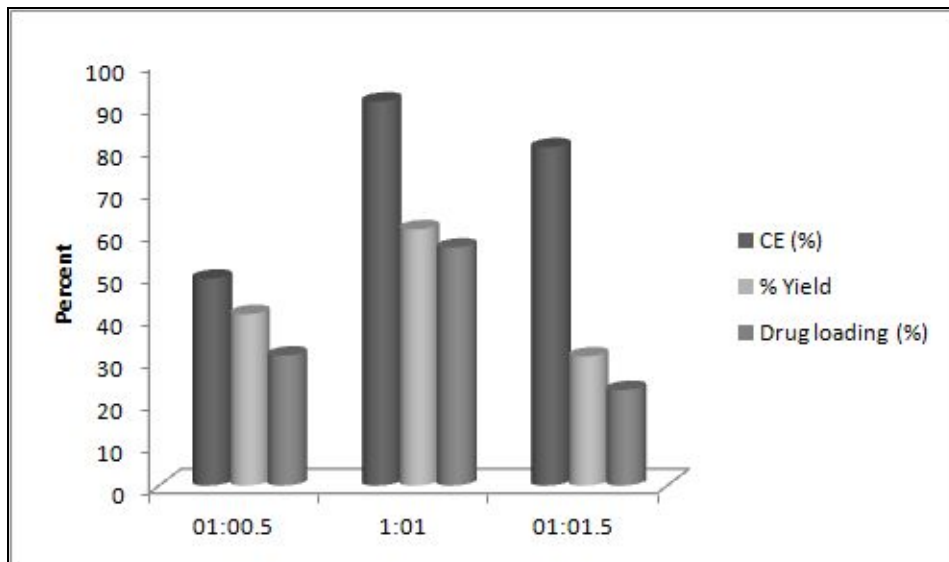
Sr. No.	Parameters	Zero order	First order	Higuchi	Koresmeyers Pappas
1.	Regression coefficient	0.8841	0.5187	0.9725	0.9752
2.	Slope	0.5999	0.009	8.2798	0.9256

**Table 5:** Drug content in nanoplex

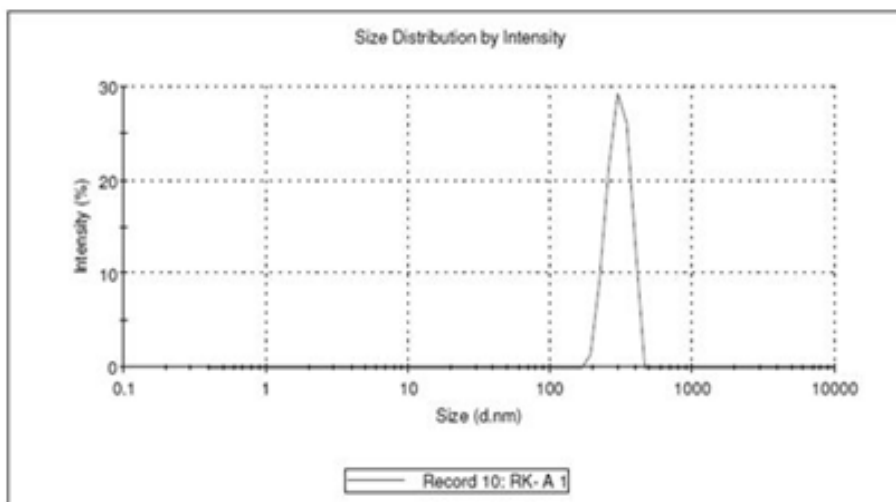
Sr. No.	Days	Drug Content (%)
1.	15	62.97
2.	30	62.56



