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Research Article

Sustained release nanosuspension of acetaminophen- formulation and *in-vitro* evaluation

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ABSTRACT

The aim of this study was to prepare and characterize nanosuspensions of poorly water soluble drug (Acetaminophen) by modified solvent diffusion method using Eudragit L-100 polymer in order to sustain the release of Acetaminophen. Nanosuspension was subjected to various studies like particle size, pH, drug content, density, drug-polymer interaction, *in-vitro* drug release and release kinetics. The spectral analysis revealed that there was no interaction and presence of drug. *In-vitro* studies showed sustained release of the drug for prolonged period.

Keywords: Paracetamol; Nanotechnology; Methylmethacrylate

INTRODUCTION

Acetaminophen (ACN) (N-acetyl-p-aminophenol) has been in use as an analgesic for home medication for over 30 years and is accepted as a very effective treatment and is an effective and safe agent used to reduce fever, cough, cold and moderate pain including instances of tension headache, migraine headache, muscular aches, general pain and toothache for the analgesic (Wang SF *et al* 2007, Koch-Weser J 1976, Clissold SP 1986, Nikles CJ *et el*. 2005). It is also useful in osteoarthritis therapy and management of cancer pain (Brandt K 2003). Generally, ACN does not exhibit any harmful side effects, but hypersensitivity or overdoses in few cases leads to the formation of some liver and nephrotoxic metabolites (Patel F 1992). Nanosuspensions are colloidal dispersions of nanosized drug particles stabilized by surfactants. They can also be defined as a biphasic system comprising of pure drug particles dispersed in an aqueous vehicle in which the diameter of the suspended particle is less than 1 µm in size (Dubey R 2006). Nanosuspension can be used to enhance the solubility of drugs that are poorly soluble in aqueous as well as lipid media. As a result, the rate of flooding of the active compound increases and the maximum plasma level is reached faster (E.g., oral or intravenous administration of the nanosuspension). This is one of the unique advantages that it has over other approaches for enhancing solubility. It is useful for molecules with poor solubility, poor permeability or both, which possess a significant challenge for the formulators. The reduction in particle size renders the possibility of intravenous administration of poorly soluble drugs without blockade of the blood capillaries. The nanosuspension can also be lyophilized or spray dried and the nanoparticles of a nanosuspension can also be incorporated in a solid matrix. Apart from this, it has other advantage of being a liquid dosage form over the solid dosage forms.

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MATERIALS AND METHODS

Eudragit L-100 procured from (Sigma Aldrich, USA), Acetaminophen given as gift sample by (fourrts India Laboratory Pvt. Ltd., Chennai), Methanol (S.D. Fine Chemicals, Mumbai), Sodium Lauryl Sulphate (S.D. Fine Chemicals, Mumbai) and all other reagents are in analytical grade.

Preparation of Nanosuspension

Nanosuspension of Acetaminophen (NS1, NS2 and NS3) was prepared according to the modified procedure of solvent-diffusion method of Rosario (Pignatello et al., 2006). Acetaminophen (100mg), Eudragit L-100 Polymer (1:0.5, 1:1 and 1:3 drug and polymer respectively) was accurately weighed and dissolved in 10 ml of Methanol with continuous stirring. This solution is considered as organic phase since it contains organic solvent methanol. The surfactant, sodium lauryl sulphate and stabilizer (100mg) were added separately to 20 ml of pure water. It was then stirred separately with a magnetic stirrer and considered this solution as aqueous solution. The organic solution was transferred drop-by-drop to the aqueous phase under continuous stirring by magnetic stirrer at room temperature, and then the formulated solution was stirred at 1500 rpm for 3 hours. Thus the nanosuspension of Acetaminophen was formulated and preserved for further use.

