

In vitro Release Kinetics Study of Diclofenac Sodium from Acrylic Polymer Coated Pellets

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ABSTRACT: The aim of the present study is to investigate the effect of Ammonio Methacrylate Copolymer Type B (Eudragit RS 30 D) on the release kinetics study of diclofenac sodium form coated pellets. The effect of the incorporation of xanthan gum into the coating formulation was also the goal of this study. Eudragit RS 30 D and xanthan gum was added into the formulation at 5:1 ratio. Different percent of this polymeric combination was loaded on to the drug-loaded pellets. It was found that the cumulative % release of drug decreased with the increase of polymer load in all cases. From all formulations it was observed that the release of diclofenac sodium in 0.1N HCl media was very low (maximum 3.5%) at first 2 hours. Better sustaining effect was found from Eudragit RS 30 D and xanthan gum combinations. Drug was released linearly along with time throughout the whole dissolution process in phosphate buffer (p^H 6.8) and it was also revealed that, in all cases the release of diclofenac sodium followed mixed release kinetics but zero order release kinetics predominates.

Key words: Diclofenac sodium, pellets, sustained release, *in vitro*, kinetic analysis.

INTRODUCTION

In the recent years the popularity of sustained release pellets dosage form is rapidly increasing. The pellet type of sustained-release preparation is often referred to as bead-type preparation. In general the beads are prepared by coating drug powder onto perforated cores called *nonpareil seeds*. The drug-coated beads generally provide a rapid-release carrier for the drug depending on the coating solution used in coating the drug. Once the drug beads are prepared, they may be further coated with a protective coating to allow a sustained or prolonged release of the drug.¹ Sustained release formulation of pharmaceutical pellet products has been widely investigated due to its tremendous demand in the pharmaceutical markets. This happens due to some

advantages shown over conventional dosage forms. A major advantage of pellet dosage form is that the pellets are less sensitive to the effect of stomach emptying. Because there are numerous pellets within a capsule, some pellets will gradually reach the small intestine and deliver the drug; where as a single tablet may be delayed in the stomach for a long time due to erratic stomach emptying.¹ The fluctuating drug concentrations in blood and tissues caused by conventional dosage forms lead to an insufficient influence on the mechanisms of disease and are related to the excessive use of drug. Various oral dosage forms able to control the rate and extent of drug delivery into systemic circulation have been prepared and studied.²⁻⁵

Aqueous film-coating dispersions generally consist of polymeric colloidal particles, a plasticizer, a pigment, and an anti-adherent agent. Most polymers employed for the film coating of pellets and tablets

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are brittle at room temperature and require the use of plasticizers to improve their handling and processing.⁶ Polymethacrylates are primarily used in oral capsule and tablet formulations as film coating agents.⁷⁻⁹ Depending on the type of polymer used, films of different solubility characteristics can be produced. Eudragit RS 30 D is the aqueous dispersion of copolymers of acrylic acid and methacrylic acid esters with a low content of quarternary ammonium groups. The dispersions contain 30% polymer.¹⁰ The quarternary groups occur as salts and are responsible for the permeability of films made from these polymers. Films prepared from Eudragit RS 30 D are less permeable to water and release the active substances through diffusion. Film coating prepared from both polymers give pH-independent release of active substance. Plasticizers are usually added to improve film properties.¹⁰ Xanthan gum is a polysaccharide gum and the aqueous solutions are stable over a wide pH range (pH 3-12) and temperatures between 10-60° C. It is widely used to prepare sustained release matrix formulations and it acts by forming hydrogel through swelling as well as releases the drug through diffusion.¹¹⁻¹⁴ As xanthan gum mainly used to get sustained effect from matrix formulations, this study is fabricated to observe its effect by using to some extent with Eudragit RS 30 D in the coating formulations of diclofenac sodium loaded pellets.