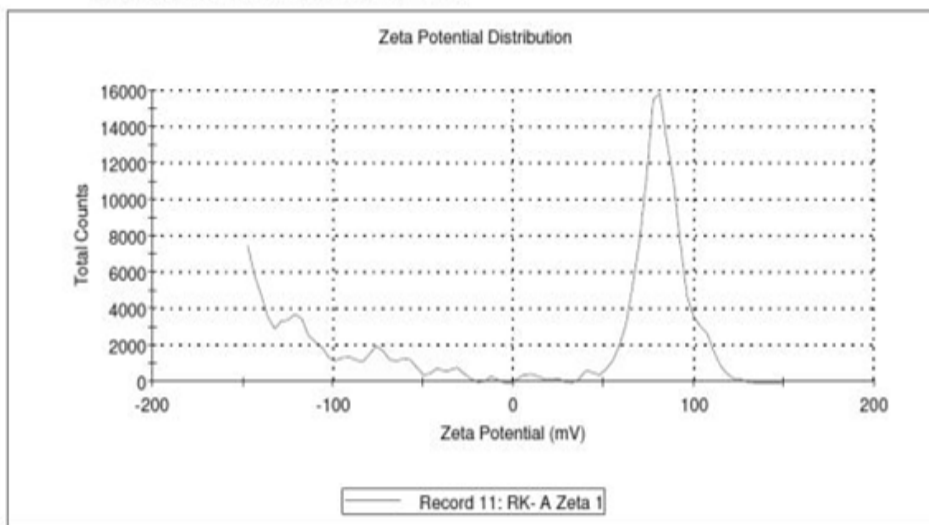
**Figure 1:** Mechanism of nanoplex formation



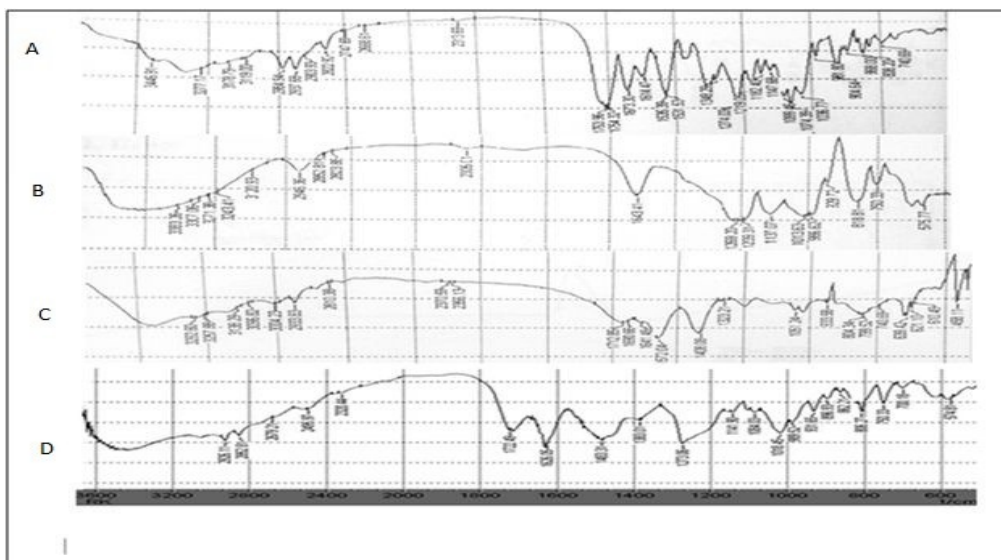
**Figure 2:** Effect of D: PE ratio on CE, % yield, Drug loading



