

# An assessment of bioavailability of acrylate based pH-sensitive complexes of lovastatin

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**Abstract:** Lovastatin (LSN), a potent anti-hyperlipidemic drug, possesses poor bioavailability due to its very low aqueous solubility. The objective of this study was to establish a relationship between increased drug solubility before reaching site of absorption or increasing drug solubility at target absorption site for accentuated bioavailability of LSN. Composites of LSN with oppositely natured pH-sensitive acrylate polymers, cationic Eudragit EPO (EPO) and anionic Eudragit L100 (L100), were fabricated with physical trituration and kneading methods. Formulations were characterized for solubility, FTIR, PXRD, DSC, SEM, dissolution and bioavailability studies in rats. Interestingly, we observed that physical mixtures of EPO outmatched its kneaded formulations, whereas the physical mixtures and kneaded dispersions of L100 were virtually similar in characteristics. EPO was superior in boosting LSN solubility in the respective medium than the L100. Moreover, EPO produced immediate release profile in gastric environment whereas L100 offered sustained release of LSN in intestinal milieu. Bioavailability studies in rats further supported the EPO formulation in terms of shorter *Tmax*, higher *Cmax* and heightened AUC.

**Keywords:** Anti-hyperlipidemic drug, solubility, drug-polymer complexes, bioavailability.

## INTRODUCTION

Hyperlipidemia, abnormally elevated plasma triglycerides and cholesterol levels, being one of the major risk factors for cardiovascular diseases and the associated morbidity, is a major health burden in this era of human civilization (Kong *et al.*, 2018). Lovastatin (LSN), obtained from *Aspergillus terreus*, is a potent anti-hyperlipidemic drug that has very poor water solubility and belongs to Biopharmaceutics Classification System (BCS) class II. Partial drug absorption on account of meager drug solubility leads to poor bioavailability and subsequent sub-optimal efficacy of an active ingredient administered through oral route (Dhirendra *et al.*, 2009). Amongst the preferred formulations techniques, drug-polymer complexation in the form of solid dispersion is considered most suitable approach for solubilizing BCS Class II compounds (Yu *et al.*, 2018). This technique tends to increase aqueous solubility of drugs, courtesy of potential drug-hydrophilic carrier association, which in turn improves pharmacokinetic properties of the pharmaceutical actives (Halder *et al.*, 2018).

Eudragit EPO (EPO), a cationic polymer consisting of methyl methacrylate, N-N-dimethylaminoethyl methacrylate and butyl methacrylate monomers (1:2:1), possesses tertiary amines that ionize at the acidic pH to make the polymer highly soluble in fluids when pH is below 5. That is why it has been successfully complexed with hydrophobic drugs having dissolution rate dependent

bioavailability (Kerdsakundee *et al.*, 2015, Lin *et al.*, 2018, Pradhan *et al.*, 2016). Eudragit L 100 (L100), an anionic copolymer based on methacrylic acid and methyl methacrylate, is soluble in intestinal fluids (pH >6). L100 has been extensively used to ensure drug release in the intestinal pH only (Khalid *et al.*, 2018, Sahu and Pandey, 2019, Soudry-Kochavi *et al.*, 2018) and can also improve the drug solubility with controlled release behavior (Sareen *et al.*, 2014).

This work investigates the effect of the two oppositely natured pH sensitive acrylate polymers, EPO and L100, on the solubility and bioavailability of the poorly soluble LSN. Drug-polymer complexes were made with kneading method and simple physical trituration at three different drug to polymer ratios. Complexes were evaluated for solubility and dissolution in both gastric (0.1 N HCl, pH 1.2) and intestinal (Phosphate buffered saline (PBS), pH 6.8) media., Fourier transform infrared (FTIR), powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC) and scanning electron microscopy (SEM) studies were conducted to probe the drug-polymer interactions and nature of drug in the formulations. Finally, Sprague Dawley (SD) rats were used to probe the *in-vivo* performance of the selected preparations.

## MATERIALS AND METHODS

Nabiqasim Industries, Pakistan provided free sample of LSN. Morgan Chemicals, Pakistan arranged gift samples of EPO and L100 from Evonik (Germany). Analytical

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grade buffer salts, ethanol, HCl and other reagents were used as received.

Male SD rats (age: 4-6 weeks, weight: 150-180 g) were acclimatized one week prior to the experimentation with ad libitum access to tap water and standard food. Animals were housed at 22±2°C and 12 h dark/12 h light cycle. All animal experiments were approved by the Institutional Review Board, Government College University Faisalabad (Ref No. GCUF/ERC/1984, Study No. 19584, IRB No. 584, Dated 06-07-2018) and were performed in line with the institutional and international guidelines for animal care and ethics.

