Design and Biopharmaceutical Evaluation of Nitrofurantoin-Loaded Ethylcellulose Micropellets

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The purpose of this study was to design and evaluate a drug delivery system of nitrofurantoin to control urinary tract infection by achieving a sustained nitrofurantoin serum and urinary level over a prolonged period of time but without the concomitant side effects. Ethyl cellulose multiparticulate micropellets containing nitrofurantoin were prepared using emulsification/solvent evaporation technique.The optimized formulations were extensively evaluated using I.R. spectroscopy, particle size analysis, Scanning Electron Microscopy (SEM), stability studies and finally *in vitro* and *in vivo* release rate studies. No drug-polymer interaction could be detected.The release of drug more or less followed zero order, first order, Higuchi and Binomial Model equations.The *in vitro* release studies were monitored over the entire pH range of the gastrointestinal tract (GIT) fluid. A linear correlation was obtained in the *in vitro-in vivo* studies.

Nitrofurantoin is a synthetic bactericidal agent useful only against urinary tract infections (UTI) because it is rapidly excreted and concentrated in the urine[1]. It has a short biological half-life of 30 minutes or less[2], and need frequent dosing with conventional dosage forms. Solubility of nitrofurantoin in aqueous media shows temperature and pH dependence[3]. Both the crystalline drug and its solution are discolored by alkali and exposure to light and decomposed upon contact with metals other than stainless steel and aluminium[4]. Due to the short biological half-life, side effects, stability problems and conducive pharmacokinetic parameters, this study was initiated to design and evaluate a rational controlled release drug delivery system of nitrofurantoin which would not only prolong the activity of the drug but also minimize side effects and toxicity.

Nitrofurantoin was generously supplied by SmithKline Beecham Pharmaceuticals India Ltd., and Eskayef Ltd., ethylcellulose (viscosity grade 14 cp, Loba Chemie, Mumbai, India). All other chemicals were obtained commercially and used as such without further purification.

The Micropellets were prepared by emulsification/solvent evaporation technique using nitrofurantoin and ethylcellulose in the ratios of 1:2, 1:1 and 2:1. The uniform dispersion of drug in an acetone solution of polymer was poured in a thin uniform stream of liquid paraffin (viscosity 87.1 cp at 30°) being stirred at 1100 rpm with an electrical stirrer (Remi Udyog, Mumbai, India) for a sufficient period of time to flash off acetone at ambient temperature. Petroleum ether was added (2 ml/min) to extract the residual amount of acetone and to rigidize the polymer coating. The micropellets were recovered by filtration, washed with cold petroleum ether (40°-60°) and dried at 40°-45° for 3 h.

The microparticles were separated into different particle size by sieving for 30 min using a nest of standard sieves (12-200 mesh) in a sieve shaker. The gold-coated samples were studied for their microstructural observations and surface characteristics in a Scanning Electron Microscope (Hitachi Model S-415A, Japan). About 100 mg accurately weighed micropellets were dissolved in 30 ml dimethyformamide. Volume was made up to 1000 ml with water and mixed well. Five milliliters of this solution were diluted to 100 ml with a solution containing 1.8% w/v of sodium acetate and 0.14% v/v of glacial acetic acid. The absorbance was measured at λ_{max} 367 nm and

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Table I - Nitrofurantoin Content (%) in Ethylcellulose Micropellets

Drug: Polymer	% Theoretical Drug Content	% Actual Drug Content in Micropellets having Average Diameter (μm)		
		715 μm (Mean±SD)	505 μm (Mean±SD)	335 μm (Mean±SD)
1:2	33.33	33.15±0.24	33.09±0.20	33.14±0.53
1:1	50.00	49.40±0.19	49.29±0.15	49.83±0.32
2:1	66.67	64.25±0.20	64.34±0.10	64.02±0.13

the content was calculated taking 765 as the value of A (1%, 1cm) at 367 nm. The I.R. spectra of nitrofurantoin, ethylcellulose and their micropellets were obtained using a Perkin Elmer, Model-883 I.R. Spectrophotometer in KBr pellets. The formulations (700 mg) were subjected to stability studies by storing them at 95%, 75% and 45% RH at room temperature for 90 days. The samples were evaluated for appearance, weight and drug content every 30 days for 3 months. One gram of formulation was placed under UV lamp for 48 hours and evaluated for appearance and drug content every 12 h.

The release characteristics of nitrofurantoin from ethylcellulose micropellets were determined over the whole pH rang of the GIT fluid starting from pH 1.2 to 7.6 with slight modification[5]. Accurately weighed dosage forms, containing approximately 100 mg of nitrofurantoin were placed in the USP XX dissolution basket maintained at 37±1° at 100 rpm. The absorbance of the samples was measured at 367 nm against respective blanks. The data obtained from the *in vitro* dissolution studies with core to coat ratios of 1:1 and 2:1 which showed superior release characteristics were analyzed in terms of different kinetic models (zero order, first order, Higuchi Model, Cube Root Equation, Binomial Equation, Weibull Equation) and regression coefficients were compared.

