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Effect of Polyvinylpyrrolidone on Physical Characteristics of Ketoprofen-loaded Polystryrene Microparticles

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Ketoprofen-loaded polystyrene microparticles containing variable amount of polyvinylpyrrolidone as a copolymer were prepared by emulsion solvent evaporation method. The effect of polymer combination and initial drug loading on physical characteristics of the microparticles were studied. Although the microparticles were prepared by emulsification using different polymer combinations, the mean diameters were confined within a narrow range. However increase in initial drug loading increased the mean diameters of the microparticles. Polystyrene was found to be highly impermeable to drug release. Incorporation of polyvinylpyrrolidone easily modulated drug release. Mechanism of drug release was found to be a complex one.

Clinical studies have revealed that conventional dose dumping dosage forms of non-steroidal anti inflammatory drugs induce several adverse effects[1]. On the other hand, controlled release tablets minimize the emergence of adverse effects maintaining a steady state plasma drug concentration[2] and increase patient compliance due to reduced frequency of administration. However, when compared with single unit sustained release tablets, multi-unit controlled release dosage forms pass through the gut avoiding the vagaries of gastric emptying and different transit rates[3] and thereby release drugs more predictably[4]. Moreover, a multi-unit system spreads over a large area of absorbing mucosa and prevents exposure to high drug concentration on a chronic dosing[5]. Quite often, modulation of release of water-insoluble drugs from a single polymer appears to be difficult. Instead, mixtures of polymers can have properties significantly better than a single polymer for achieving desired release of drugs. The objective of this work is to study the feasibility of using mixtures of polystyrene and polyvinylpyrrolidone to modulate release chracteristics of ketoprofen which has been used as a model non-steroidal antiinflammatory drug.

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Ketoprofen and polystyrene (Grade McG-100) were obtained as generous gift samples from M/S Rhone Poulenc (I) Ltd., Mumbai and M/S. Hindustan Polymers, Kolkata respectively. Polyvinylpyrrolidone (Mol. wt. 40 000) was purchased from M/S. Loba Chemie, Mumbai. Span 80 was purchased from Fluka, Switzerland. Heavy liquid paraffin, Chloroform A.R., acetone A.R., n-hexane was purchased from S. D. Fine Chem., Mumbai.

Ketoprofen-loaded (20, 40 and 60% w/w) microparticles

were prepared by emulsion solvent evaporation method using polystyrene (PS) and polyvinylpyrrolidone (PVP) in different ratios as matrix materials. Required amount of polymer(s) and ketoprofen were dissolved in a mixture of chloroform and acetone at 15°. The solution was emulsified at 300 rpm in heavy liquid paraffin containing 0.1% v/v span 80 and maintained at 15°. After 3 h of continuous stirring at ambient temperature, the microparticles were separated by filtration, washed with 3x25 ml of n-hexane. Following air drying the microparticles were vacuum dried at 60°. The experiment was repeated with 20-60% w/w ketoprofen using a constant PS and PVP ratio. Each formulation was prepared in duplicate. The dried microparticles were sized through a nest of BS standard sieves. Dried microparticles were vacuum coated with gold film and were observed under scanning electron microscope (model S415A, Hitachi, Japan) for surface topography.

Accurately weighed microparticles were dissolved in chloroform-acetone mixture and ketoprofen was extracted in USP phosphate buffer (pH 6.8). The solution was assayed for drug content at 259 nm spectrophotometrically (Model 200-20, Hitachi, Japan). Release of drug from accurately weighed microparticles, equivalent to about 25 mg of ketoprofen, were studied at 75 rpm in USP phosphate buffer (pH 6.8, 900ml, 37±1°) following USP Paddle method. Aliquots of the dissolution medium were withdrawn at predetermined times and were replenished immediately with the same volume of fresh dissolution medium. The samples, following suitable dilution, were assayed spectrophotometrically at 259 nm.

Thin layer chromatography was performed by dissolving ketoprofen and drug-loaded PS microparticles in chloroform and applying on precoated silica gel 60 aluminum backed TLC sheet. The sheet was developed with chloroform:methanol:ammonia (120:60:0.5) system in a Camag Chamber for 20 min. The sheet was dried and examined under UV light. Infrared spectra of ketoprofen and ketoprofen–loaded PS microparticles were determined in the range of 4000-400 cm^{-1} from KBr pellets using an IR spectrophotometer (model IR–700, Jasco, Japan).

