DRUG RELEASE MECHANISM OF SPARINGLY SOLUBLE ANTI-INFLAMMATORY DRUG FROM PVP LOADED NANOCARRIER

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During the last two decades one of the most important problems in drug formulations has been low aqueous solubility of new molecules. However, numerous technique, such as milling, co-solvent solubilization and solid dispersion have been used conventionally for aqueous solubility enhancement and the rate of solubility. In this study, the effect of surfactants in *in vitro* dissolution and solubility of indomethacin in various fluids such as purified water (pH 6.4), sodium lauryl sulphate (SLS), Cetyl tri methyl ammonium bromide (CTAB), Polyvinylpyrrolidone (PVP 44000) have been determined. Enhanced solubility was observed at 7.2 phosphate buffer and 3×10^{-6} M PVP. In aqueous media, Indomethacin (INMN) exhibits very poor solubility at 37°C (mg/mL). 7.2 phosphate buffer with PVP 44000 (3×10^{-6} M) increased the solubility 7.05 folds, indicating that the incorporation of INMN into the micelle was significant. Scanning Electron Microscopy (SEM) to examine the surface topography morphology of fractured of sectioned surface, to analyze the surface of polymeric drug delivery system that can provide important information about the SEM analysis. Topographical (TEM) image suggested the absence of the chemical interaction between the drug and carrier. Particle size distribution of INMN loaded liquid nanoparticles were determined by dynamic light scattering (Malvern Zetasizer).

Keywords: Indomethacin, nanoparticles, PVP 44000, Dissolution, SEM, TEM.

Introduction

INMN is a number of the non-steroidal anti-inflammatory drugs (NSAIDs) [1]. The drug is described as poorly soluble and highly permeable (class II) drug [2]. Because poorly water soluble drugs often show low absorption and weak bioavailability, improvement in dissolution rate and solubility are important for development of drug preparations [3-4]. It has been established

that the active ingredient in solid dosage form must undergo dissolution before it is available for absorption from gastrointestinal tract. The rate of absorption of poorly water-soluble drug, formulated as an orally administered solid dosage form, is controlled by its dissolution rate in the fluid present at the absorption site, i.e. the dissolution rate is often the rate–determining step in drug absorption. Therefore, the solubility and dissolution behavior of a drug are the key determinants of its oral bioavailability [5-8].

Over the years, a variety of solubilization techniques have been studied to improve the dissolution rate of this widely used antirheumatic agent, to obtain more rapid and complete absorption includes –

i) Reducing the particle size to increase surface area thus increasing the drug dissolution rate [9-13],

ii) Solubilization in surfactant systems [14-15],

iii) Formation of water-soluble complexes [16-17],

iv) Liquisolid compacts [18-25],

v) Manipulation of the solid state of a drug substance to improve drug dissolution, i.e. by decreasing crystalinity of the drug substance through formation of solid solutions [26-27].

The most common method is to increase solubility and dissolution rate by using surfactants.

It is possible to modify the release behavior of the drug by the introduction of swellable polymer such as polyvinylpyrrolidone.

According to the different characteristics of the polymer used these drug delivery systems exhibit different release kinetics and swelling behavior [28-29]. As the swelling behavior of such systems will be directly related to the drug release mechanism, it is important to understand such behavior.

Material and Methods

The Indomethacin drug obtained from Glenmark Pharmaceutical as a gift sample and PVP (AR grade) was purchased from British Drug House (BDH). SLS was purchased from Hi Media. PEG was obtained from Merck and CTAB was purchased from Chemical Drug House (CDH). All Other reagents used were of AR grade. Distilled water was used during the entire experiment.

Determination of λ_{max} of pure INMN

10 mg accurately weight drug was transferred into a 100 mL calibrated volumetric flask. The drug was dissolved in pH 7.2 buffer + PVP 44000 (at its CMC). The volume was made up to the mark with maintaining the pH (7.2) and CMC of PVP 44000 (3×10^{-6}). The absorbance of INMN scanned over the range of 200-400 nm. The spectrophtometric analysis of all INMN samples was performed at 319 nm UV-visible spectrophotometer.

Solubility determination:

An excess amount of sample was placed in different fluids such as distilled water, PEG 400, PEG 4000, SLS, CTAB, and PVP 44000 at phosphate buffer 7.2. The samples were shaken at 37°C in a horizontal shaker. The supernatant was filtered through a Millipore filter (pore size 0.45 μm). The surfactants concentrations were taken at their CMCs values. 1 mL of the filtrate was immediately diluted and assayed spectrophotometrically at 319 nm. All experiments were conducted in triplicate.

Table 6.2: Solubility of INMN in different media

S. No.	Sample	Wt. of drug (mg)	Overall volume (mL)	Absorbance (at 319 nm)	Solubility increase in fold
1.	INMN + Distilled water	15	25	0.140	1.00
2.	INMN + CTAB	15	25	0.506	3.61
3.	INMN + PVP 44000	15	25	0.928	6.62
4.	INMN + PEG 400/CTAB	15	25	0.318	2.27

5.	INMN + SLS	15	25	0.480	3.42
6.	INMN + PEG 4000/PVP 4000	15	25	0.910	6.50
7.	INMN + PEG 4000	15	25	0.218	1.55
8.	INMN + PEG 400	15	25	0.496	3.55
9.	INMN + PVP 44000 + Phosphate buffer (7.2)	15	25	0.988	7.05