MATERIALS AND METHODS

Materials that are used throughout the experiment are diclofenac sodium (Square Pharmaceuticals co. Ltd. Bangladesh), Sucrose (Cerestar, Netherland), Lactose (The Lactose Co. of Newzealand Ltd. Newzealand), Maize Starch (Cerestar, Netherland), Purified Talc (Asian Mineral, Thailand), Titanium Dioxide (Warner Jenkinson, Italy), Triethyl Citrate (Morflex Inc.USA), Kollidon 30 (BASF, Germany), Eudragit RS 30 D (Rohm Pharma., Germany), Xanthan gum (Gumix Int., USA). All the other chemicals used were of analytical grade.

Preparation of diclofenac sodium sustained release pellets. Powder layering method was chosen to prepare the nonpareil seeds (NPS) first with sucrose, lactose, Kollidon 30 and purified water in the Centrifugal Fluidized Coater (Table 1). After completion of the process, NPS was dried at 60-70 °C for 6-7 hours in hot air oven and sieved through 25 & 30 mesh respectively to get the desired size (25/30) then loaded onto conventional coating pan and mixture of diclofenac sodium powder & maize starch was loaded on NPS with simultaneous spraying of kollidon 30 & water solution (Table 1). After completion of the process, drug loaded pellets was dried at 50-60 °C for 4-5 hours in hot air oven and then sieved through 20 & 25 mesh to get the desired size.

Table 1. Core and coating formulation of diclofenac sodium sustained release pellets (weights are in g).

| Materials | Formulations | | | | | |
|-------------------|--------------|-------------|-------------|-------------|-------------|-------------|
| | 5% polymer | 10% polymer | 15% polymer | 20% polymer | 25% polymer | 30% polymer |
| Diclofenac Sodium | 110 | 110 | 110 | 110 | 110 | 110 |
| Sucrose | 75 | 75 | 75 | 75 | 75 | 75 |
| Lactose | 90 | 90 | 90 | 90 | 90 | 90 |
| Maize Starch | 60 | 60 | 60 | 60 | 60 | 60 |
| Kollidon 30 | 25 | 25 | 25 | 25 | 25 | 25 |
| Eudragit RS 30 D* | 50 | 100 | 150 | 200 | 250 | 300 |
| Xanthan Gum | 3 | 6 | 9 | 12 | 15 | 18 |
| Purified Talc | 1.8 | 3.6 | 5.4 | 7.2 | 9 | 10.8 |
| Titanium Dioxide | 0.9 | 1.8 | 2.7 | 3.6 | 4.5 | 5.4 |
| Triethyl Citrate | 2.7 | 5.4 | 8.1 | 10.8 | 13.5 | 16.2 |
| Water up to | 350 | 600 | 900 | 1200 | 1500 | 1700 |

*30% dispersion commercial grade is used.

Then coating suspension was prepared by using Eudragit RS 30 D, xanthan gum, purified talc, titanium dioxide, triethyl citrate & water (Table 1). Drug loaded pellets were loaded in the fluid bed coater & coating suspension was sprayed. After

completion of spraying, the coated pellets were dried at 50-60 °C for 5-6 hours in hot air oven and sieved through 18 & 22 mesh to get the desired size (18/22) of the diclofenac sodium sustained release pellets (Figure 1).