### Preparation of Drug-Polymer Complexes

Carrier polymers and drug at different ratios (table 1) were triturated with the aid of ethanol (solvent) using glass pestle and mortar for an hour. Ethanol was completely evaporated from the kneaded mixtures by placing them in the oven for 24 hours. Obtained dried mass was pulverized and stored in desiccator. Similarly, physical mixtures were prepared without the use of ethanol. QPE and QPL represent the physical mixtures, whereas, QKE and QKL indicate the kneaded formulations of LSN with EPO and L100, respectively.

**Table 1:** Drug-polymer complexes of LSN with EPO and L100 at varying ratios

Formulation	EPO	L100	LSN
QPE-1	1	-	1
QPE-2	2	-	1
QPE-3	4	-	1
QKE-1	1	-	1
QKE-2	2	-	1
QKE-3	4	-	1
QPL-1	-	1	1
QPL-2	-	2	1
QPL-3	-	4	1
QKL-1	-	1	1
QKL-2	-	2	1
QKL-3	-	4	1

### Solubility studies

An excess amount of pure drug or formulations was added into the 10mL of 0.1 N HCl, pH 1.2 or PBS, pH 6.8, vigorously vortexed for 5 min and subjected to shaking for 72h at 37°C. Afterwards, the mixtures were centrifuged, filtered (0.45µ nylon syringe filters) and assayed spectrophotometrically at 238nm using UV-Vis spectrophotometer, CE-7400S, Cecil, UK.

### FTIR, PXRD, DSC and SEM

FTIR spectra were acquired from Agilent Cary 600 FTIR spectrometer (Agilent, USA) at 4000 to 650 cm<sup>-1</sup> scan range. Scans were made at a resolution of 2 cm<sup>-1</sup>. Data were collected in the transmission mode and analysis was made by using Essential FTIR.

PXRD was obtained from powder X-ray diffractometer (PANalytical X'Pert Pro-MPD Powder Diffractometer, Philips, Netherland) in the range of 5-60° with Cu-Kα radiation at 40kV and 30mA. Scans were executed at a step size of 0.02° and a rate of 3°/min.

DSC analysis was performed using thermal analyzer (SDT Q600, V20.9 Build 20, TA instruments, USA) by sealing samples in an aluminum pan and heating at the rate of 10 °C/min. Analysis was carried out under nitrogen gas flow to ensure inert environment.

Surface morphology of gold coated pure drug and selected formulations was assessed via SEM (Vega 3 LMU, Tescan, Czech Republic) at a voltage of 8 kV.

### In vitro drug release studies

Dissolution behavior of pure drug and drug-polymer complexes was monitored over USP apparatus 2 (DT 70, Pharma Test, Germany) in 900mL of freshly prepared 0.1 N HCl, pH 1.2 or PBS, pH 6.8 at 37±0.5°C and 50 rpm. Accurately weighed quantities of formulations were placed into the dissolution medium. 5mL of sample aliquots were drawn at regular intervals with the replacement of fresh medium maintained at same temperature. Samples were assayed for the dissolved drug after filtration with membrane filters (0.45 µ).

### Pharmacokinetic study

Pure drug and selected preparations were given orally by gavage to the over-night fasting rats (n=6) at a dose of 100mg/kg of LSN. Blood samples (300µL) were collected at appropriate intervals from the retro-orbital sinus of the rats into the heparinized tubes. Plasma samples, separated by centrifugation at 5000 rpm for 10 min, were frozen at -20°C till drug assay performed over RP-HPLC (Shimadzu HPLC equipment, quaternary LC-20AD, DGU-20A5 degasser, SPD-20A UV-Vis detector). Acetonitrile: 0.01% phosphoric acid (40:60 v/v) was used as a mobile solvent at a flow rate of 1mL/min along with Promosil C-18 column (4.6×150 mm, 5 µm, 100 Å) as the stationary phase. Drug was extracted by liquid-liquid extraction. 100µL plasma was spiked with 10µL of internal standard (simvastatin, 5µg/mL) and diluted with 900 µL acetonitrile. Mixture was vortexed for 2 min and then centrifuged at 5000 rpm for 10 minutes to separate the supernatant organic solvent. Separated layer was vacuum dried in the oven. Afterwards, the dried residue was reconstituted with the 100 µL mobile phase, vortexed and injected (20µL) into the HPLC system.