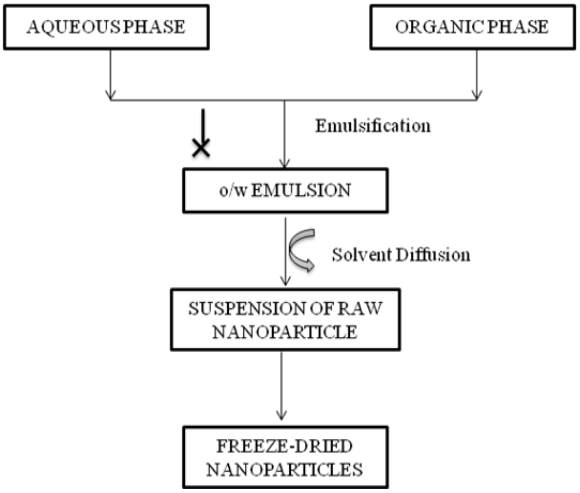

Figure 1: Flow chart for the formulation of Nanosuspension

EVALUATION

Particle size

Approximately 5ml of the nanosuspension was transferred into the sample cell of the particle size analyser (Microtrac, Blue Wave). The particle size was determined by low angle forward scattering of laser light that has passed through a sample cell.

Drug content

The amount of drug present in nanosuspension was calculated from absorbance values determined by using UV-Vis spectrophotometer (Perkin-Elmer Inc, USA). The percentage of drug was calculated using the following formulae

$$\%\ drug\ content = \frac{Sample\ absorbance\ X\ Dilution\ factor\ X\ Volume\ taken}{Label\ claim\ \times 100}$$

Density

The density of the acetaminophen nanosuspension was determined according to the monograph of Indian Pharmacopeia 1996, using the specific gravity bottle (Pycknometer). Density is given by formula.

$$Density\ (D) = \frac{M}{V\ \times 100}\ gm/lr$$

Where

D=density of liquid

M=mass of the liquid

V=volume of the specific gravity bottle.

pH

pH of the formulation was measured using digital pH meter with glass electrode as reference (model – 355 M/s Systronic, india)

Fourier transforms infrared spectroscopy (FT-IR)

The FT-IR spectra were recorded on samples of pure drug, pure polymer and formulation in a KBr pellet technique. The pellets were prepared on KBr press under hydraulic pressure of 150 kg/cm^2; the spectrums were scanned over the wave number range 3600-400 Cm^{-1} at ambient temperature with resolution of 4cm^{-1} using FT-IR model – 2500 apparatus and formulated nanosuspension was analyzed on ATR mode of FT-IR and spectra were recorded.

In-vitro drug release study

The *In-vitro* drug release studies of Acetaminophen nanosuspension was performed by dialysis bag method with dialysis membrane (Himedia, mumbai) using USP dissolution apparatus type 2 containing 900 ml of distilled water as dissolution medium with stirring rate of 100 rpm at 37°C. Acetaminophen Nanosuspension (5ml) was added into the dialysis membrane and fitted to the paddle and continued the run and at predetermined time intervals 5ml of samples were withdrawn from the centre of medium vessel for a period of 5 hours and replaced by same volume of fresh medium to maintain sink condition. The aliquot samples were diluted with suitable dilutions and measured using a UV-Visible spectrophotometer at 249 nm. The amount of drug present in each aliquot was determined from standard calibration curve. The data obtained from *in-vitro* release studies were fitted with various kinetic equations like zero order, First order, Higuchi, Corsmeyar-peppas, Hixson – Crowell and release exponent (n) was calculated.

Figure 2: *In-vitro* dissolution of Nanosuspension by dialysis bag model

RESULTS AND DISCUSSIONS

The particle size of the nanosuspension plays a vital role in the drug release. So it is necessary to determine the particle size. The particle size distribution of formulation was obtained in narrow ranges from 145nm to 86 nm and the average particle size was found to be 95 ± 8 nm shown in figure 3.