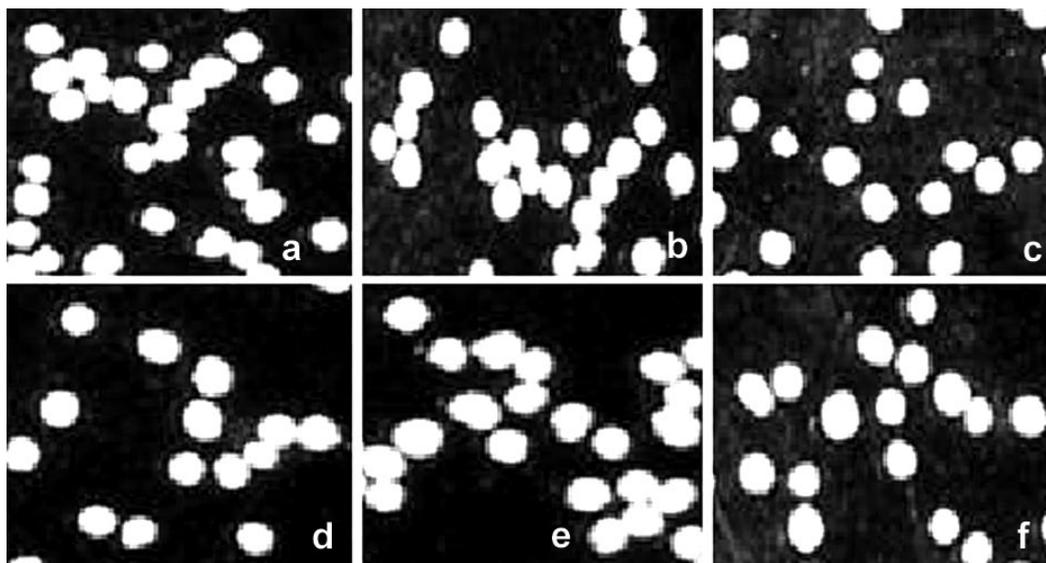


Figure 1. Diclofenac sodium sustained release pellets (dried & sieved) coated with different percent of Eudragit RS 30 D and xanthan gum (5:1 ratio) load. [(a): 5% polymer load, (b): 10% polymer load, (c): 15% polymer load, (d): 20% polymer load, (e): 25% polymer load, (f): 30% polymer load]

In vitro dissolution study. The dissolution of diclofenac sodium sustained release pellets was studied by Erweka (Germany) dissolution tester USP (XXVIII) using USP apparatus 1 (Basket method). Diclofenac sodium sustained release pellets equivalent to 100 mg of diclofenac sodium was poured in 900 ml of 0.1 N hydrochloric acid medium at 37 ± 0.5 °C with a rotation of 100 rpm for 2 hours. At the end of 2 hours the media was removed and drug content was determined spectrophotometrically at 276 nm. Then 900 ml of phosphate buffer (Na_3PO_4) pH 6.8 was placed in each vessel and rotated at 100 rpm at 37 ± 0.5 °C for 10 hours. Five ml samples were drawn every one hour and replaced by fresh medium to maintain the volume constant and drug content was determined spectrophotometrically at 276 nm.

RESULTS AND DISCUSSION

Diclofenac sodium was loaded on nonpareil seeds by powder layering method and finally coated with aqueous dispersion of acrylic polymer (Eudragit RS 30 D) and xanthan gum combination using fluid bed coater. The drug release was studied by in vitro dissolution using USP basket method. Although xanthan gum was incorporated into the coating formulations for sustaining effect but it creates problem during preparation of coating solution and increases the solution volume more. This also creates difficulties in spraying and finally at the end of process the surface of the pellets found rough.

When diclofenac sodium loaded pellets were coated with 5 to 30% percent of the combination of Eudragit RS 30 D and xanthan gum polymers (5:1 ratio), then it was revealed that the polymers have significant release retarding effect in acid media and from all formulations maximum 2.5% drug was

released at first 2 hours (Figure 2). In the buffer media, it was found that the drug release decreases gradually along with the increase in percent of polymer load from (5 to 30%) and when the cumulative percent of drug release was plotted against time a linear relationship was observed in every formulation and was found to release the drug at a uniform rate in most cases (Figure 5a) which may be due to the presence of xanthan gum.¹⁵⁻¹⁷ It

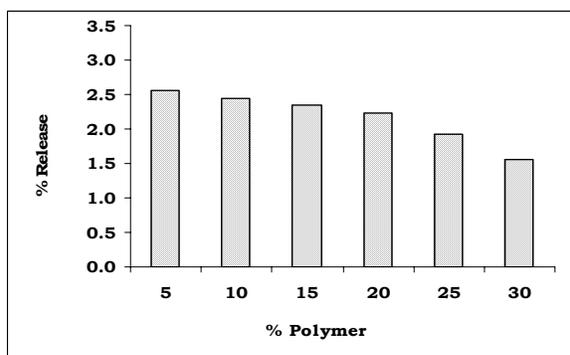


Figure 2. Release of diclofenac sodium from different percent of Eudragit RS 30 D & xanthan gum (5:1) coated pellets at two hours in 0.1N HCl.