## RESULTS

### Solubility studies

Solubility studies were conducted in the simulated gastric (0.1 N HCl, pH 1.2) and simulated intestinal media (PBS, pH 6.8) to assess the performance of each polymer in both conditions. Solubility of pure LSN was only 16.98±0.17

$\mu\text{g/mL}$  and  $18.90 \pm 0.02 \mu\text{g/mL}$  in acidic and basic media, respectively. Absence of ionizable groups have been deemed for pH independent poor solubility of LSN (Serajuddin *et al.*, 1991). Solubility of LSN in the acidic media increased with the increase in the proportion of the EPO but decreased with the increase of L100 (fig. 1a). The inverse behavior was observed in the alkaline conditions (fig. 1b). Interestingly, physical mixtures prepared by EPO (QPE 1-3) were more good at improving the drug solubility than the kneaded complexes (QKE 1-3) formulated at same drug to polymer ratios. QPE-1, QPE-2 and QPE-3 caused an overall increase of almost 1373%, 1587% and 1828% in the drug solubility, respectively. Whereas, increase in solubility manifested by QKE-1, QKE-2 and QKE-3 was 1170%, 1278% and 1610 %, respectively.

L100 dispersions increased the solubility of LSN in the alkaline medium (fig. 1b) but the raise was very small as compared to the performance of EPO in acidic conditions. The overall solubility raise of LSN was nearly 101%, 108

%, 166%, 161%, 161% and 189% for QPL-1, QPL-2, QPL-3, QKL-1, QKL-2 and QKL-3, respectively. Nonetheless, the L100 kneaded formulations possessed better solubilities than their counterpart physical mixtures that indicates that ethanol as a solvent favors the complexation between LSN and L100. However, difference between QKL-3 and QPL-3 was statistically insignificant ( $p > 0.05$ ).

#### FTIR, PXRD, DSC and SEM

In order to identify the possible interactions among components of a formulation, FTIR studies have been frequently employed in the literature (Salmani *et al.*, 2015). fig. 3 shows the FTIR spectra of LSN, polymers and the formulations. The bands observed at 3537, 3019, 2967, 2929, 2866, 1722, 1696, 1457, 1379, 1260, 1215, 1073, 1055, 969 and  $868 \text{ cm}^{-1}$  in the LSN spectrum corresponded to alcohol OH stretching, alkene stretching, methyl C-H asymmetric stretching, methylene C-H asymmetric stretching, both methyl and methylene groups asymmetric stretching, lactone stretching, carbonyl ester

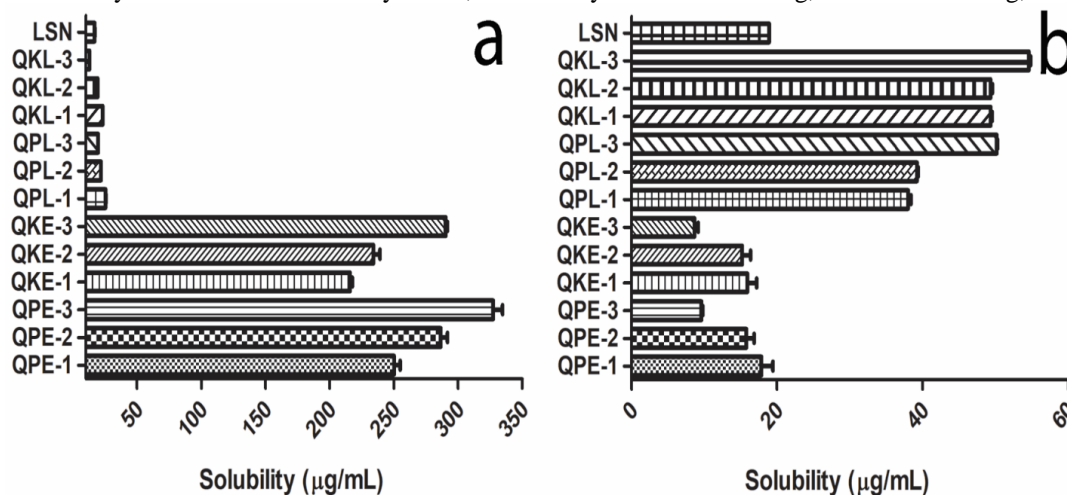


Fig. 1: Solubility of pure LSN and drug-polymer complexes at  $37^\circ\text{C}$  in 0.1 N HCl, pH 1.2 (a) and PBS, pH 6.8 (b).