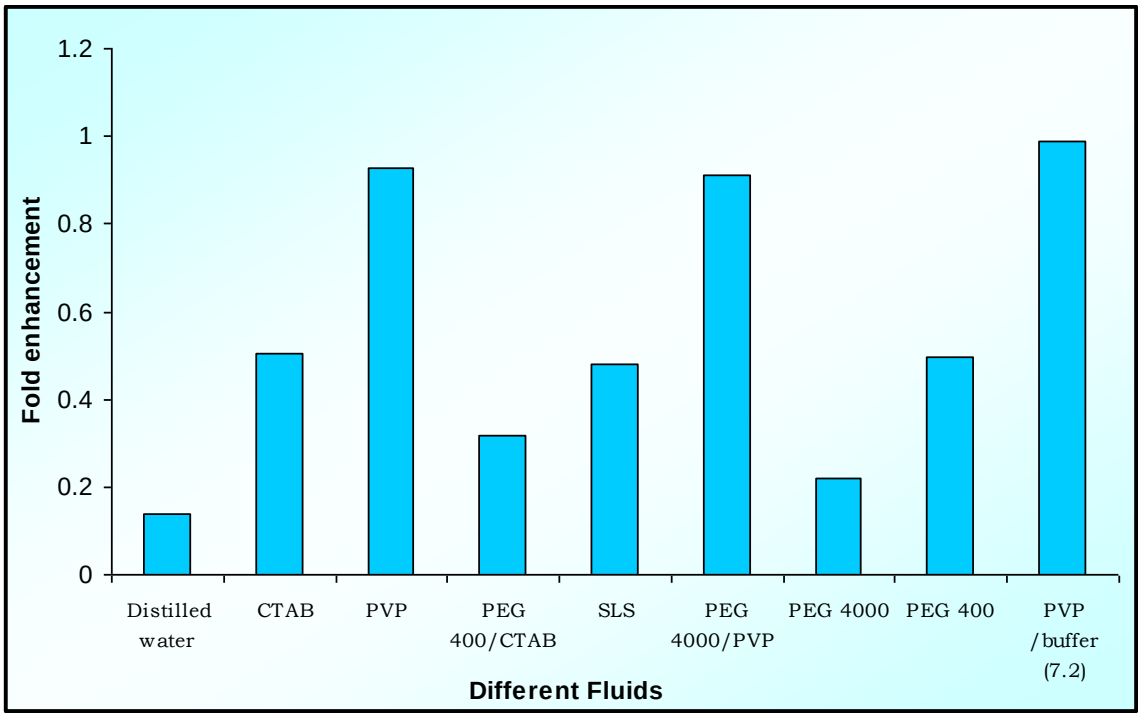

Fig. 1: Solubility determination of INMN in different fluids

***In Vitro* dissolution study:**

1. **Apparatus:** Electrolab TDT-08L USP apparatus.
2. **Dissolution Media:** Phosphate buffer (7.2) + 3×10^{-6} M PVP 44000
3. **Rotation speed**: 50 rpm.

4. **Preparation of INMN standard solution:** 10 mg INMN USP standard was weighed precisely, put in 100 mL volumetric flask and made up to the mark with dissolution media.

5. **Test preparation:** A batch of 20 tablets of INMN (75 mg) was procured for comparative studies of three brands. The dissolution experiments was performed using USP apparatus at 37° ± 0.5°C with paddle speeds of 50 ± 5 rpm in 750 mL dissolution medium. A 5 mL sample was withdrawn at different time intervals and filtered through syringe filter (pore size 0.45 μm). The same volume of fresh medium was replaced to maintain constant volume. The sample was suitably diluted and analyzed using UV-visible spectrophotometer at 319 nm.

6. **Time point:** Dissolution amount was measured separately at 5, 10, 15, 20, 25, 30 and 60 minutes.

PREPARATION OF NANOPARTICLES

Nanoparticles made of polymeric micelles are better targetable materials, because (i) these particles have a hydrophilic surface and (ii) their size are much less than diameter 100 nm, The bulk cores of these particles are hydrophobic so it is suitable for INMN hydrophobic drug. In this method, monomer phosphate buffer pH 7.2 in PVP 44000 are polymerized to form nanoparticles in an aqueous solution drug (0.1%w/v) is incorporated either by being dissolve in the polymerization medium or by absorption on to the nanoparticles after polymerization completed. The mixture was stirred for 24 hrs. The nanoparticles suspension is then purified to removed various stabilizers and surfactants employed for polymerization by ultracentrifugation and to produce small particle size, often a high- speed homogenization or ultrasonication may be employed [30]. The primary role of stabilizers and surfactant is to inhibit excessive crystal growth or particle aggregation/agglomeration in the solution [31]. This technique has been reported for making polybutylcyanoacrylate or poly (alkylcyanoacrylate) nanoparticles [32-33]. Nanocapsule formation and their particle size depend on the concentration of the surfactant and stabilizers used [34].

Fig. 1 shows the enhance solubility of INMN in different fluids as function of surfactant concentration.

Enhanced solubility was observed at 7.2 phosphate buffer and 3×10^{-6} M PVP. In aqueous media, INMN exhibits very poor solubility at 37°C (mg/mL). 7.2 phosphate buffer with PVP

44000 (3×10^{-6} M) increased the solubility 7.05 folds, indicating that the incorporation of INMN into the micelle was significant.

The dissolution behavior of INMN with 7.2 phosphate buffer and PVP 44000 was examined by plotting the percentage of drug released against time as shown in Fig. 2. The initial dissolution profile of the INMN was observed in the first 30 minutes was a linear relationship.