Conventional tablets (100 mg) and the capsules containing ethylcellulose micropellets were administered orally to female human volunteers (27 years of age, average weight 50 kg, average height: 160 cm). Since urinary excretion studies are the method of choice[6,7] and clearance is independent of urinary pH, urine samples were collected up to 12 hours at 2 hours interval. A volume of 100 ml water was provided to the volunteers after each collection to ensure adequate urine volume. The samples were frozen to provide stability and convenience in analysis and were allowed to thaw immediately before use. To 1 ml of the urine collected, 4 ml of 1% urea solution was added. The mixture was heated on a boiling water bath for 15 minutes. The absorbance was measured on a double beam spectrophotometer at 400 nm using appropriate blank. The amount of drug present was read directly from the standard curve. Between the studies, a two weeks wash out period was allowed.

Optimization of the variables produced discrete and spherical micropellets in good yield. At a constant stirring speed of 1100 rpm, the size distribution shifted towards smaller micropellets with drug polymer ratio of 1:1. With the ratios of 1:2 and 2:1, the distribution shifted towards bigger micropellets. The micropellets obtained were absolutely spherical in shape with smooth surfaces. Uniformity of drug content in each fraction of each of the formulations indicated the reproducibility of the manufacturing method as shown in Table-1. The Infrared studies showed that no potential interaction exists between the drug and the polymer. The appearance, weight and drug content of the micropellets in all three formulations remained unaltered at 45% and 75% RH and at room temperature but showed stability problems at 95% RH and at room temperature. Ethylcellulose micropellets hardly showed any variation in drug content and did not exhibit any color change as was the case with pure drug after exposure to UV lamp for 48 h.

Dissolution profiles of nitrofurantoin micropellets over the whole pH of the GIT fluid starting from pH 1.2 to pH 7.6 are depicted in Fig. 1. The second formulation (1:1) showed the best release profile with the longest steady state phase, releasing more than 95% of drug and a sustaining action for more than 8 h. The third formulation (2:1) also showed a reasonably good release pattern with more than 80% and a sustaining action of 5.5 h. But the

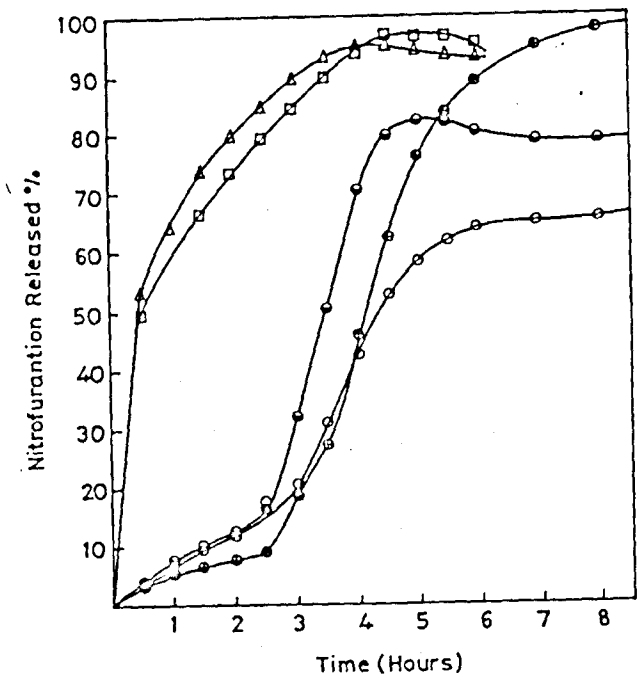

Fig. 1 : *In Vitro* Dissolution Profiles of Nitrofurantoin (Δ . Commercial Table-100 mg, □Pure drug powder, O 1:2 D:P ratio, ⊗1:1 D:P ratio, ◉ 2:1 D:P ratio)

first formulation (1:2) showed a very poor release profile. It was unable to release more than 70% of drug even after 8 h of dissolution due to its very thick coating. The release followed a mixed kinetics.

The batch prepared with drug-polymer ratio of1:1 and an average micropellet diameter of 715 μm released 75% of the drug in about 6 h and the release was sustained for more than 8 h. This formulation was subjected to *in vivo* studies in human volunteers. Nitrofurantoin concentrations in urine obtained after oral administration of the conventional tablets (100 mg) and micropelleted dosage form in female human subjects are presented in Fig. 2. Nitrofurantoin is bacteriostatic at a concentration of 32 μg/ml or less[2]. With conventional dosage form, there was a sharp rise in its urine concentration, leading to the formation of a peak at about 4th h following oral administration. After attaining the peak level, there was a sharp decline in the nitrofurantoin concentration in urine much below the therapeutically effective drug concentration of 32 μg/ml. On the other hand, the nitrofurantoin concentration-time profile, obtained after oral administration of micropelleted dosage form was characterized by the absence of sharp peak and the drug level in the urine was sustained and maintained in the therapeutic level for a