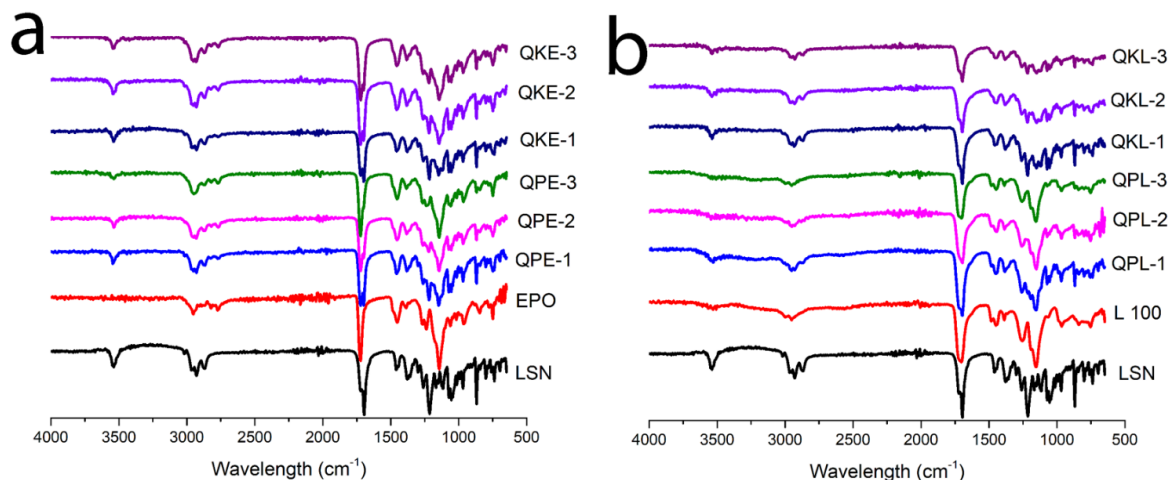


Fig. 2: FTIR spectra of pure LSN and EPO formulations (a) and L100 formulations (b).

stretching, methyl asymmetric bending, methyl symmetric bending, lactone C-O-C asymmetric bending, ester C-O-C asymmetric bending, lactone C-C symmetric bending, ester C-O-C symmetric bending, alcohol C-OH stretching and C-H of tri-substituted alkene, respectively. LSN spectrum was parallel to the spectrum reported elsewhere (Yadava *et al.*, 2015); which asserts that the drug used in this research was pure.

FTIR spectrum of EPO is displayed in fig. 2a. Stretching of asymmetric methyl, non-protonated dimethylamine, stretching of carbonyl ester, bending of methyl C-H, stretching of ester C-O, C-N stretching of aliphatic amines and/or C-O stretching of ester group were visible at 2952, 2821 and 2773, 1722, 1453, 1267 and 1237, and 1144  $\text{cm}^{-1}$ , respectively. These peaks are in-line with the already reported spectrum of EPO (Moustafine *et al.*, 2017). L100 spectrum is shown in figure 3b, similar to the published research (Ozgunduz *et al.*, 2018). CH vibrations were identified at 3000, 2952, 1483 and 1386  $\text{cm}^{-1}$ . Vibration of carboxylic C=O was prominent at 1703  $\text{cm}^{-1}$ . Peaks at 1260, 1192 and 1155  $\text{cm}^{-1}$  were representative of ester vibrations.

LSN crystalline form was evident in the PXRD (fig. 3) as mentioned in the literature (Riekes *et al.*, 2017). Whereas, both EPO (fig. 3a) and L100 (fig. 3b) showed that increasing the polymer resulted in substantial decrease in the crystallinity of the drug which also conforms to the

previous reports (Chen *et al.*, 2014, Meng *et al.*, 2015). It was amazing to find out that physical mixtures also reduced the drug crystallinity and the difference between the complexes formed by both methods was marginal for either polymer.

LSN has been reported to show melting of its crystals around 170°C (Wu *et al.*, 2011), our results (fig. 4) also comply with the previous findings. fig. 4a and b show thermograms of formulations prepared by EPO and L100, respectively. Slight broadening and shift in the melting point of the drug was observed for all the preparations. Overall, the decrease in sharpness of the endothermic peak was directly related to the polymeric contents of the dispersions. But, EPO formulations and specifically the physical mixtures showed more loss of the characteristic sharp endothermic peak of the drug than the rest of formulations.

