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# Preparation, Characterization and Drug Delivery Applications of Polyethylene Glycol/Corn Starch Microspheres

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The tablet form of microspheres for oral drug delivery system was prepared by the phase separation method by using the blends of polyethylene glycol (PEG) and corn starch in different ratios. Ciprofloxacin hydrochloride was used as a model drug to study the sustained release of drug from the vehicle. The as prepared microspheres were characterized by optical microscopy to analyze the morphology and size. The result shows that the average sphere size was found to be in the range of 10 µ to 40 µ. Decrease in the size of microspheres with agglomeration was observed with the increase in concentration of polyethylene glycol. Drug delivery study was carried out in the USP dissolution apparatus and the release kinetics was measured by using UV-visible spectrometer at the $\lambda_{max}$ of 278 nm. The results indicate that the release kinetics varies with the ratio of polyethylene glycol and corn starch present in the microspheres and certain formulations shows sustained release of the drug. Based on the obtained results these blends can be proposed as a drug delivery vehicle for the sustained release of ciprofloxacin.

**Keywords: Starch, Polyethylene glycol, Sustained release, Ciprofloxacin hydrochloride, Drug delivery system.**

## INTRODUCTION

Various drugs are used for cancer, pulmonary, cardiology, radiology, gynaecology, oncology, *etc*. and delivered by different drug delivery systems [1]. Drug delivery systems that can specifically control the release rate or target drugs to the specific body site have a huge market in the health care sector. In the last two decades the pharmaceutical industry have endorsed a progressive interaction among the fields of polymer and material science, resulting in the development of novel drug delivery systems [2]. Among them microsphere based drug delivery system has gained enormous attention due to its wide range of application as it covers targeting the drug to particular site to imaging and helping the diagnostic features. Drug delivery technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as microspheres, nanoparticles, liposomes, *etc*. which regulates the release and absorption characteristics of the drug. Microspheres constitute an important part of these particulate drug delivery systems by virtue of their small size. It is the carrier linked drug delivery system in which particle size ranges from 1-1000 µm in diameter having a core of drug and entire outer layer of polymer as a covering material [3,4]. The bonding mechanism of the microspheres is dependent of the constitutive nature of the polymer (molecular weight, flexibility of polymer chains, spatial conformation, swelling/water uptake, charge), of the dosage form properties (size, shape, surface, density, drug characteristics and loading) and of surrounding environment (pH, applied strength/shear, initial contact time, temperature, mucin surface charge, mucin turnover) [5,6]. However, the success of these microspheres is limited due to their short residence time at the site of absorption [7,8]. Starch is a biodegradable polymer suitable for the production of microspheres and a promising carrier for the drug delivery. Starch based blends possess an enormous potential to be widely used in the biomedical and environmental fields, as they are biodegradable, inexpensive and an almost unfailing source of raw material [9]. In addition to that, starch provides a wide range of applications in microsphere based treatment [2]. It has a long tradition as an excipient in drug formulations [10].

The key objective of the current study is to prepare the microspheres with the blends of corn starch and PEG. However, starch cannot fit into some controlled drug delivery systems, as many drugs are released quickly from the starch based systems, due to considerable swelling and quick enzymatic degradation in biological systems [9,11]. One of the efficacious mechanisms is introduced in this study to improve the properties of starch by blending it with PEG, which is extensively employed in pharmaceutical and biomedical fields. The viability of ciprofloxacin loaded polymeric microspheres as a

drug delivery system was verified by evaluating its dispersion, size, *in vitro* studies.

## EXPERIMENTAL

Polyethylene glycol (PEG) 4000 LR with an average molecular weight of 3500-4500 was purchased from Sisco research laboratory. Starch was purchased from SISCO research laboratory. Ethanol 99 % vol/vol was supplied by Sigma Aldrich was used without additional purifications. Barium chloride (99 %, Qualigens, India), KCl (99.9 %, AR, SDFCL, India), Glucose (99.5 % Sigma Aldrich), Calcium chloride AR (98 % Qualigens Fine Chemicals), NaCl (99.9 %, SDFCL) and $KH_2PO_4$ (99.5 %, AR, Thomas Baker, India) double-distilled water was used throughout the experiment. Other materials were of analytical grade and were used as received.