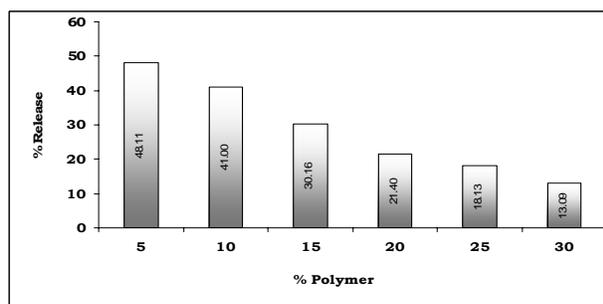


Figure 3. Burst phase release of diclofenac sodium from coated pellets at 1 hour in phosphate buffer

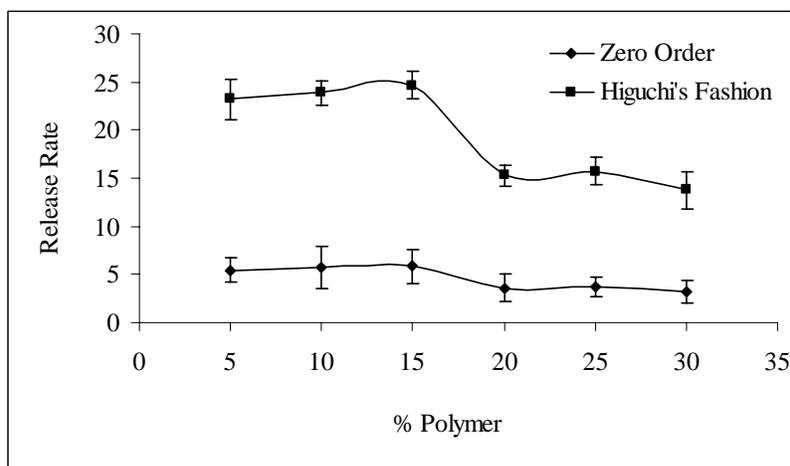


Figure 4. Release rate of diclofenac sodium from coated pellets at different % of polymer load.

xanthan gum. Xanthan gum displays a high degree of swelling due to water uptake and a small degree of erosion due to polymer relaxation.¹⁵⁻¹⁹ As Eudragit RS 30 D has initial release retarding nature, contrary xanthan gum is a swellable polymer and due to swell up in the media it facilitates the gel formation at the surface of the pellets which helps the drug to come out easily. Also the short path length for lower

percent of polymer load (5 to 15%) may play the role to behave this way and about 85%-95% drug was released by maintaining the sustained effect for 10 hours (Figure 5a). Again for higher percent of polymer (20 to 30%) loaded pellets only about 40% drug was released within 10 hours. While the percent of polymer increased the low permeability nature of Eudragit RS 30 D was increased simultaneously and

on the other hand the swelling rate of xanthan gum was decreased which might play the role to retard the release of the drug vigorously and a big difference in

drug release was observed between 15% to 20% or more polymer load throughout the whole dissolution