Morphology of the pure drug and selected preparations (QPE-3, QKE-3, QPL-3 and QKL-3) are shown in fig. 5. Well defined crystals of drug with rectangular dimensions and rough edges are prominent in fig. 5a which is quite typical of the crystalline LSN (Patel *et al.*, 2008). The crystallinity of drug was not observed in the selected formulations indicating that both physical trituration alone or in the presence of solvent (kneading) produced drug loaded matrices with marked reduction in the drug crystallinity. Lack of crystalline drug in the SEM images

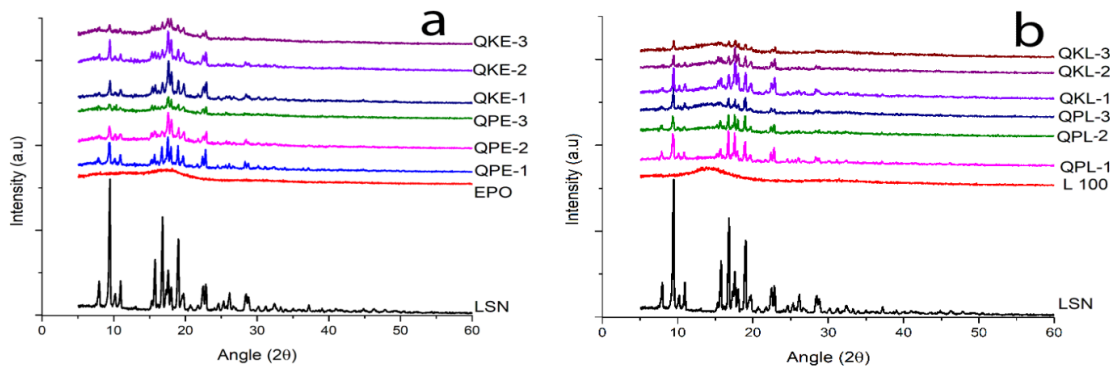


Fig. 3: PXRD of pure LSN and drug-polymer complexes with EPO (a) and L100 (b).

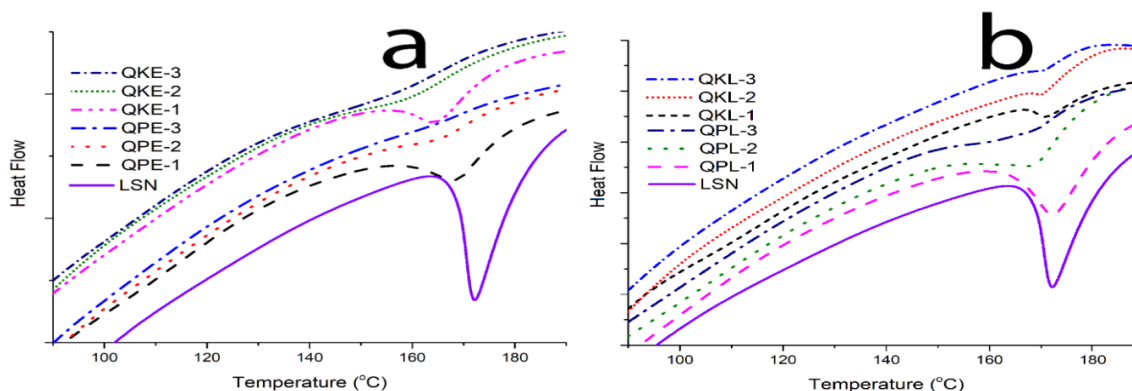


Fig. 4: DSC of pure LSN and drug-polymer complexes with EPO (a) and L100 (b).

also support the notion that LSN complexation with the acrylate polymers improved its solubility.

### ***In vitro drug release studies***

Pure LSN had a very poor dissolution rate (<20% dissolved within 2h) in both conditions (0.1 N HCl, pH 1.2 and PBS, pH 6.8). A very rapid drug dissolution (> 60%) was observed with EPO in acidic conditions just within 5 min for all EPO preparations (fig. 6a). Whereas, QPE-3 and QKE-3 showed almost 80% drug release within 5 min. So, higher EPO levels speeded up the drug dissolution process. L100 based formulations did not offer significant change in the drug release owing to the poor solubility of L100 in gastric medium.