**Microsphere preparation:** Ciprofloxacin loaded PEG/corn starch microspheres have been prepared by phase separation method. Briefly, starch was dissolved in 10 mL of water and PEG in 12 mL of ethanol by continuous stirring until a homogeneous solution was obtained. Then, accurately weighed amount of ciprofloxacin hydrochloride was dissolved in the polymer solution. Four different compositions of the blends were prepared and the ratios are 1:9, 2:8, 3:7 and 4:6 respectively. The solution mixture was vigorously stirred in a magnetic stirrer at 37 °C to ensure uniform dispersion. The entire assembly was kept for mechanical stirring upto 5 h to allow the ethanol to evaporate. The mixture was poured in a petri plate and dried at room temperature for the formation of microspheres. The assigned formulation concentrations are tabulated in Table-1.

TABLE-1
FORMULATION COMPOSITION OF THE BLENDS

| Ratio of PEG/Corn starch | PEG (mg) | Corn starch (mg) | Ethanol (mL) | Water (mL) | Ciprofloxacin hydrochloride (mg) |
|---|---|---|---|---|---|
| – | – | 600 | 12 | 10 | 60 |
| 1:9 | 60 | 540 | 12 | 10 | 60 |
| 2:8 | 120 | 480 | 12 | 10 | 60 |
| 3:7 | 180 | 420 | 12 | 10 | 60 |
| 4:6 | 240 | 360 | 12 | 10 | 60 |

**Microsphere characterization:** As prepared microsphere samples morphology was observed by using an optical microscope (Carl zeiss, Imager a 1 M). The shape and surface topography of ciprofloxacin-loaded microsphere blends were examined using a scanning electron microscope (JEOL JSM 840®, 10KV, Tokyo, Japan). The hardness of the microsphere is measured by special dedicated hardness tester. The drug release kinetics was studied by using UV-visible spectrometer (Hitachi, U- 2800 Spectrophotometer, Japan)

**Preparation of gastric juice:** In 1000 mL of deionized water, analytical grade of 3.5 g of glucose, 2.05 g of NaCl, 0.60 g of $KH_2PO_4$, 0.11 g of $CaCl_2$ and 0.37 g of KCl were dissolved in the same order. The solution was sterilized and pH was brought down to 2.0 by adding 1 M HCl and then the volume of the solution was made up to 1 L [12].

**Procedure for the measurement of release kinetics:** The dissolution studies was performed in USB dissolution apparatus equipped with a basket at a stirring speed of 100 rpm maintained at a constant temperature of 37 ± 1 °C. Drug release kinetics of the PEG/corn starch microspheres was performed in 900 mL of simulated gastric juice as a dissolution medium. 2 mL of the sample was withdrawn at 15 min interval and the drug concentration was determined spectrophotometrically at the $\lambda_{max}$ value of 278 nm. The initial volume of the dissolution fluid was maintained by adding 2 mL of fresh dissolution fluid after each withdrawl.

**Effect of pressure on the release kinetics:** Exactly, weighed quantity of the microspheres was filled into a die of 12.3 mm diameter using a little pressure and then, hydraulic pressure was applied to form the tablet (Fig. 1). The microspheres were made into tablets at different pressures (5 and 10 tons) and their effect on hardness on the release kinetics was studied. For each formulation, the hardness of the tablets was examined by Monsanto hardness tester to measure the crushing strength of the tablets. The mean hardness was calculated and expressed in $kg/cm^2$.


Fig. 1. Tablet form of the drug loaded blended microsphere

**Optical microscopic analysis:** The morphology and particle size of the microspheres was determined by the optical microscope and the images were recorded with a camera attached to the microscope using Clemex image analysis software. The sample was placed on the slide so as to have minimum possible destruction. The images of microspheres were recorded at 100 μm magnification.

**Scanning electron microscopy analysis:** Scanning electron microscopy was performed with a JEOL JSM 840®, 10 KV, scanning electron microscope (JEOL, Tokio, Japan). The samples were attached to circular stubs with double-sided adhesive tape and coated with gold-palladium using a Sputter Coater Polaron SC7640 (Thermo VG Microtech, East Grinstead, West Sussex, UK). Samples were viewed by scanning the whole specimen and an area deemed to be representative of the sample was photographed at magnifications up to 100×.

## RESULTS AND DISCUSSION

**Optical microscopic analysis:** The optical microscope image (Fig. 2) of the PEG/corn starch blend microspheres shows the formation of microspheres with the average sphere size falls in the range of 10 to 40 μ. The microsphere prepared with less PEG content is found to be more spherical and the spheres were found to be agglomerated when the concentration of corn starch was decreased. The images (Fig. 3) of corn starch microsphere shows uniform size microspheres without any agglomeration and the particles were slightly distorted spherical in shape.

**Scanning electron microscopy:** In order to gain a clear insight into the surface topography of the microspheres the images were recorded at two different magnifications (Fig. 4).