As a general conclusion, the faster drug dissolution was observed at pH 7.2 and PVP 44000 (3×10^{-6} M). PVP was oriented on to surface of INMN particles and decreased drug surface tension. This led to the extreme higher interaction of drug to PVP 44000 and increased drug wettability. During dissolution the interfacial layer between the dissolving front and the dissolution bulk medium became rich of carrier since the drug was rapidly dissolved.

The release rate process by simply comparing the correlation coefficient values of lines collected from graphical presentation of different mathematical models. The model with highest correlation coefficient is then selected. To find out the mechanism of drug release from immediate release capsules of INMN in phosphate buffer + PVP 44000, the data were treated in different mathematical model like zero order, first order, Korsmeyer, Higuchi equation. The release data were plotted according to these models. From the linear portions of curves, slope and correlation coefficient (r^2) were calculated. With the Korsmeyer plot, linearity was noted highest in all formulations using all data points. The data yielded apparently straight line with Korsmeyer plot ($r^2 > 0.978$). The values of release rate exponent (n), calculated as per the equation proposed by Korsmeyer *et al*, ranged between 0.66 –0.71. The values of 'n' indicate anomalous (non-Fickian or coupled diffusion/relaxation) drug release. It is concluded that the INMN released from immediate release tablet follows Korsmeyer's release kinetics i.e. log % of drug release *vs.* log time.

Scanning Electron Microscopy (SEM) to examine the surface topography morphology of fractured of sectioned surface, to analyze the surface of polymeric drug delivery system that can provide important information about the SEM analysis.

Fig. 11 displayed SEM photographs for INMN, PVP 44000 + pH 7.2 phosphate buffer. The drug crystals seemed to be irregular shape and size. The physical mixture of the drug and the

carrier showed the presence of drug in the crystalline form. Similar observations were earlier reported with PEG 4000. Topographical (TEM) image suggested the absence of the chemical interaction between the drug and carrier.

Particle size distribution of INMN loaded liquid nanoparticles were determined by dynamic light scattering (Malvern Zetasizer). I achieved the smallest particle size distribution in the nano range. In this work, assuming that precipitation occur in appropriate conditions. Narrower distributions were observed as polymer - drug ratio was perfect [Fig.10].

Therefore, it can be concluded that perfection in polymer – drug concentration may cause a reduction in the particle size distribution up to some extent.

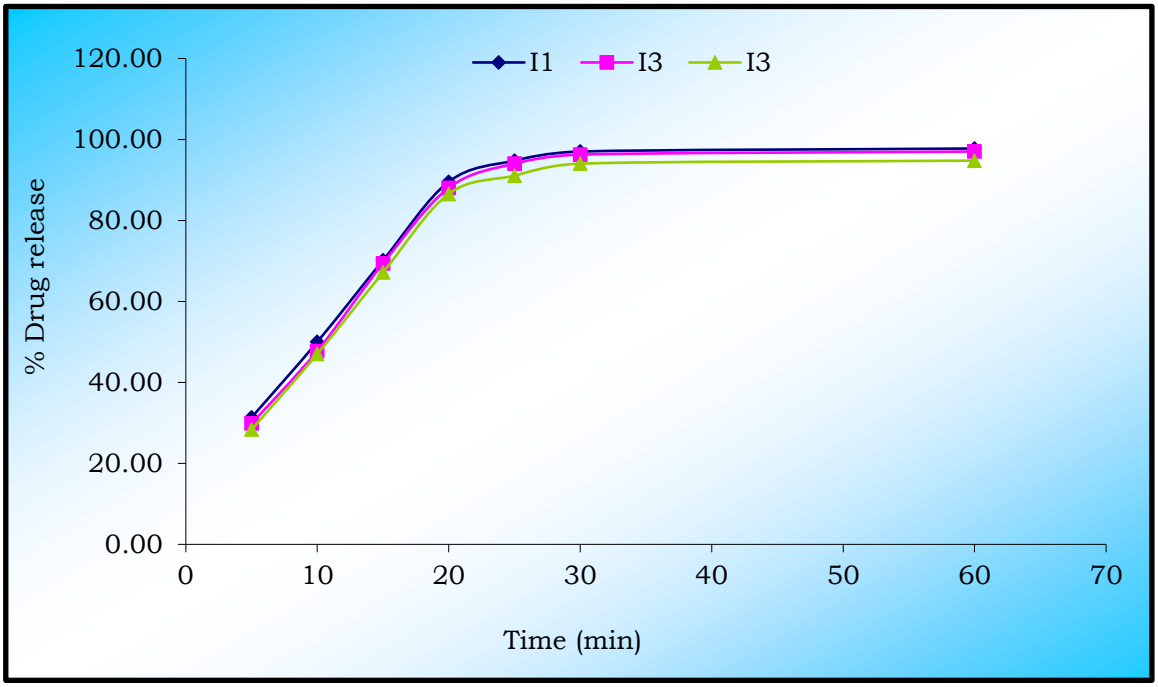

Fig. 2: Dissolution profile (n=3) of three commercial products of INMN in polymeric micellar media (Zero order plot)