The drug content for the three different nanosuspension formulations was estimated by keeping pure drug as standard. The percentage of drug content was found to be 99.25% for NS1, 102.12% for NS2 and 100.96%

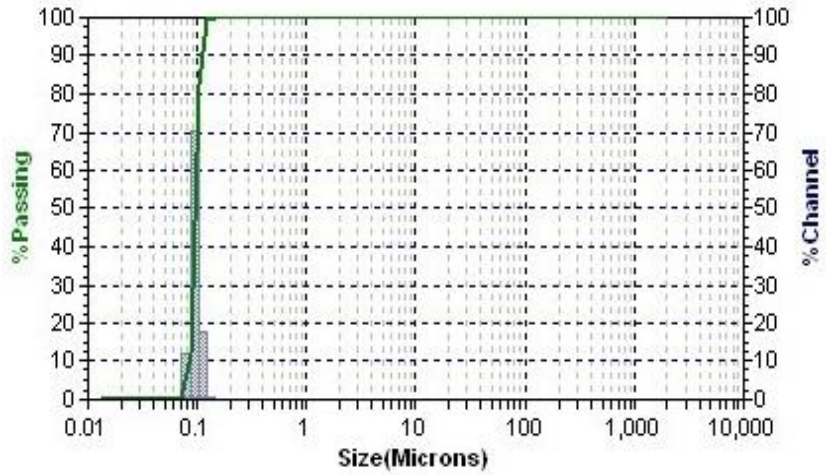

Figure 3: Average particle size of Acetaminophen nanosuspension NS2 (Drug: Polymer, 1:1)

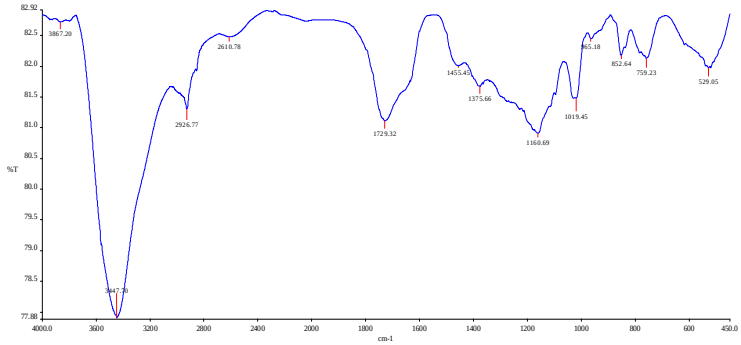

Figure 4: FT-IR spectra of Eudragit

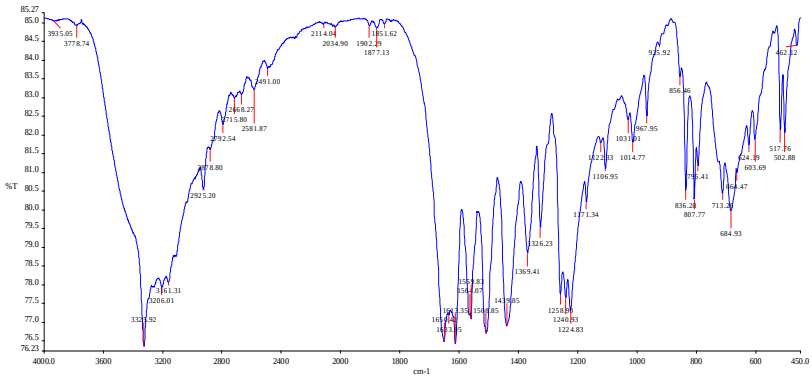

Figure 5: FT-IR spectra of Acetaminophen

for NS3. Thus the values are within the Pharmacopeial limits.

Density of the Acetaminophen nanosuspension of three different ratios was found to be 1.01088 gm/ml, 1.02628 gm/ml and 1.02852 gm/ml for NS1, NS2 and NS3 respectively. The pH of the Acetaminophen nanosuspension of three different ratio formulations was found to be for NS1- 6.32, NS2- 6.83 and NS3- 5.53 (Senthil Kumar. C et al 2010).

The IR spectra of pure drug and nanosupension formulation were compared to confirm the presence of drug in the formulation. Wave number at 3313.37 cm^{-1} (O-H Stretch, H-bonding), 1638.33 cm^{-1} (N-H Bond) and 1015.49 cm^{-1} (C-N Stretch) reveals the there is no interactions and the presence of drug in the formulation shown in figure 4-6.