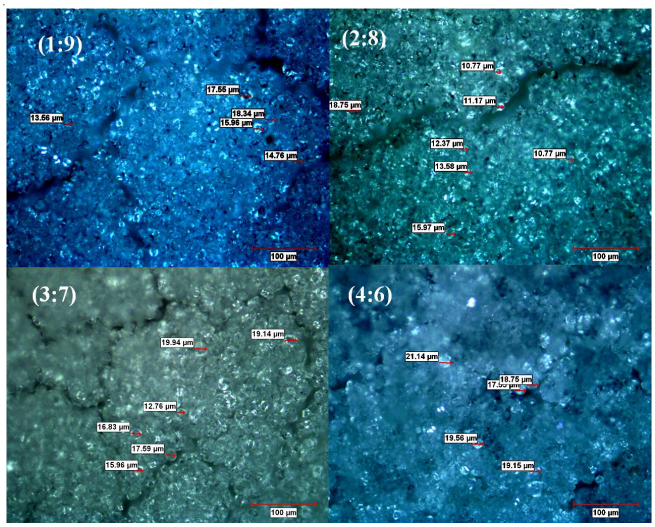


Fig. 2. Optical microscope images of PEG/corn starch blend microspheres

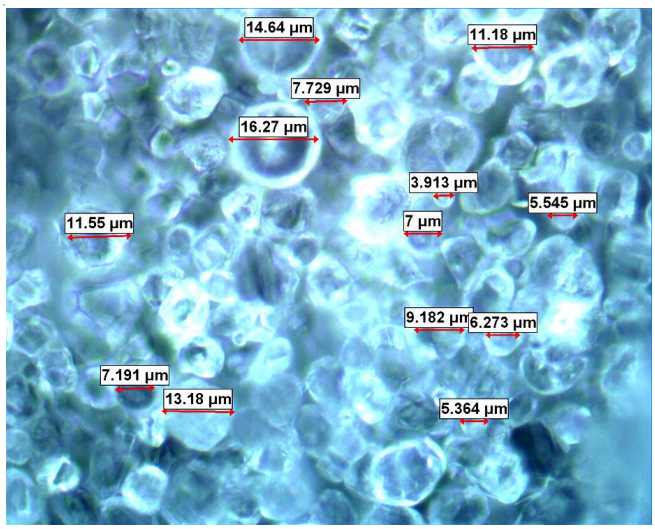


Fig. 3. Optical microscope image of corn starch microspheres

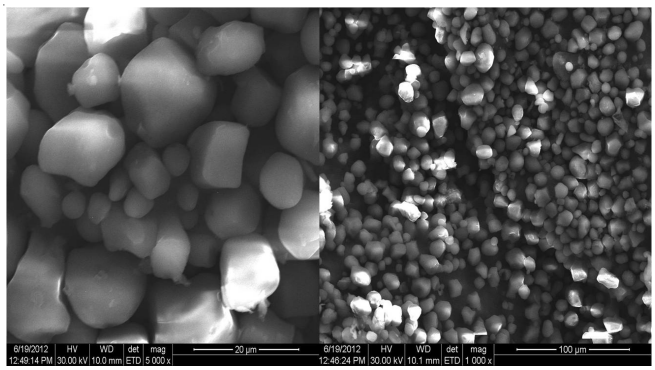

Fig. 4. Spherical and chain of globule clusters of PEG/corn starch microspheres

A close examination of images indicates that at lower magnification the microspheres appear almost spherical and the surface was smooth. The SEM micrographs of PEG/corn starch microspheres reveals that no drug crystals were found on the surface. However some of the microspheres were found to be elongated. Most of the microspheres appears to be solid, round shaped particles and have a smooth surface with clusters in appearance. Particle size analysis shows that the microspheres distributed between 5 to 21 µm which is in agreement with optical microscope analysis.

**Size distribution of the microspheres:** Addition of PEG leads to considerable change in the size of the microspheres. Increase in concentration of PEG results in the decrease in the size of microspheres. The 4:6 ratio shows the higher size morphology of 10-21 µ. The size analysis of the microspheres is listed in the Table-2.

TABLE-2
DIMENSIONS OF MICROSPHERES ON VARYING THE RATIOS OF PEG/CORN STARCH

| Ratio of PEG/Corn starch | Size of microspheres (µ) |
|---|---|
| Corn starch | 5-16 |
| 1:9 | 10-17 |
| 2:8 | 10-18 |
| 3:7 | 10-19 |
| 4:6 | 10-21 |

***In vitro* drug release studies:** *In vitro* drug release was performed in simulated gastric juice and the release profile of the drug loaded microspheres with different polymer ratios is compared in Fig. 5. As the concentration of PEG increases from 1:9 to 4:6, the drug release kinetics is found to be high. Increasing the amount of PEG in the formulation resulted in the increase in size of the microsphere as a result there is a increase in the dissolution rate of drug present in the surface.