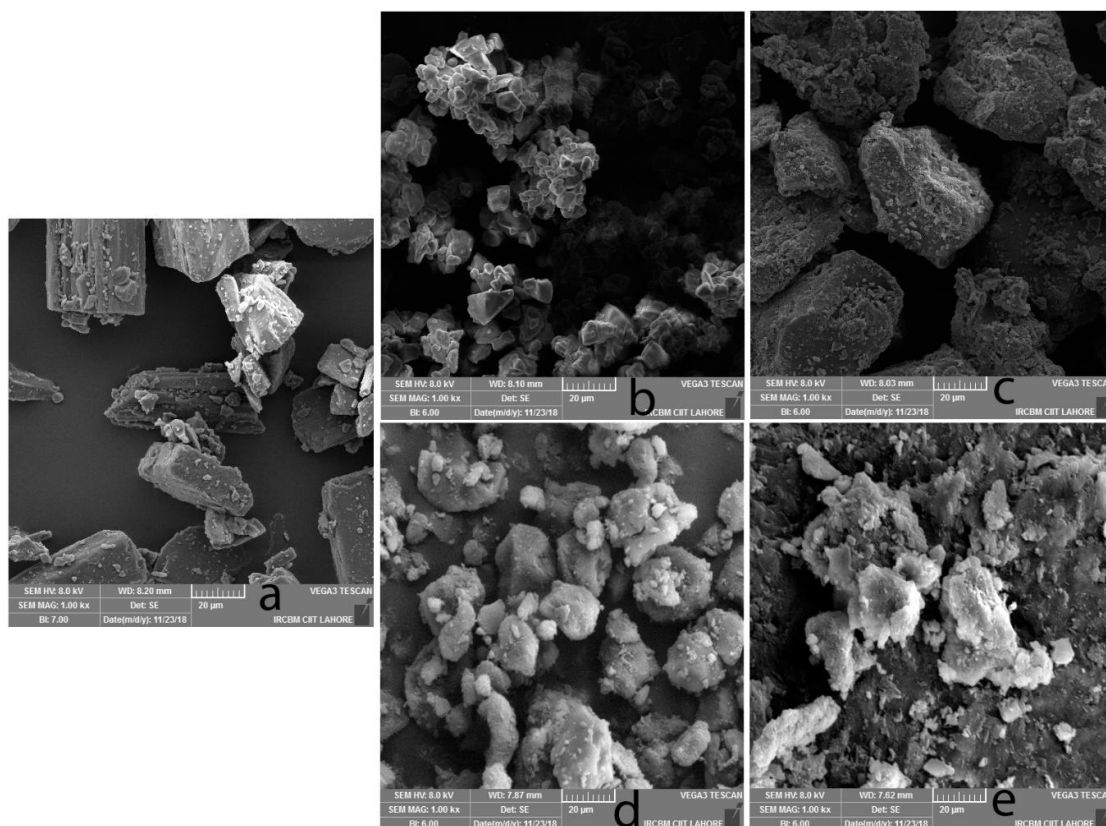
Similarly, EPO did not affect the drug release behavior in alkaline medium as EPO itself precipitates at pH above 5.5. L100 preparations do yielded 100% drug release within 2h but all the preparations followed somewhat sustained release phenomenon (fig. 6b). In addition, kneaded formulations yielded slightly lower release rate than the physical mixtures which could be attributed to the marginally better interaction of the LSN with L100 in kneaded form as apparent from the solubility data. Overall, the greater ratio of L100 in preparations (QPL-3 and QKL-3) led to a more controlled release. Previously, naproxen loaded L100 micro particles were observed to show burst release at lower polymer/drug ratios, which

diminished when the polymer/drug ratio was raised to 4:1 (Maghsoodi, 2009). We also observed that at 1:1 L100/LSN ratio (QPL-1 and QKL-1), almost 50% drug was released within 5 min. While, 25-30 % drug release was noticed at 4:1 L100/LSN ratio for the same duration.

### ***Pharmacokinetic study***

Keeping in view of all the above characterization, physical mixture based dispersions at a polymer/drug ratio of 4:1 were selected for the *in vivo* experimentation. fig. 7 shows the pharmacokinetic performance of the QPE-3, QPL-3 and pure LSN in the over-night fasting rats after single oral administration. Both formulations, QPE-3 and QPL-3, improved the bioavailability of the LSN.