The dissolution study was performed in order to find the percentage of drug release in three different formulations. At 15 minutes, 54.081% of drug was released from the pure drug in water, 29.050% of drug released from NS1, 27.250 % drug released from NS2 and 14.725% of drug released from NS1 (Figure 7). This shows that the amount of polymer influence the drug release. Thus the sustainability of the drug was increased by increasing the concentration of the polymer. The *in-vitro* release kinetics was shown in table 1. This show that the drug release follows Corsmeyar-peppas equation and the NS3 formulation possesses non-fickon and all other formulations possess fickon principles.

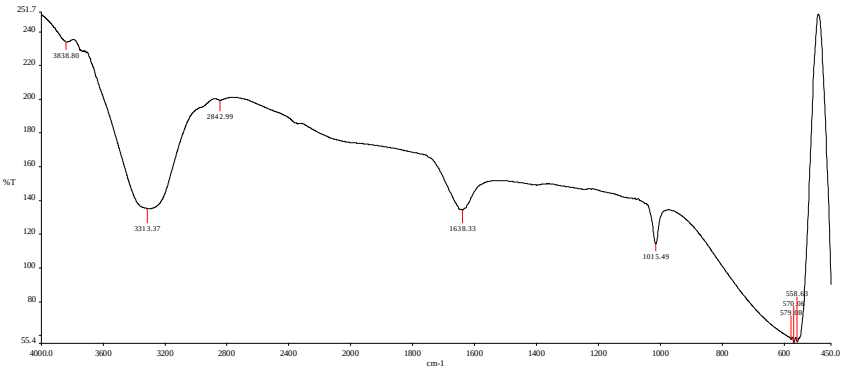

Figure 6: FT-IR spectra of Acetaminophen nanosuspension NS2 (1:1 Drug and polymer ratio)

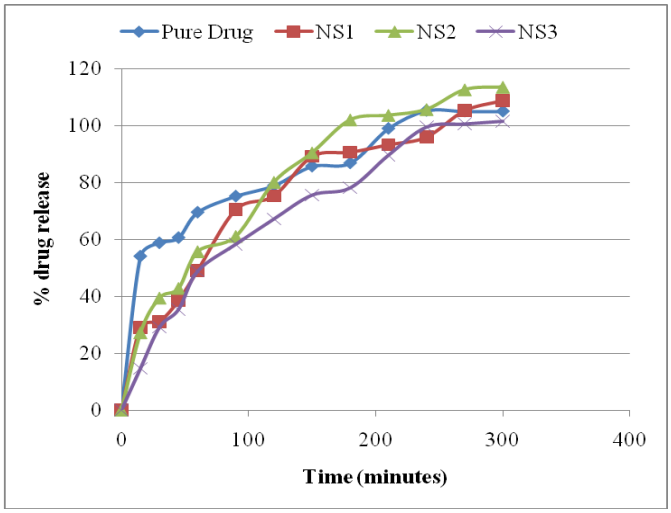

Figure 7: *In-vitro* drug release of Acetaminophen nanosuspension at various time intervals with different Ratio of Drug and Polymer

NS1- Drug: Polymer in the ratio of 1:0.5, NS2- Drug: Polymer in the ratio of 1:1, NS3- Drug: Polymer in the ratio of 1:3.

Table 1: *In-vitro* release kinetics of different formulations and their n-values

Formulations/ models	R^2					
	Zero Order	First Order	Higuchi	Corsmeyar-peppas	Hixon-crowell	n
Pure drug	0.848	0.8513	0.639	0.836	0.602	0.216
NS1	0.907	0.8513	0.913	0.962	0.843	0.495
NS2	0.915	0.8513	0.816	0.982	0.91	0.499
NS3	0.932	0.8513	0.948	0.975	0.794	0.617

NS1, NS2, NS3 represents the Drug: Polymer ratios of 1:0.5, 1:1 and 1:3.

CONCLUSION

The polymeric nanoparticles of paracetamol was prepared using EudrajitE100 as drug retarding agent and evaluated for its physical and chemical parameters. The result suggest that the commonly used analgesic and anti-pyretic drug gives better sustained release for more than 6 hours and can be used in the nanoparticles form for better results.

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