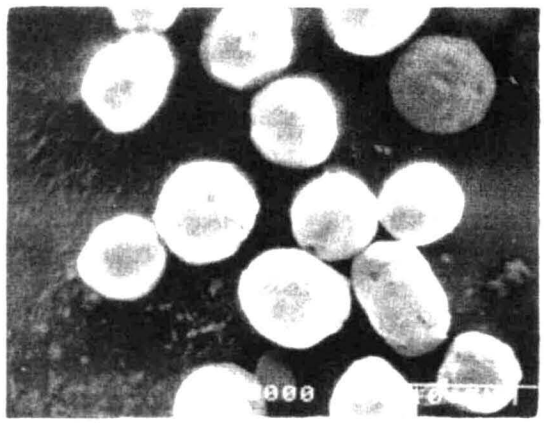
Although the principle of emulsification was used to prepare microparticles, results of sieve analysis revealed that the mean diameters of about 76-88% microparticles were confined within a narrow range of 650-730 μm. This indicates that mixture of two polymers can be used to adjust the size of the microparticles in a more practical way. Keeping the polymer combination constant, increase in initial drug load from 20-60% increased the viscosity of the polymer solution resulting in the formation of microparticles having larger diameter (640-700 μm).

Scanning electron micrographs showed that microparticles made of PS were spherical and discrete having smooth surface (fig. 1a). As the proportion of PVP was increased, the surface of the microparticles tended to become wavy (fig.1b) possibly due to differential precipitation of the polymers as the organic solvents diffused out. At the highest PVP concentration used, the microparticles became elongated and aggregated (fig. 1c).

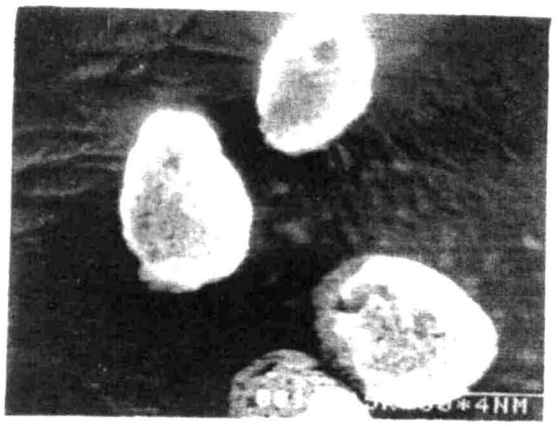
Actual drug contents in different sized microparticles containing 40% drug load and prepared with different polymer combinations were found in the range of 38.2–40.3% with a maximum co-efficient of variation 1.57%. When the initial drug loading was varied from 20 to 60% keeping PS:PVP constant at 90:10, actual drug contents were found similar to the respective theoretical drug loadings with coefficient of variations from 0.91–5.94%.

After an initial small release no further release of ketoprofen occured from PS microparticles upto 7 h (fig. 2). Estimation of residual drug content in PS microparticles after dissolution revealed that summation of released drug and residual drug approached almost 100%. Qualitative TLC analyses showed that R_f value of ketoprofen obtained from PS microparticles was the same as that of the pure drug. IR spectroscopy revealed that the absorption bands for OH, carboxylic C=0 and ketonic C=0 stretching of ketoprofen embeded in PS appeared at 2976, 1697 and 1655 cm^{-1} respectively and were similar to those obtained for the pure drug. Although inconclusive without further investigation, apparently it appeared that there was no interaction between PS and ketoprofen. Instead, PS appeared to be highly impermeable to the drug. However, incorporation of PVP in PS microparticles brought about increase in drug release. Similar improved release for water-insoluble drugs have been reported[7-9]. Further, the release of drug from the microparticles prepared with a constant PS-PVP ratio increased with increase in initial drug loading.

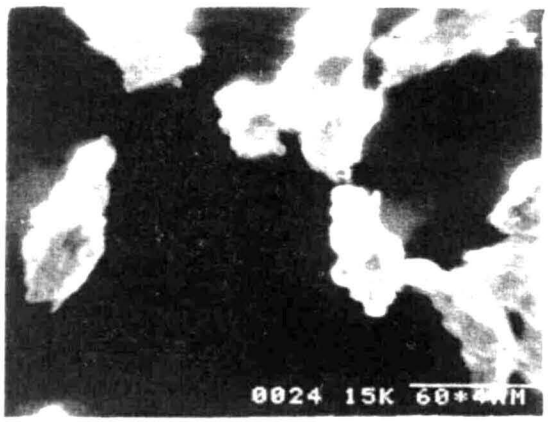
When log percentage of drug remaining to be released vs. time was plotted (fig. 3) in accordance with first order equation, straight lines were obtained ($r = 0.977 - 0.998$). On the other hand, when release data of each of the formulations were plotted according to Backer–Lonsdale equation, $3/2[1-(1-F)^{2/3}]-F=Kt$, where, F is the fraction of drug released at any time t, acceptable linearity was observed



a)



b)



c)

Fig. 1: Scanning electron micrographs of microparticles.

Ketoprofen-loaded microparticles were prepared with polystyrene: polyvinylpyrrolidone 100:0 (a), 95:5 (b), 75:25 (c).

