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Interaction and release kinetics study of hybrid polymer blend nanoparticles for pH independent controlled release of an anti-viral drug

D. Ramyadevi [a,*], K.S. Rajan [b,1]

[a] School of Chemical and Biotechnology, SASTRA University, Thanjavur 613401, Tamil Nadu, India
[b] Centre for Nanotechnology & Advanced Biomaterials (CeNTAB), School of Chemical & Biotechnology, SASTRA University, Thanjavur 613401, Tamil Nadu, India

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ABSTRACT

Incompatible interactions of polymers with active chemical entity offer variable challenges in drug delivery kinetics. This study focuses on development of hybrid polymer blend nanoparticles with amphiphilic (Poly Vinyl Pyrrolidone) and hydrophobic (Ethyl cellulose and Eudragit RSPO) polymers to encapsulate maximum drug without significant incompatibility. Optimized nanoparticles developed using Acyclovir model drug exhibited 80% entrapment with size and surface charge of 100 nm and +26 mV, respectively. Spherical morphology and solid state transition of drug from crystalline to amorphous in nanoparticles was confirmed by SEM and XRD analysis. pH independent *in-vitro* drug release was observed in four different media with initial burst release followed by sustained release for >12 h. Statistically significant difference ($P < 0.05$) was observed in percentage of drug release from each formulation in different media. H-bonding and hydrophobic interactions between drug and polymer (FTIR, TG-DTA analysis and Makoid–Banakar Kinetics) and diffusion of drug from matrix nanospheres followed by pore transport were the key factors for effective drug release kinetics. Uptake of nanoparticles by corneal epithelial cells was more prominent within 30 min, however viability of cells was not altered significantly. Release kinetics and interactions studies revealed the suitability of polymer blend nanoparticles for better encapsulation and sustained release of the drug.

Abbreviations

ACV	Acyclovir
PVP	Poly Vinyl Pyrrolidone
EC	Ethyl cellulose
ERSPO	Eudragit RSPO grade
SEM	scanning electron microscopy
TG-DTA	thermo gravimetric – differential thermal analysis
FT-IR	Fourier transform – infra red spectroscopy
XRD	X-ray diffraction

1. Introduction

1.1. Nanocarriers of crosslinked polymers and co-polymers

Polymeric nanoparticles loaded with active therapeutic agents have been proved as successful drug delivery systems to achieve controlled release of drugs at the required site of action. Uses of biodegradable (natural and synthetic) polymers minimize the risk of accumulation and its toxicity. Several co-polymers at different ratios of monomers and some polymers with controlled molecular architecture were explored to accomplish the different types of drug release based on diffusion, degradation, erosion, swelling, *etc.* These systems offer considerable merits in terms of drug loading, controlled release, biocompatibility and stability. Yet certain polymers exhibit demerits like processing difficulties, accumulation of degraded monomers in body. Another approach for achieving desired controlled drug release profile of drugs has been attempted through polymer blended systems [1].

1.2. Hybrid polymer blend nanoparticles

Combination of polymers yielding hybrid blend mixtures are used in different dosage forms like controlled release matrix tablets, hydrogels, microparticles, nanospheres, *etc.* Amorphous blending of polymers for formulation of nanoparticles has been identified to effectively vary physico-chemical interactions and drug release pattern [1,2]. The present work was aimed to investigate the possible interactions and kinetics of drug release for optimized polymer blend nanoparticles, prepared using combination of hydrophilic and hydrophobic polymers. Experiments were carried out to determine appropriate PVP and EC/ERSPO ratio to achieve higher entrapment

* Corresponding author. Tel.: +91 9843361266.
E-mail addresses: ramya@scbt.sastra.edu (D. Ramyadevi), ksrajan@chem.sastra.edu (K.S. Rajan).
[1] Tel.: +91 9790377951; fax: +91 4362 264120.

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efficiency (EE). Nanoparticles were formulated by simple nanoprecipitation technique [3], with Acyclovir as a model drug and experimented for the interaction studies and drug release kinetics study.

1.3. Selection of model drug

Acyclovir is one of the successful antiviral molecules, and is more stable. But, its less water solubility and poor permeability leads to low bioavailability. Polymeric nanoparticles of Acyclovir have been shown to improve availability and activity of drug, by enhancing its cellular uptake and also controlling release for prolonged period [4,5]. Its pharmacokinetic parameters and effective therapeutic benefits through diverse routes of administration have attracted the interest for this research, to optimize a suitable polymer blend for its pH independent drug release kinetics. The present study is anticipated to provide an understanding of the effects of polymer blend composition on drug entrapment, particle size, morphology, stability, drug–polymer interactions, release behavior, cellular toxicity and uptake.

2. Materials and methods

2.1. Materials

Acyclovir (ACV) and Eudragit RSPO (E-RSPO) were received as gift samples from Matrix India Pvt. Ltd. and Glukem Pharma Pvt. Ltd. Hyderabad, India respectively. Poly Vinyl Pyrrolidone K 30 (PVP K 30) and Ethyl cellulose (EC) were purchased from SD Fine Chem Pvt. Ltd., Mumbai, India and Pluronic F127 (PF127) was procured from Sigma Aldrich, Mumbai, India.