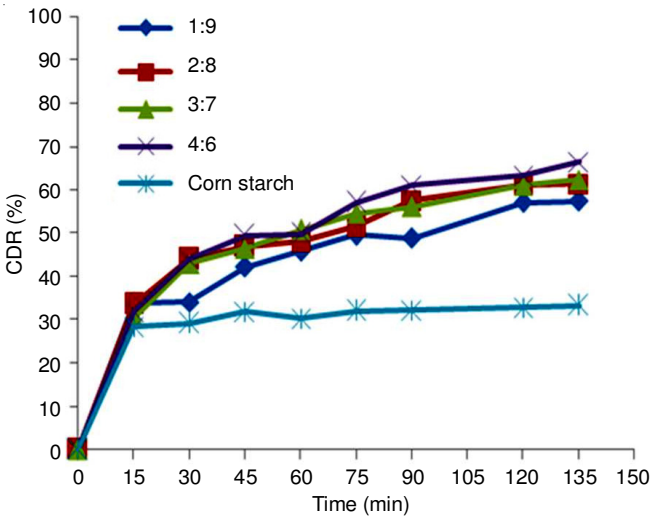


Fig. 5. Release kinetics of ciprofloxacin from PEG/corn starch microspheres

The reason behind the increase in release kinetics may be that the hydrophilic nature of PEG might have induced the release of drug. Hence by varying the concentration of constituents in the microspheres, the release kinetics can be tailored to the requirement.

Among the various ratios of PEG/corn starch blends prepared, the 4:6 ratio showed a rapid release rate of about 68 % of the loaded drug and the blend prepared with 1:9 ratio shows the lowest and sustained release of 60 % of the drug from the matrix. The blend prepared with 3:7 ratio shows a consistent release and comparatively the release rate is higher than the 1:9 ratio. Since the experiment was carried out based

on the transition period of 2 h in the intestine, the release of the drug was found to be in the range of 30-70 % within the transit time. The drug release is found to be a burst release in first 30 min and then the release is found be sustained. This may be due to the sudden release of the drug from the surface due to dissolution in the beginning and as the time progress the release is purely depends on the diffusion of the drug from the core, which is found to be highly sustained. Increase in the amount of PEG in the blend, makes the blend more hydrophilic and as a result, drug release is faster from PEG because of the higher hydration rate and swelling characteristics of the ethylene glycol. Hydrophilic PEG enhances the diffusivity of drug in the polymer carriers.

*In vitro* release studies showed that ciprofloxacin hydrochloride release changed according to the different compositions. In particular, tablets with a higher concentration of PEG showed a higher release of antibiotic with respect to the tablets with lower PEG content.

**Effect of pressure on hardness and % release of the drug:** Tablets were prepared by hydraulic pellet press by applying a pressure of about 4 and 5.3 Kg for 1 min to form a tablet. When the pressure applied to make the tablets is decreased from 10 to 5 tons, there is a considerable change in the hardness of the tablet, which may influence the release kinetics of the drug. The change in hardness with respect to the pressure applied on the tablet is represented in the Fig. 6.

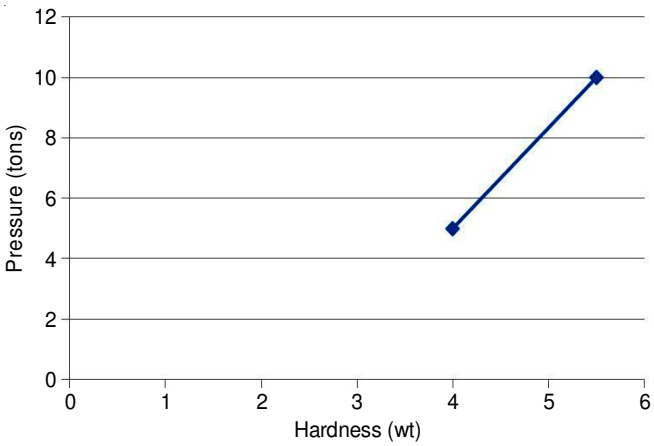


Fig. 6. Graph showing the effect of pressure on tablet hardness

The amount of pressure applied affects hardness of the tablet as it affects disintegration and dissolution of the drug present in the tablet. A force of about 4 kg is considered the minimum requirement for a satisfactory tablet and it is found to be fulfilled in the present study.