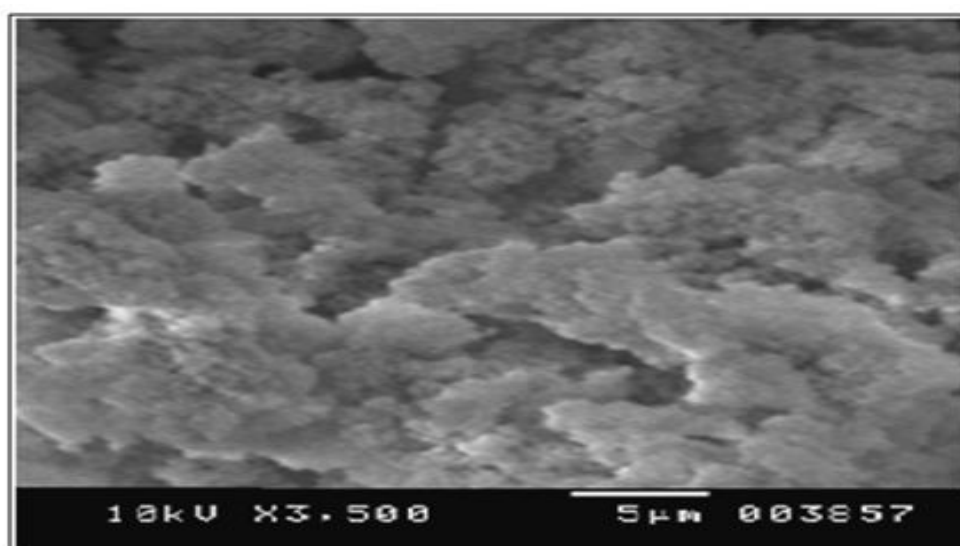
**Figure 3:** Particle size of nanoplex



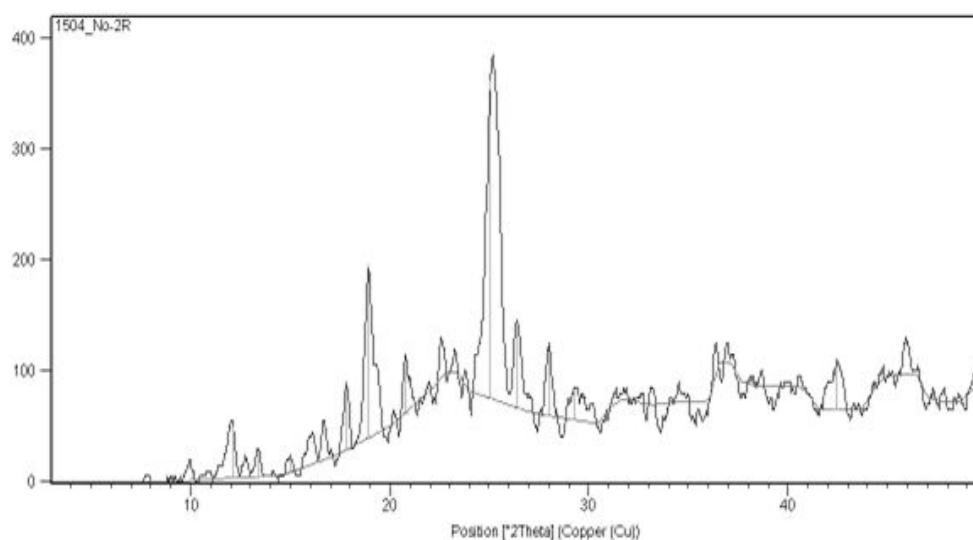
**Figure 4:** Zeta potential of nanoplex