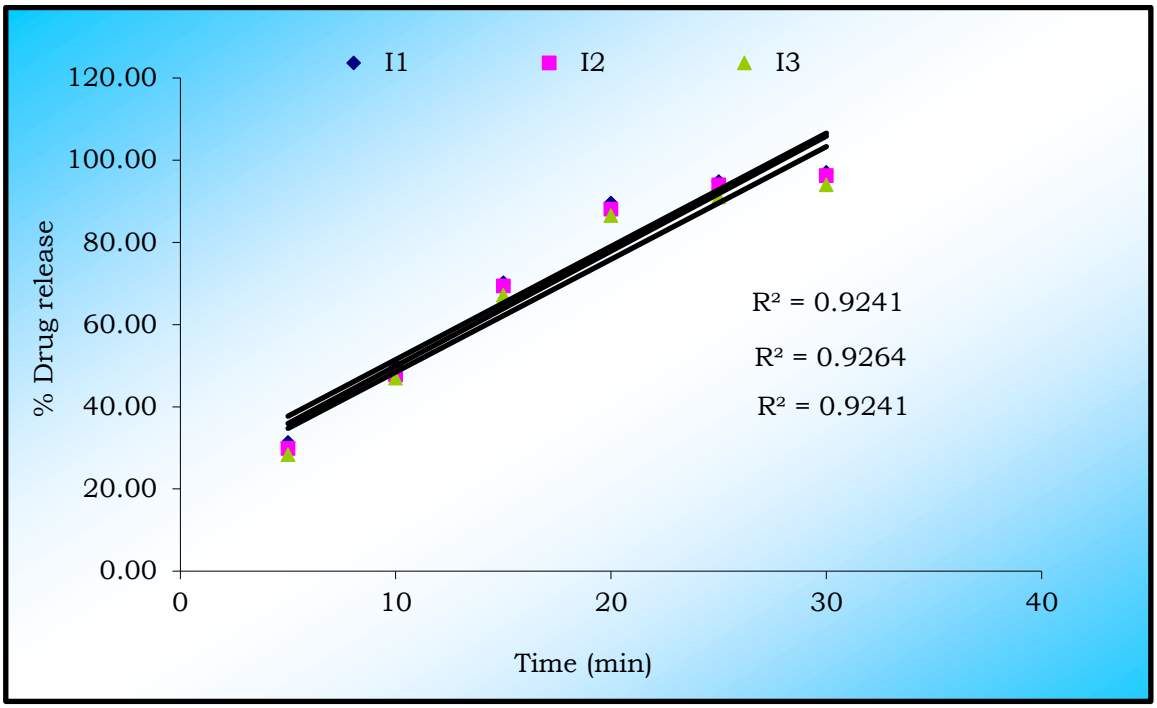

Fig. 3: Regression plot for zero orde

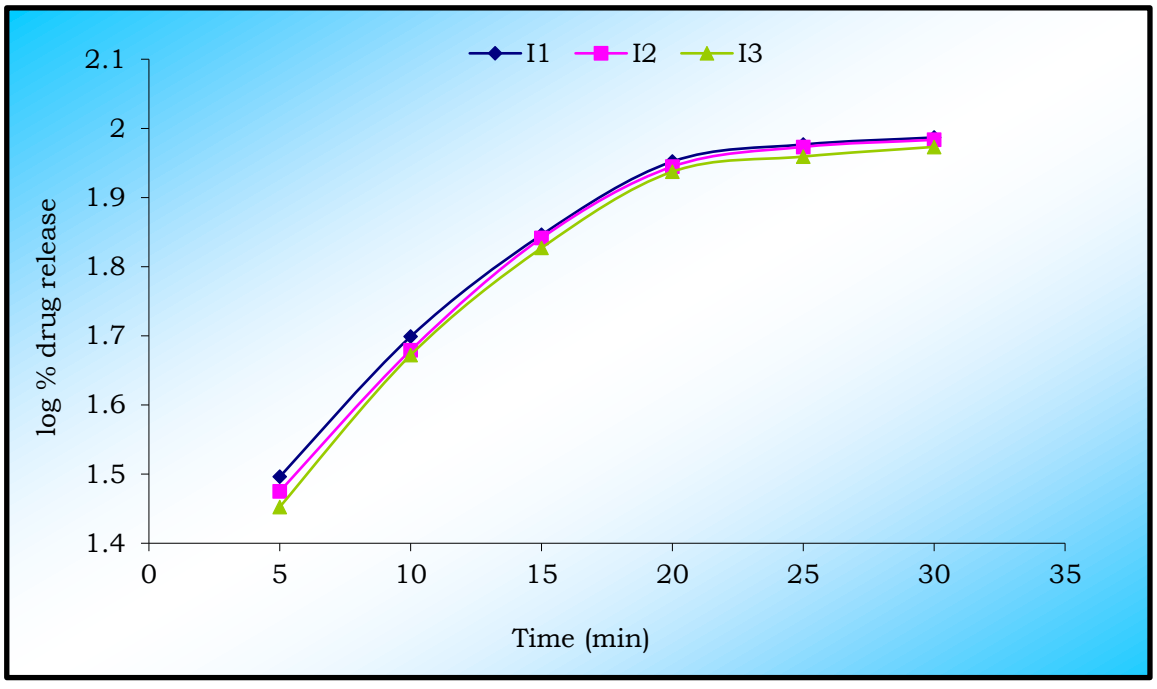

Fig.4: First order plot

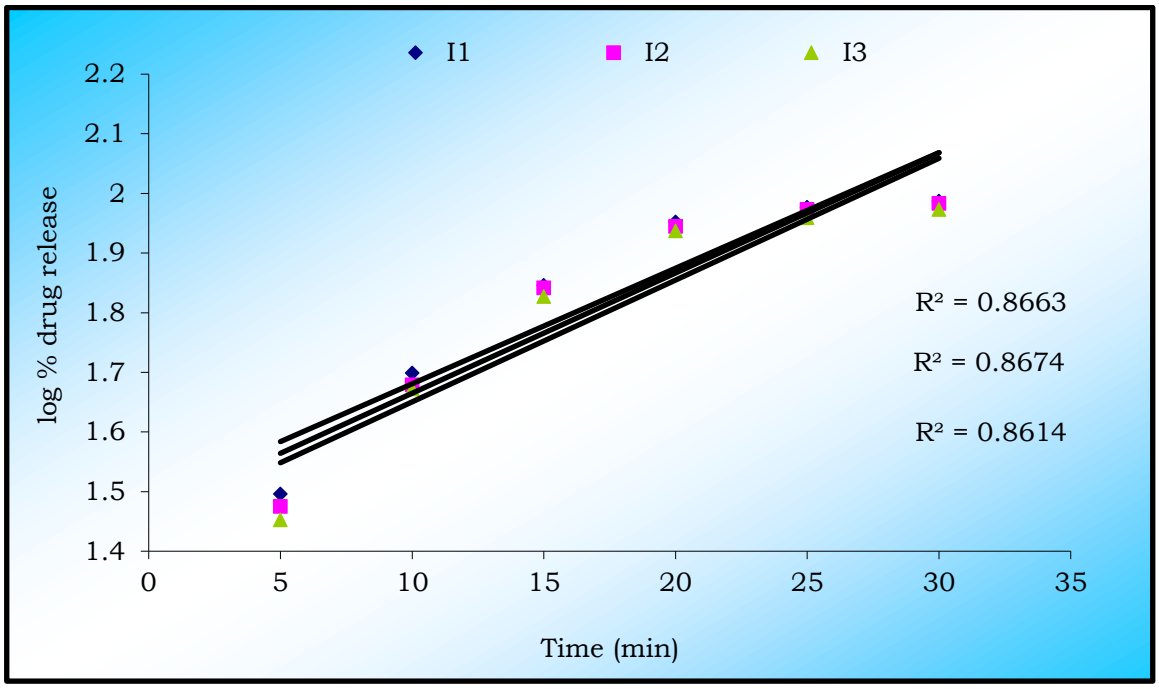

Fig.5: Regression plot for first order

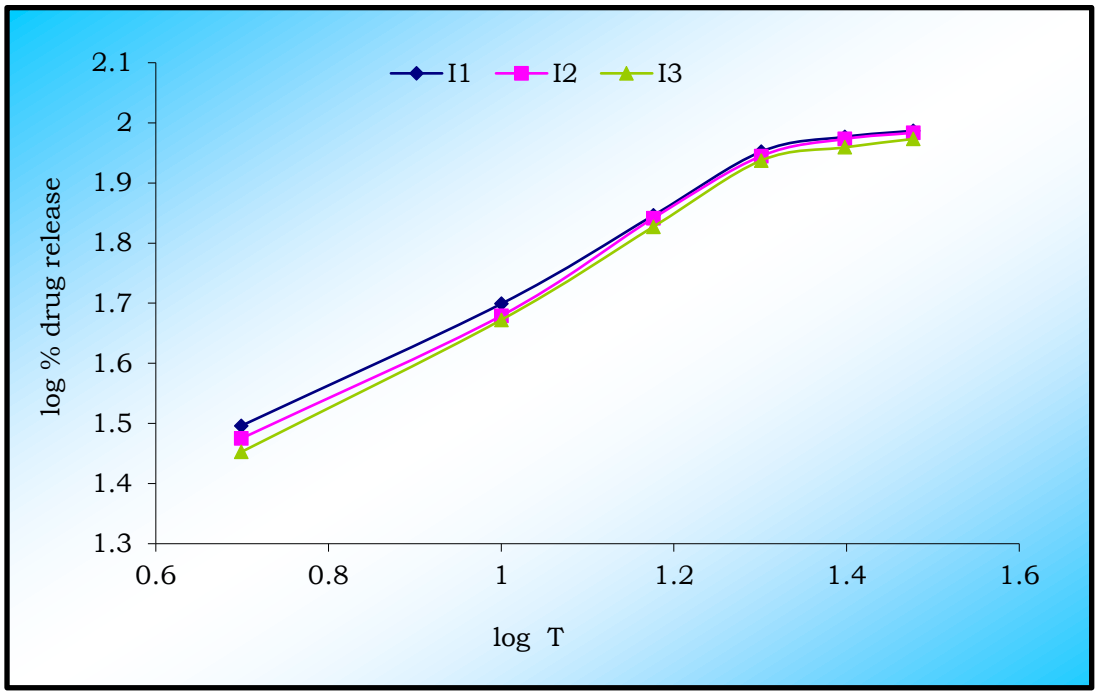

Fig. 6: Korsmeyer Plot