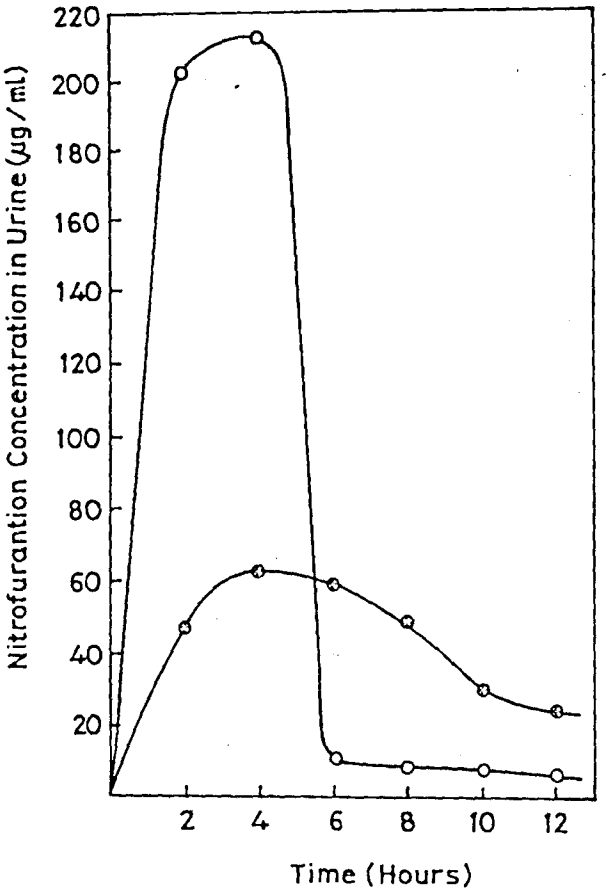

Fig. 2 : Urinary Excretion Profiles of Nitrofurantoin in human volunteers following Oral Administration of (O) Conventional Tablets (100 mg) and (⊗) Ethylcellulose Micropellets

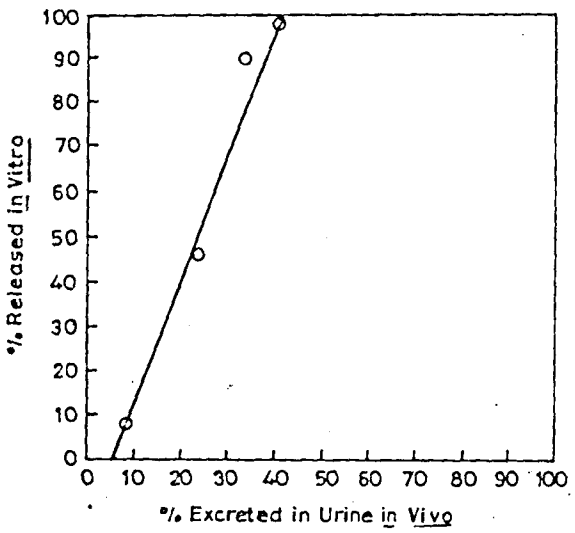

Fig. 3 : *in vitro-in vivo* Correlation for Nitrofurantoin-loaded Ethylcellulose Micropellets

sufficient period of time for more than 12 h. After 12 h the total amount of nitrofurantoin excreted from the conventional tablets was 64.36%, but with the capsule containing ethylcellulose micropellets, it was 48.94% of the administered dose. That means the drug was still being excreted even after 12 hours of administration in the second case. Again, the oral administration of conventional tablets resulted in certain side effects such as nausea, headache and gastric irritation. One of the subjects also complained of skin eruptions, a common allergic reaction of nitrofurantoin. But none of the volunteers who were administered the sustained release capsules experienced any adverse reactions characteristic of the conventional dosage form. The amount excreted from the sustained release preparations was lower than the amount excreted by the conventional dosage form; therefore, the absorption from the micropellets would be slower than the latter. Since the first step in the absorption of a drug is the release from the dosage form and the release of drug from the micropellets was slow, it could be predicted that the absorption rate would be low as well which explains the absence of side effects markedly noticed with the conventional tablets. Per cent released *in vitro* versus per cent excreted in urine *in vivo* (Fig. 3) showed a linear correlation indicating that the results were statistically validated.

In conclusion, nitrofurantoin-loaded discrete, smooth and spherical ethylcellulose micropellets having high degree of incorporated drug can be successfully prepared by emulsion/solvent evaporation technique. The designed controlled release formulations exhibited prolonged and sustained release of nitrofurantoin serum level. Thus, the therapeutically effective plasma drug concentration could be maintained at pseudo steady state level for more than 12 hours without untoward side reactions.

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