Table 2 displays the PK parameters calculated by non-compartmental analysis.  $T_{max}$  of QPE-3 was much earlier than the QPL-3 and the pure LSN. This decrease in the  $T_{max}$  would contribute to attaining therapeutic effect very quickly with the dose administration. QPE-3 also produced approximately 45% and 142% greater  $C_{max}$  than the QPL-3 and pure LSN. Whereas, QPL-3 achieved more or less 66% higher  $C_{max}$  than the LSN. Correspondingly, QPE-3 caused approximately 66 % and 143% increase in the  $AUC_{0-t}$  than the QPL-3 and LSN, respectively. QPL-3 was also able to boost  $AUC_{0-t}$  by nearly 64% than the pure drug. Plasma  $T_{1/2}$  remained virtually same for all the tested preparations.

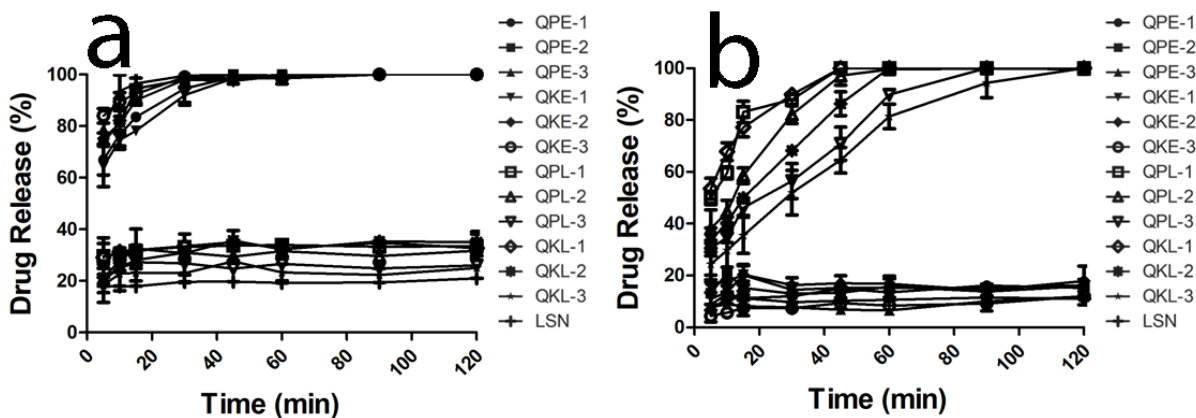


**Fig. 5:** SEM photographs of LSN (a), QPE-3 (b), QKE-3 (c), QPL-3 (d) and QKL-3 (e) at a magnification of 20  $\mu\text{m}$ .

**Table 2:** PK parameters of LSN obtained from oral administration of pure LSN and selected drug-polymer complexes in fasting rats (n=6)

Formulations	PK Parameters			
	$C_{max}$	$T_{max}$	$AUC_{0-t}$	$T_{1/2}$
QPE-3	4351±886*#	1	20312±4638*	2.72±0.002
QPL-3	2992±873*	2	13702±4687	2.69±0.077
LSN	1800±907	2	8344±6176	2.52±0.559

\* indicates  $p < 0.05$  vs LSN, # indicates  $p < 0.05$  vs QPL-3



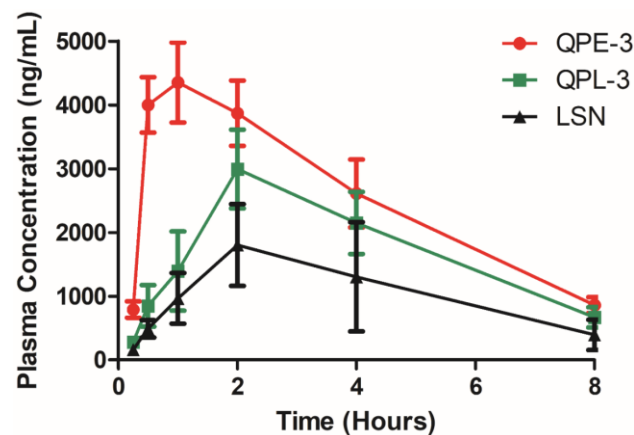
**Fig. 6:** *In-vitro* drug release behavior of pure LSN and the drug-polymer complexes in 0.1 N HCl, pH 1.2 (a) and PBS, pH 6.8 (b).