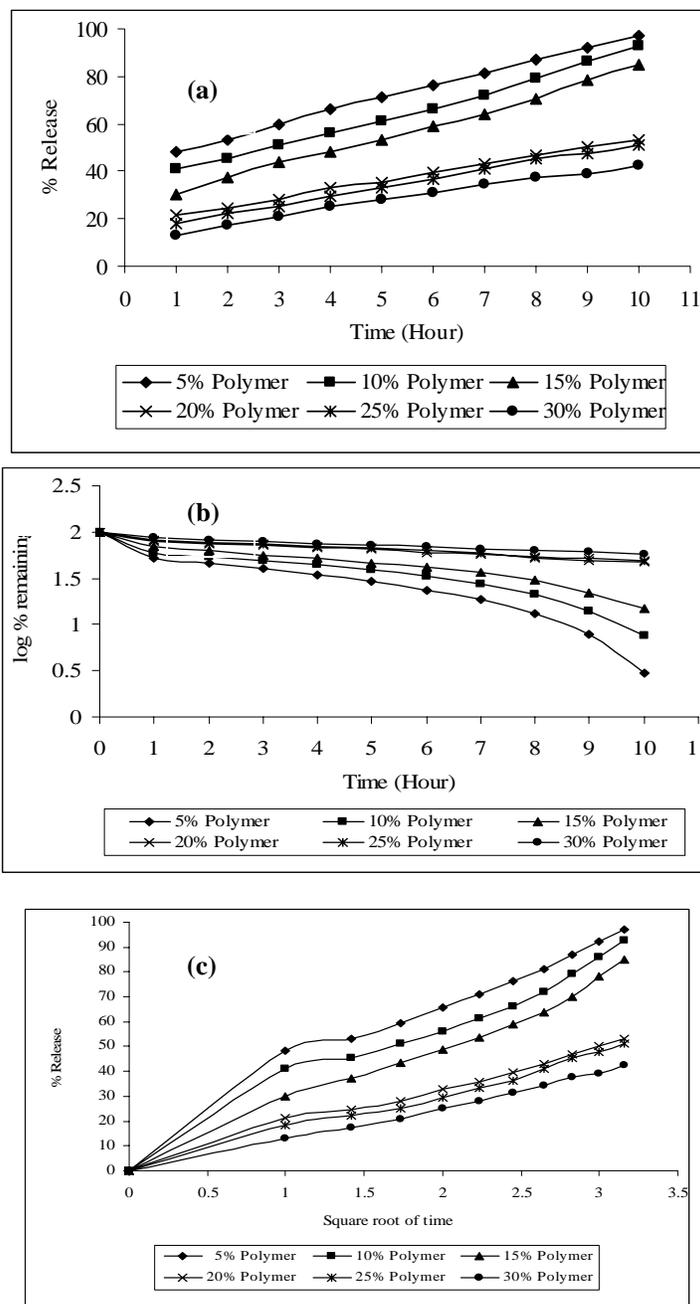


Figure 5. Diclofenac sodium release kinetics from Eudragit RS 30 D & Xanthan gum (5:1) coated pellets in phosphate buffer. [a-Zero order, b-First order, c-Higuchi plot]

process (Figure 5a). But the low permeability properties of Eudragit RS 30 D as well as the swelling & erosion behavior of xanthan gum may

lead the drug to release linearly throughout the whole dissolution process in aqueous media at pH 6.8.²⁰⁻²¹

In most of the cases it was revealed that the release kinetics of diclofenac sodium from the coated pellets appeared to follow the mixed release kinetics of zero order ($r^2 > 0.99$), first order ($r^2 > 0.90$) as well as Higuchi's release kinetics ($r^2 > 0.95$) (Figure 5a,5b,5c & Table 2) but zero order release kinetics predominates. The release rate of diclofenac sodium from the coated pellets was

seemed to be parallel between the zero order and Higuchi's release kinetics but the highest rate and extend of drug release was observed in Higuchi's release kinetics (Figure 4). In case of 20% or more polymer load the release rate was decreased suddenly, which indicates the more release retarding capability of two polymers during more polymer-drug ratio.

Table 2. Correlation coefficient data (r^2) at different percent of polymer load.

| Polymer combination | % (w/w) polymer | Correlation coefficient (r^2) | | |
|------------------------------------|-----------------|-----------------------------------|-------------|---------|
| | | Zero Order | First Order | Higuchi |
| Eudragit RS 30 D-Xanthan Gum (5:1) | 5 | 0.9989 | 0.9093 | 0.9847 |
| | 10 | 0.9951 | 0.9137 | 0.9566 |
| | 15 | 0.9949 | 0.9445 | 0.9674 |
| | 20 | 0.9987 | 0.9613 | 0.9803 |
| | 25 | 0.9982 | 0.9735 | 0.9779 |
| | 30 | 0.9923 | 0.9741 | 0.9939 |

CONCLUSION

Although both of the polymers showed better sustaining effect of drug from the coated pellets but from manufacturing point of view xanthan gum may not be a suitable polymer used in the coating formulation due to its swelling properties in aqueous media. Due to its presence the volume of coating solution increases and so as the overall coating time. The surface of the pellets becomes rough during coating and after drying phase. So future research may be initiated which will minimize these problems.

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