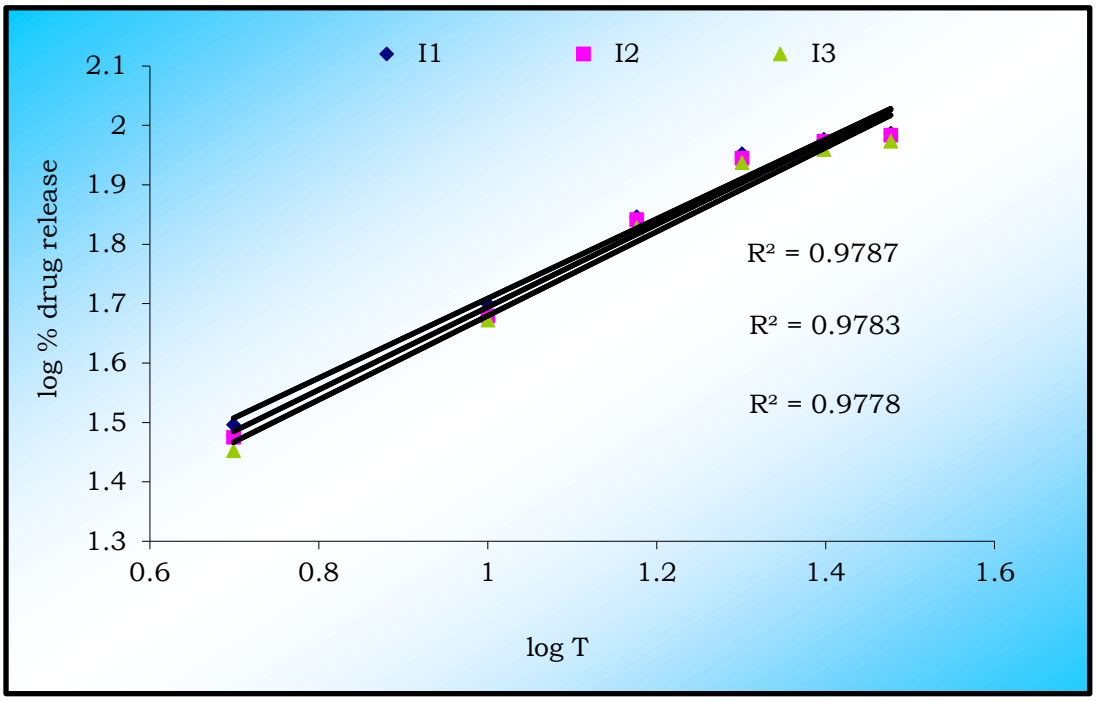

Fig. 7: Regression plot for Korsmeyer model

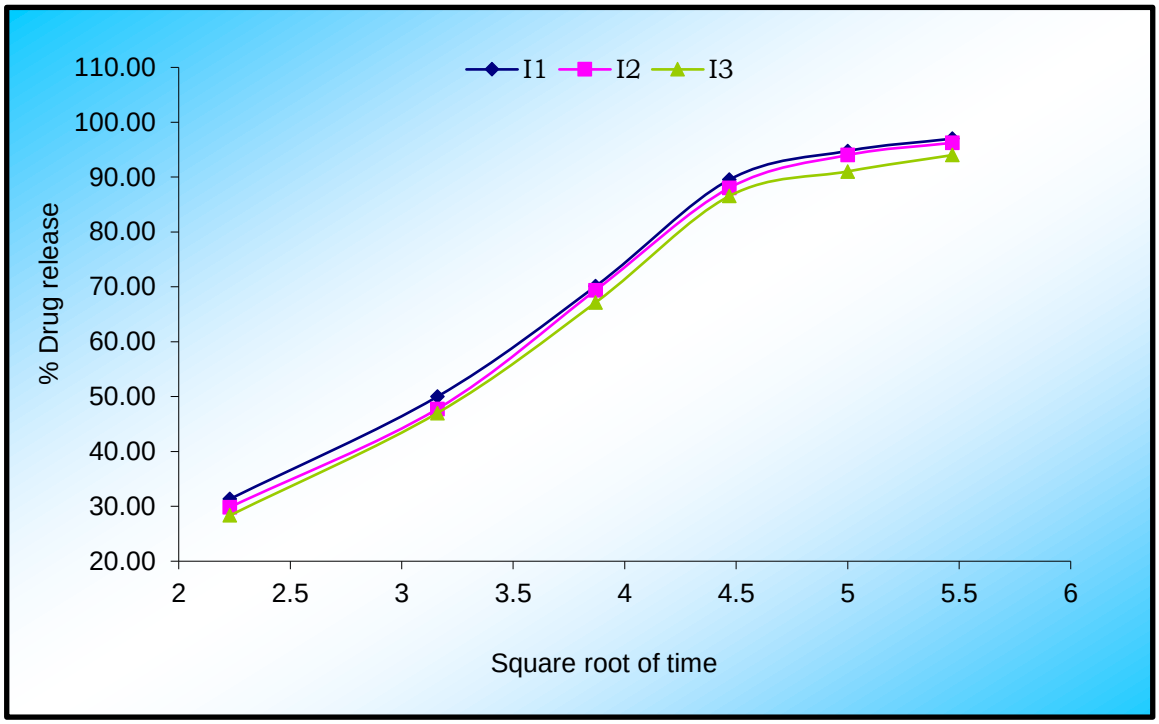

Fig. 8: Higuchi plot

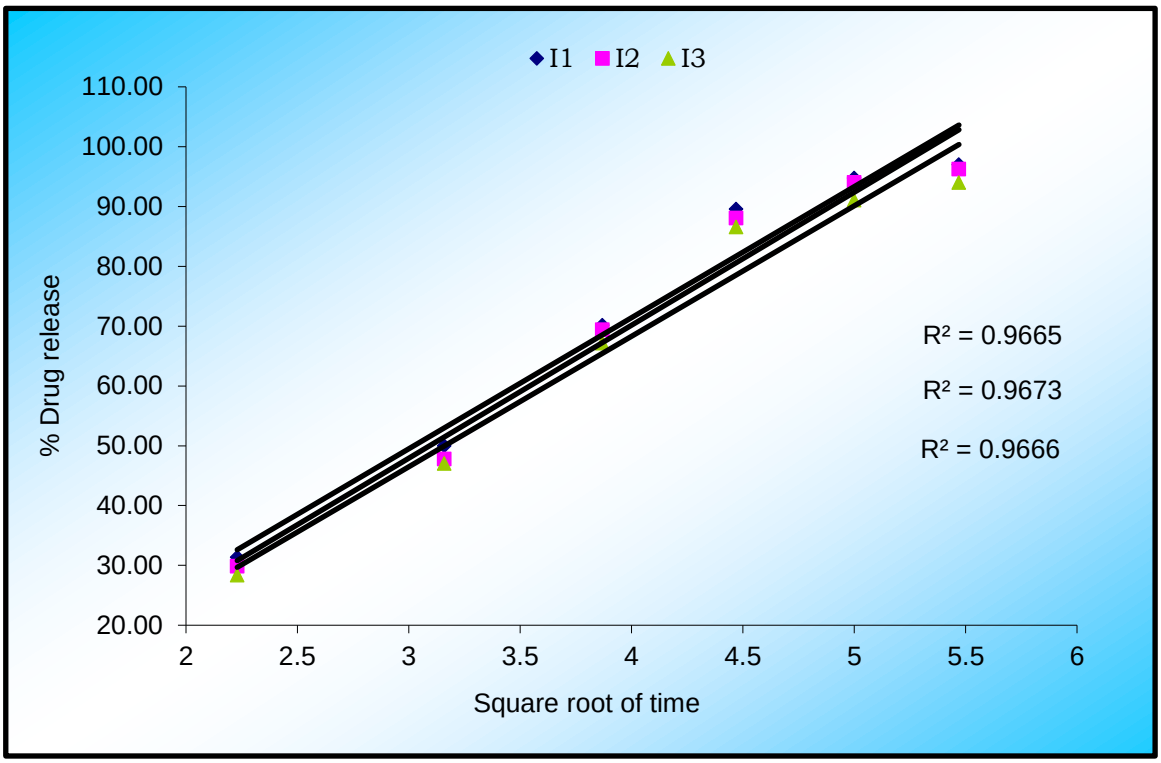

Fig. 9: Regression plot for Higuchi model

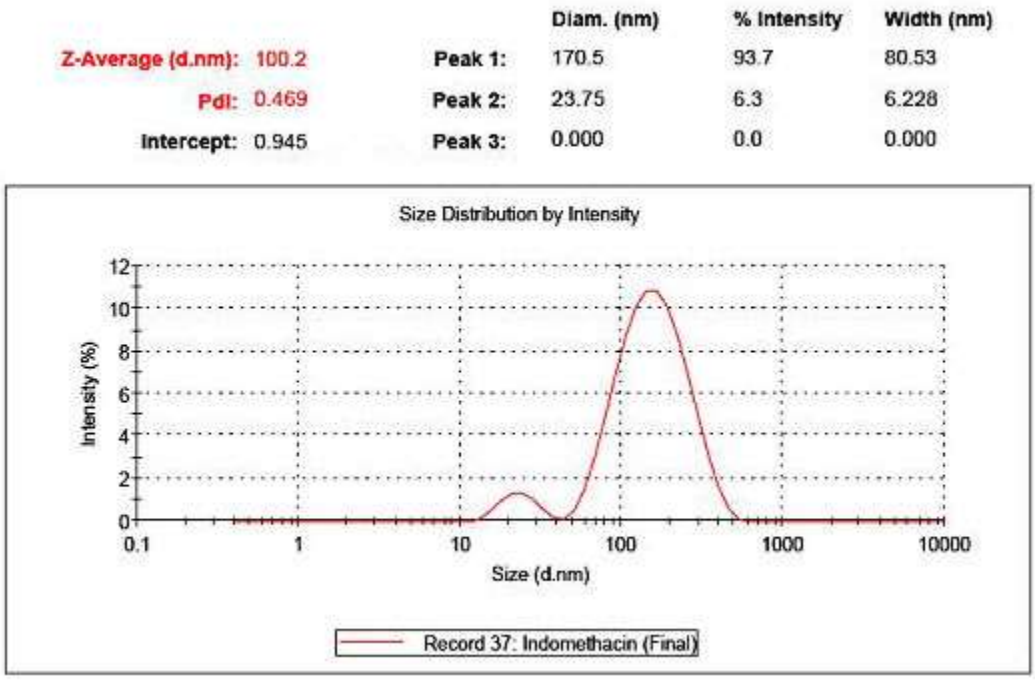