2.2. Optimization of polymer blend nanoparticles

The influence of concentrations of PVP (10–30 mg/ml), EC/ERSPO (5–20 mg/ml) and surfactant concentration (10 mg/ml or 5 mg/ml) for encapsulation of Acyclovir in nanoparticles has been investigated. The requisite mass of each polymer was individually weighed and dissolved in 5 ml of methanol. About 50 mg of drug was weighed and dissolved in 10 ml of surfactant (PF127) solution. The organic phase was transferred into aqueous phase dropwise, with moderate magnetic stirring at room temperature until organic solvent evaporated completely, with spontaneous formation of nanoparticles [3,6]. The formulation was centrifuged at 3000 rpm for 20 min to remove microparticles and unentrapped drug. The supernatant solution was again ultracentrifuged using cooling ultracentrifuge (Sigma 3K30, Osterode Am Harz, Germany) at 16,000 rpm for 30 min at −10 °C, where the nanoparticles were pelleted. This pellet was re-dispersed in distilled water using cyclone mixer (Remi CM101 DX, Mumbai, India) to get uniform nanoparticle dispersion which was freeze-dried (Christ Alpha 2-4 LD Plus, Osterode Am Harz, Germany).

2.3. Entrapment efficiency of nanoparticles

The supernatant solution obtained after the ultracentrifugation was suitably diluted and drug content was estimated with UV–visible spectrophotometer (Evolution 201, ThermoScientific, USA). The EE was calculated using the formula [7],

$$\%\,\text{Entrapment efficiency} = \frac{(\text{total drug content} - \text{drug content in supernatant})}{\text{total drug content}} \times 100 \quad (1)$$

2.4. Physical characterization of nanoparticles

The size distribution and surface charge of the ACV loaded nanoparticles was measured using Zeta Sizer (Nano Series ZS, Malvern, UK) based on the principle of dynamic light scattering and the charge conductivity, respectively. The polydispersity and zeta potential was measured to assess the stability of the formulation and optimize the level of surfactant required. Surface morphology was observed using Field Emission Scanning Electron Microscope (FESEM) (JSM 6701F, JEOL, Japan). Nanoparticles were sputter coated with platinum using auto fine coater (JFC 1600, JEOL, Tokyo, Japan), and then placed in sample holder for viewing the image. The change in morphological features of the nanoparticles after the drug release was also observed [8].

2.5. Drug–polymer interaction studies

Nanoparticles were subjected to FTIR spectroscopy (PerkinElmer System 200, Shelton, Connecticut, USA) after uniform blending with dried IR grade potassium bromide crystals and pelletized into thin disc using hydraulic pellet press (Kimaya Engineers, Thane, India) at 60 kg/cm^2. The pellet was placed in sample holder and IR spectrum was recorded between wave number ranging 4000–400 cm^{-1}.

The XRD patterns of pure ACV and the drug-loaded polymer nanoparticles were compared using the X-ray diffractometer (D8 FOCUS, BRUKER, USA) with Cu-Kα radiation at 1.5418 Å. The analysis was performed at 2θ values from 10° to 60° with a step size of 0.01°/min. The thermal interaction of drug and polymers in nanoparticles was studied by comparing its TG-DTA (TA Instrument, Q100, Michigan, USA) profile with pure drug and polymers. It is used to check their identity, purity and to predict possible physical or chemical modifications of the drug. Around 2–5 mg of each sample was placed in an aluminum pan and heated at the rate of 10 °C/min and results were presented in terms of weight loss and heat flow against temperature [9].

2.6. In vitro drug release studies

In vitro drug release of selected nanoparticles, showing >60% entrapment of ACV was studied by dialysis method using four different media individually [10]. Media 0.1N HCl with pH 1.2 was used to simulate gastric fluid (without enzymes), phosphate buffer of pH 7.4 to mimic systemic environment, simulated vaginal fluid (pH 4.2) for vaginal route of administration and simulated tear fluid (pH 7.4) to study drug release in ophthalmic region. Nanosuspension sample was taken in dialysis bag and immersed in vial containing the media, maintained at 37 °C ± 2 °C and 100 rpm. The media is withdrawn at periodic time intervals and replaced with same volume of fresh media. The collected samples were analyzed using UV–visible spectrophotometer for estimation of percentage of drug released. Experiments were performed in triplicates and data was presented as the mean ± S.D.

2.7. Kinetics of drug release

Mechanism of drug release from nanoparticles was elucidated by predicting the drug release kinetics. The data obtained from drug release studies were fitted to various models such as zero-order, first-order, Higuchi, Hixon, Korsmeyer–Peppas, Hopfenberg, Baker–Lonsdale, Makoid–Banakar, Weibull and Gompertz models using DD-solver software. The values of R^2, n (release exponent), K (rate constant) and SSR (sum of squared residual) were compared for each formulation and the possible kinetics of drug release was deduced [11].

2.8. Cytotoxicity studies

Human corneal epithelial cells gifted from Sankara Nethralaya Eye Hospital, India were cultured in Dulbecco's modified eagles (DME) medium/F12 and maintained at 37 °C in 5% CO_2 and 95% relative