**Figure 5:** FT-IR spectra of (A) Norfloxacin, (B) Dextran sulfate, (C) Physical mixture, (D) Nanoplex



**Figure 6:** SEM image of nanoplex



**Figure 7:** XRD pattern of norfloxacin



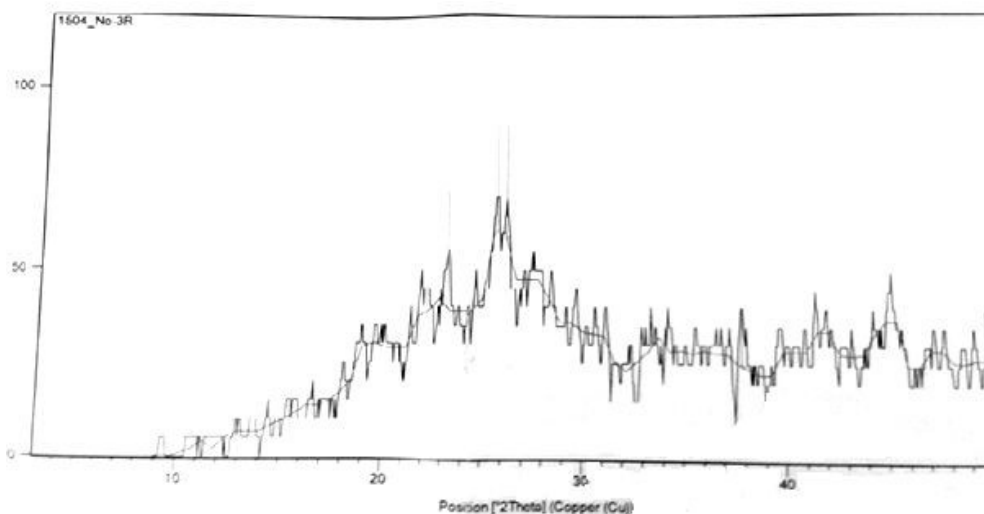


Figure 8: XRD pattern of nanoplex

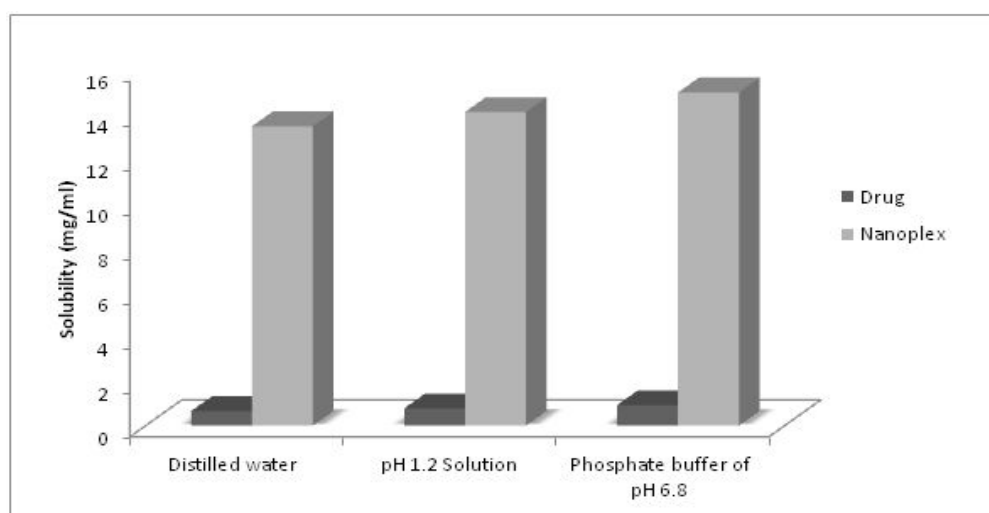


Figure 9: Solubility study of drug and nanoplex

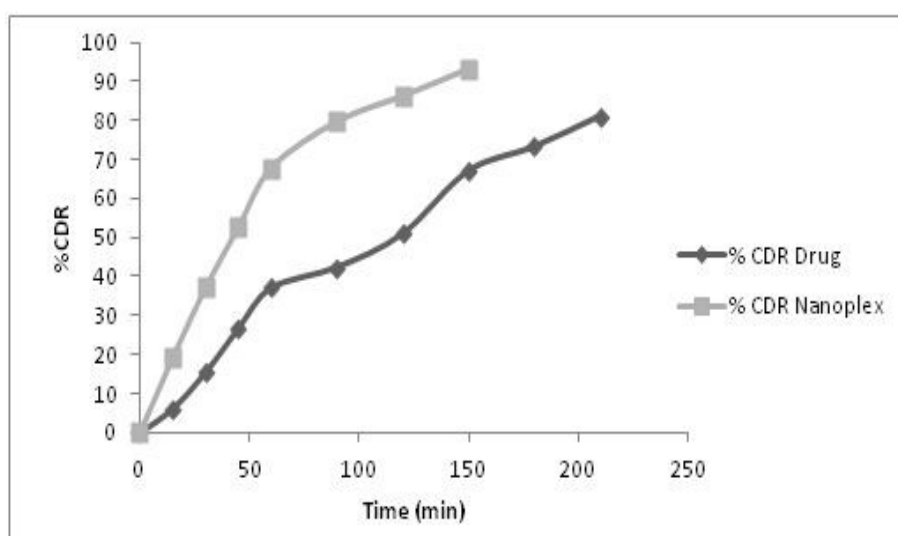


Figure10: Drug release study of nanoplex

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