## DISCUSSION

LSN is a known HMG-CoA reductase inhibitor that lowers the bad lipids in the blood. However, its therapeutic potential is limited by its lower aqueous solubility (Sarangi *et al.*, 2018) which results in very poor bioavailability (~5%) (Leone *et al.*, 2018). Ethanol was selected as the solvent for the preparation of kneaded formulations, as both polymers (EPO and L100) and drug are soluble in it. Use of a common solvent ensures greater compatibility between drug and polymer in the kneaded complexes (Volkova *et al.*, 2017). EPO has a low glass transition temperature ( $T_g$ ) than the L100 (Parikh *et al.*, 2016), the decreased crystallinity in the physical mixtures of EPO and LSN could be due to the generation of heat during the hour long trituration process. This heat might be sufficient to induce fusion between the EPO and LSN, whereas the higher  $T_g$  of the L100 could not allow this behavior in its physical mixtures. It shows that EPO made a very good complex with the drug. Similarly, Leonardi and Salomon (2013) found out that physical mixture of benzimidazole with PEG 6000 was equally effective in improving the drug dissolution rate as compared to the preparations made with solvent evaporation (Leonardi and Salomon, 2013), as a matter of fact, PEG 6000 is also a low  $T_g$  polymer (Altamimi and Neau, 2017). This could explain the higher solubilities of the EPO physical mixtures than their counterpart kneaded dispersions.

The observations made in solubility studies, PXRD and DSC assay iterate that physical grinding of EPO with the

LSN not only facilitates the reduction in drug crystallinity but also allows better interaction of the polymer with the drug at molecular level. Both hydrophilic polymers interacted with the drug at the molecular level for reducing its crystallinity and then the subsequent solubility improvement. EPO based formulations showed noticeably lower intensities than the L100 preparations. Decreased crystallinity leads to greater surface area which in return boosts the solvation of drug molecules (Abuzar *et al.*, 2018). Additionally, these findings also imply superior interaction between LSN and EPO rather than LSN and L100.



**Fig. 7:** Plasma concentration vs time profile of pure LSN and selected drug-polymer complexes in fasting rats (n=6) after single oral administration (dose=100 mg/kg).

FTIR spectra of the dispersions made with EPO and L100 are depicted in fig. 2a and 2b, respectively. It is clear from the respective spectra that LSN maintained its chemical integrity in all the formulations whether these were physical mixtures or kneaded dispersions. The decrease in the vibrational intensities of the LSN in the dispersions' spectra owes to the coinciding vibrations of the polymers and/or the weak non-covalent interplay among the drug molecules and the polymers (van der Waal's interaction or hydrogen bonding). The slight shift in alcohol OH stretching of LSN to slightly higher wavelength in EPO based preparations designates hydrogen bonding in these complexes.

It is obvious from the results that rapid dissolution of the drug in the gastric media provided by EPO permitted maximum drug to be available in the molecular form that could be readily absorbed from the intestine. L100 also improved the bioavailability but it is evident from our findings that the delayed drug dissolution and the sustained release behavior of the polymer hinders complete LSN absorption. It could be inferred that delayed drug release from QPL-3 might have caused most of the drug to be released after the formulation crossed the absorption window in the small intestine.

Cationic charge of the acrylate (EPO) could also be another reason for better absorption of the LSN. Alasino *et al.* studied the interaction of EPO with the lipid-monolayer membranes to mimic the biological membranes and recognized the charge driven interaction b/w EPO and lipidic membrane (Alasino *et al.*, 2012). Banerjee *et al.* reported EPO based intestinal mucoadhesive device for the delivery of insulin and proposed the interaction of the positively charged EPO chains with the oppositely charged mucin for enhanced drug absorption (Banerjee *et al.*, 2016). Hence, the prompt drug dissolution and the interaction of the cationic EPO with the gastrointestinal membrane could rationalize the superior bioavailability of QPE-3 in this study. Guo *et al.* reported higher bioavailability for fast dissolving LSN rod nanocrystals than the slow dissolving spherical nanocrystals (Guo *et al.*, 2015). They suggested that fast dissolution of the drug permits major part of the drug to reach the circulation due to saturation of the metabolizing enzymes.

## CONCLUSION

This study reveals that drug-polymer complexes based on physical trituration of LSN with EPO at 4:1 ratio can significantly improve the drug's solubility and hence its bioavailability and pharmacodynamic activity in a pH dependent manner. Solid-state characterization, drug polymer interactions and morphology studies also support the performance of the EPO physical mixture formulation. *In-vitro* dissolution studies exposed immediate release by EPO preparations whereas L100 formulations promoted

delayed and somewhat extended release of drug. Bioavailability results address that presentation of drug in already solubilized form at the site of absorption rather than solubilizing the drug at the target region in a sustained release manner would significantly improve the drug absorption and its overall beneficial effects. Furthermore, absence of solvents in the method and the extra steps involved in the solvent removal could prove to be pivotal in commercial acceptance of this approach.

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