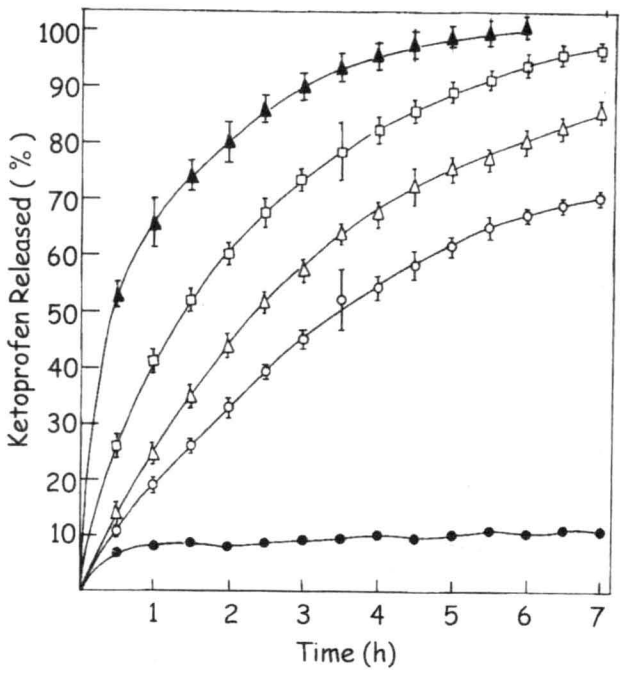


Fig. 2: Release profiles of ketoprofen.

Release profiles of ketoprofen from microparticles having average diameter 650 μm, drug load 40% and prepared with polystyrene : polyvinylpyrrolidone 100:0 (●), 97.5:2.5 (○), 95:5 (△), 85:15 (□) and 75:25 (▲).

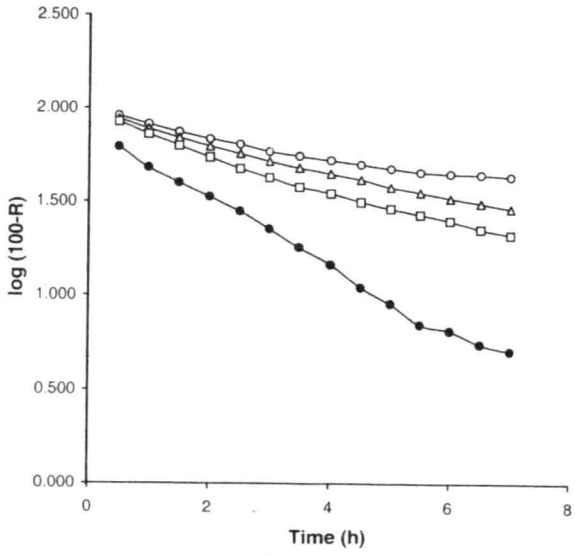


Fig. 3: First order release profiles.

Apparent first order release profiles of ketoprofen from microparticles prepared with polystyrene : polyvinylpyrrolidone 97.5: 2.5 (○), 95: 5 (△), 85:15 (□) and 75:25 (●).

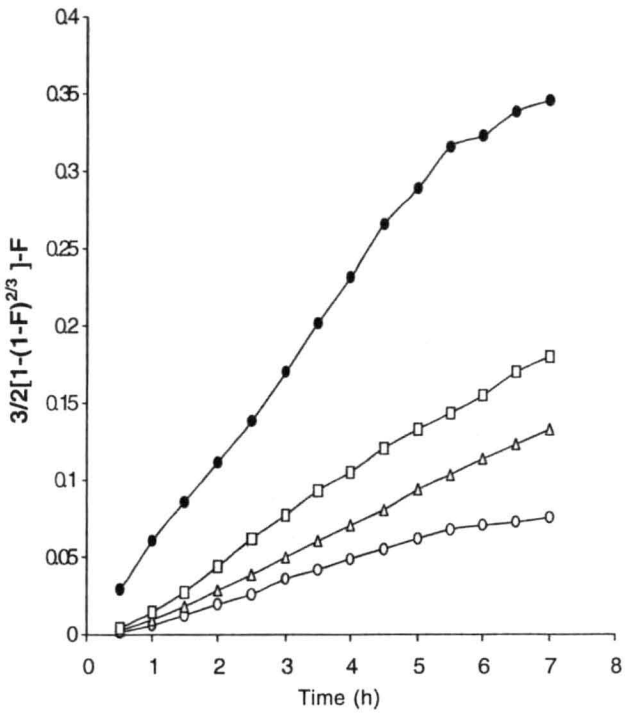


Fig. 4: Diffusion controlled release profiles.

Apparent diffusion controlled release profiles of ketoprofen from microparticles prepared with polystyrene: polyvinylpyrrolidone 97.5:2.5 (○), 95:5 (△), 85: 15 (□) and 75:25 (●).

(r=0.980–0.998). Quick dissolution of PVP in aqueous fluid forms pores and subsequently drug concentration in the matrix decreases quickly leading to exponential decline in release[11]. Again as PVP dissolves, the thickeness of gel layer formed around the microparticles leads to diffusion controlled drug release[12]. Thus evaluation of exact mechanism of drug release from PS–PVP microparticles became difficult.

The results indicate that release of ketoprofen from the microparticles prepared with PS and PVP as matrix materials could be modulated to achieve desired drug release by changing the polymer ratios and initial drug loading in the microparticles.

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