Fig. 10: Size distribution of INMN

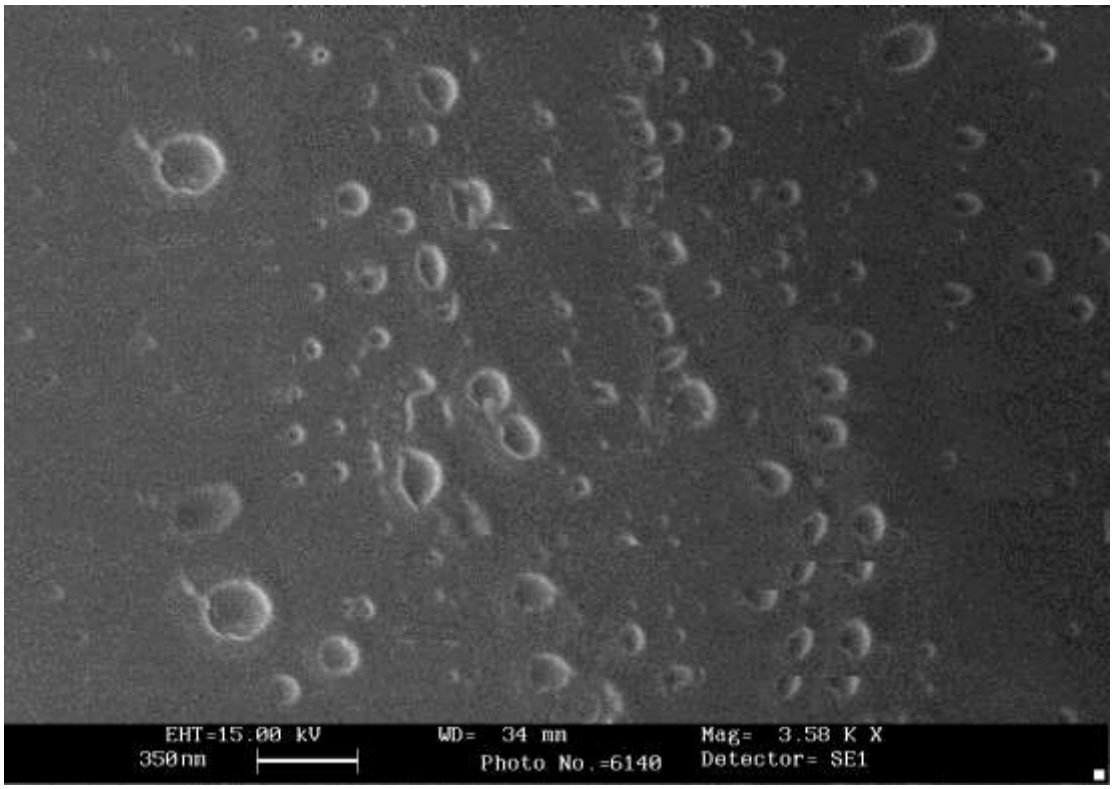

Fig. 11: SEM Image of INMN

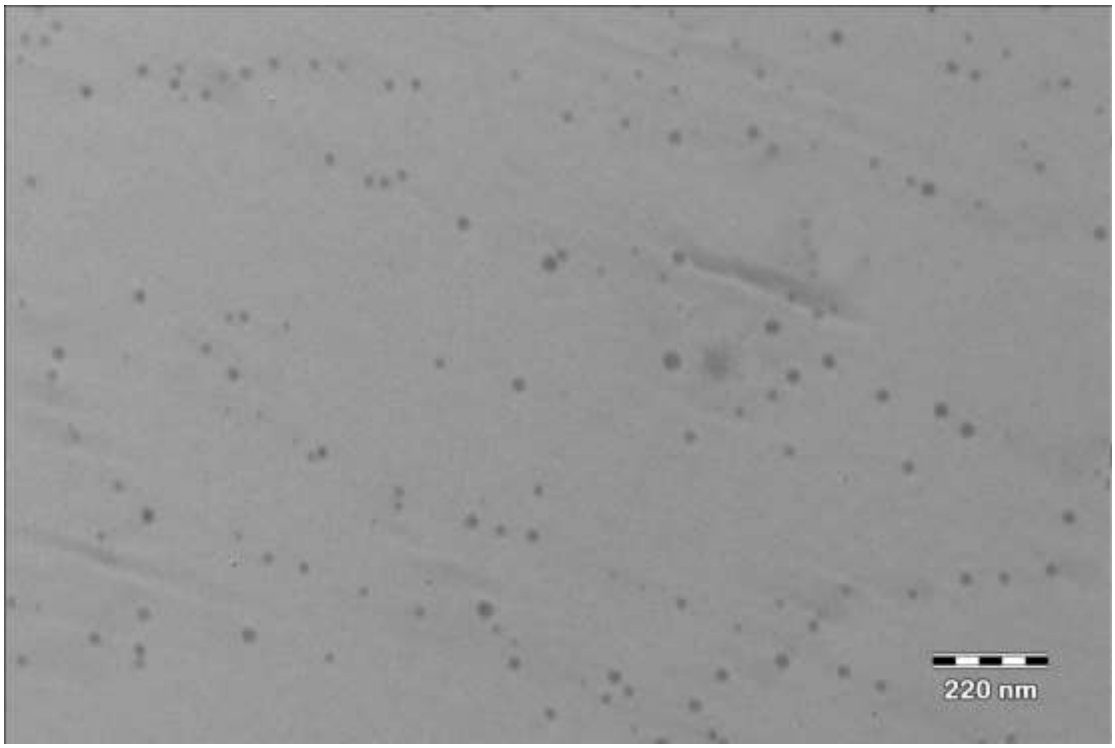

Fig. 12: TEM Image of INMN

Conclusion

This work has been shown to be the comparative in-vitro bioavailability study of INMN and nanoparticle of INMN through the comparative dissolution study and also compile the release behavior of drug. Furthermore, this work is the first to show that the dissolution profiles follow Korsmeyer-Peppas model. Nanoparticle drug delivery systems seem to be a viable and promising strategy for the biopharmaceutical industry. They have advantages over conventional drug delivery systems. They can increase the bioavailability, solubility and permeability of many potent drugs which are otherwise difficult to deliver orally by the nanoparticles.

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