It is observed that there is a considerable increase in the release kinetics when the pressure applied to make the tablets is decreased from 10 to 5 tons and it is evident from the Figs. 7 and 8. Generally greater the pressure applied the harder will be the tablet and so the particles will be packed very tightly and the release is diffusion mediated. Due to this reason it will take more time for the tablets to release the drug into the gastric juice, which is evident from the results obtained. At low pressure, the tablet will be less hard and so the particles will be loosely packed and due to this the drug release from the matrix will

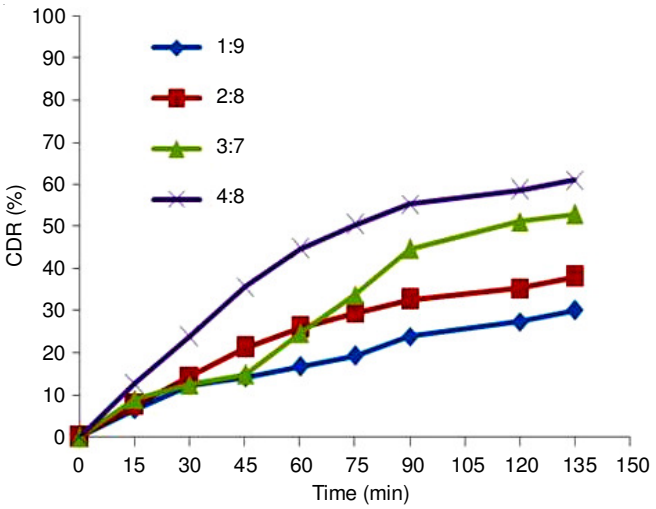


Fig. 7. Release kinetics of ciprofloxacin from PEG/corn starch microspheres (5 tons pressure)

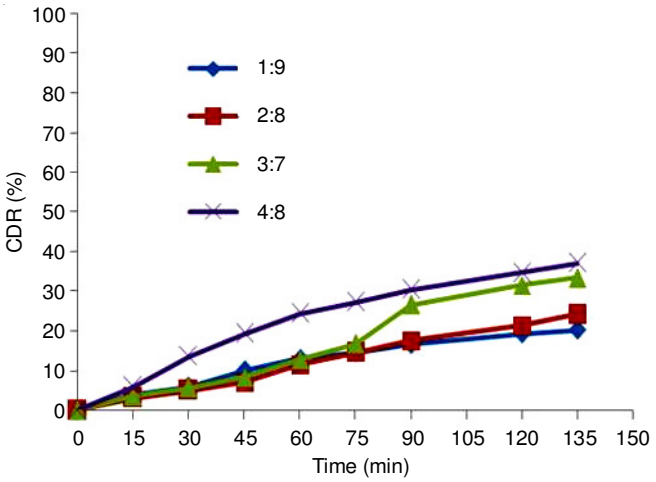


Fig. 8. Release kinetics of ciprofloxacin from PEG/corn starch microspheres (10 tons pressure)

be rapid. The influence of hardness on the release percentage is listed in the Table-3.

TABLE-3
HARDNESS AND % RELEASE AT THE VARYING PRESSURES OF THE PEG/CORN STARCH BLEND

| Ratio of PEG/corn starch microspheres | Hardness | | Release (%) | |
|---|---|---|---|---|
| | 5 tons (kg) | 10 tons (kg) | 5 tons (%) | 10 tons (%) |
| 1:9 | 4 | 5.3 | 30 | 19 |
| 2:8 | 4 | 5.3 | 38 | 24 |
| 3:7 | 4 | 5.3 | 53 | 33 |
| 4:6 | 4 | 5.3 | 60 | 36 |

## Conclusion

The microsphere containing PEG/corn starch blend was succesfully prepared and the release kineics of antibiotics from the tabletted martix was studied. It is observed that with the increase in the ratio of PEG in the blend the release kinetics of the antibiotic was found to increase where as with the increase in the ratio of corn starch in the blend, the release kinetics is found to be sustained. In the case of microspheres with a high

PEG content, the drug could diffuse out faster due to its hydrophilic nature. Also found that the size of the microspheres decreases with the increase in the amount of PEG. It is concluded that by varying the ratio between starch and PEG the desired dosage of drug may be delivered within the transit time. It is observed that when the pressure applied to make the tablets is decreased from 10 to 5 tons there is a considerable increase in the % release of the drug. Also from results it can be concluded that less harder the tablet, greater will be the % release of the drug.

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