

Effect of Acrylic Polymers on the Physical Parameters and *in vitro* Release Kinetics of Diclofenac Sodium Sustained Release Pellets

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Abstract

The aim of the present study is to investigate the effect of Ammonio Methacrylate Copolymer Type A (Eudragit RL 30 D) and Ammonio Methacrylate Copolymer Type B (Eudragit RS 30 D) on the release kinetics study of diclofenac sodium form coated pellets. Eudragit RS 30 D and Eudragit RL 30 D were added into the formulation at 5:1 ratio. Different percent of this polymeric combination was loaded on to the drug-loaded pellets. Loss on drying value as well as bulk density of coated pellets increase along with the increase in polymer level. It was found that the cumulative percent 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 2.87 %) at first 2 hours. Better sustaining effect was found from Eudragit RS 30 D and Eudragit RL 30 D 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 zero order kinetics.

Key words: Diclofenac sodium, Eudragit RL 30 D, Eudragit RS 30 D, Aqueous coating, Physical parameters, Kinetics of drug release

Introduction

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 coat

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ed with a protective coating to allow a sustained or prolonged release of the drug (Andrew and Shargel 1941). 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 (Andrew and Shargel 1941). 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 (Bidah and Vergnaud 1991, Bravo *et al.* 2002, Ford *et al.* 2000, Jayasagar *et al.* 2001).

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 are brittle at room temperature and require the use of plasticizers to improve their handling and processing (Chuanbin and James 2001). The most widely used aqueous polymer dispersions for sustained-release coating applications are either ethylcellulose-based (Aquacoat ECD, Surelease) or acrylate-based i.e. polymethacrylates (Eudragit RL 30 D, Eudragit RS 30 D, Eudragit NE 30 D and others) products. Because of ethylcellulose's relatively high glass-transition temperature (T_g) and pseudolatex nature, ethylcellulose aqueous dispersions require adequate plasticization, with the end product needing further curing steps. Although Eudragit products are true latex with low T_g 's, particle coalescence at room temperature is still slow and

incomplete, necessitating accelerated curing conditions and/or the incorporation of water-soluble additives (Augsburger *et al.* 2000). Polymethacrylates are primarily used in oral capsule and tablet formulations as film coating agents (Dreher and Lehmann 1973, Dreher and Lehmann 1981, Obi and Okor 1990). Depending on the type of polymer used, films of different solubility characteristics can be produced. Eudragit RL 30 D and Eudragit RS 30 D are aqueous dispersion of copolymers of acrylic acid and methacrylic acid esters with a low content of quaternary ammonium groups (Kibbe 2000, Lehmann 1996). The dispersions contain 30 % polymer. The quaternary groups occur as salts and are responsible for the permeability of films made from these polymers. Films prepared from Eudragit RL 30 D are readily permeable to water and to dissolve active substances, whereas films prepared from Eudragit RS 30 D are less permeable to water and release the active substances through diffusion (Abmus *et al.* 2001, Lehmann 1996). Film coatings prepared from both polymers give pH-independent release of active substance. Plasticizers are usually added to improve film properties (Kibbe 2000). Eudragit RS 30 D and Eudragit RL 30 D are extensively being used by Eskayef Bangladesh Ltd for manufacturing of Diclofenac SR pellets as bulk. This study was fabricated to observe the effect of Eudragit RS 30 D in combination with Eudragit RL 30 D while used for

the coating of diclofenac sodium loaded beads.

(Rohm Pharma., Germany). All the other chemicals used were of analytical grade.

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 RL 30 D and Eudragit RS 30 D

Preparation of diclofenac sodium sustained release pellets

Powder layering method was chosen to prepare the diclofenac sodium beads. At first required amount of Polyvinyl pyrrolidone (Kollidon 30) was dissolved in Isopropyl alcohol according to Table I to prepare binding solution. Then desired size (25/30) of Nonpareil seeds (NPS) was loaded onto conventional coating pan (Ganson, India) and mixture of diclofenac sodium powder, lactose and maize starch (Table I) was loaded

Table I. 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
Nonpareil seeds (NPS)	120	120	120	120	120	120
Lactose	75	75	75	75	75	75
Maize starch	35	35	35	35	35	35
Polyvinyl pyrrolidone (K-30)	20	20	20	20	20	20
Isopropyl alcohol up to	180	180	180	180	180	180
Eudragit RS 30 D*	50	100	150	200	250	300
Eudragit RL 30 D*	10	20	30	40	50	60
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	120	240	360	480	600	720

*30 % dispersion commercial grade is used

manually on NPS with simultaneous spraying of binding solution. After completion of the process, drug loaded pellets was dried at 60^o C for 5.5 hours in hot air oven (Non-perforated tray drier) and then sieved through 20 and 25 mesh to get the desired size (Fig. 1).

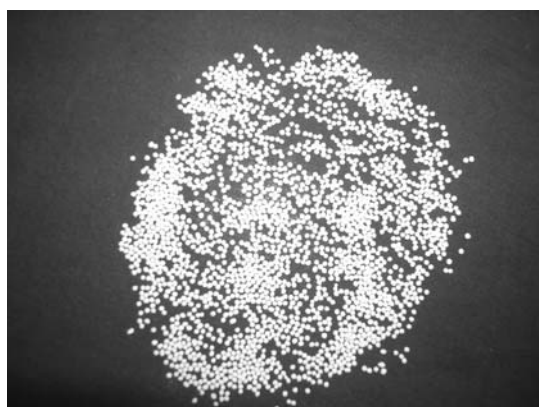


Fig. 1: Drug loaded beads (dried and sieved) containing diclofenac sodium prepared by powder layering technology.

Then coating suspension was prepared by using Eudragit RS 30 D and Eudragit RL 30 D (5 % polymer (w/w) on dry basis at a ratio of 5:1 with reference to 360.00g drug loaded beads), purified talc, titanium dioxide, triethyl citrate and water (Table I). Drug loaded pellets were loaded in the fluid bed coater and coating suspension was sprayed. After completion of spraying, the coated pellets were dried at 60^o C for 5 hours in hot air oven and sieved through 18 and 22 mesh to get the desired size (18/22) of the diclofenac sodium sustained release pellets. Same

process was applied for 10 %, 15 %, 20 %, 25 % and 30 % polymer load (Table I).

***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^o ± 0.5^o 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 (Na₃PO₄) p^H 6.8 was placed in each vessel and rotated at 100 rpm at 37^o ± 0.5^o C for 10 hours. 5ml samples were drawn every one hour and replaced by fresh medium to maintain the volume constant and drug content was determined spectrophotometrically (Shimadzu, UV-1650PC, Japan) 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 polymers such as Eudragit RS 30 D and Eudragit RL 30 D combination using fluid bed coater. The drug release was studied by in vitro dissolution using USP basket method.

Table II. Physical parameters of the drug loaded beads and coated pellets with different % of polymer load (n=3)

Parameters	Drug loading	Coating					
		5 % Poly-mer load	10 % Poly-mer load	15 % Poly-mer load	20 % Poly-mer load	25 % Poly-mer load	30% Poly-mer load
Batch size (g)	360.00	360.00	360.00	360.00	360.00	360.00	360.00
Appearance	White spherical pellets	Off-white spherical pellets	Off-white spherical pellets	Off-white spherical pellets	Off-white spherical pellets	Off-white spherical pellets	Off-white spherical pellets
% Yield	85.77 (±2.31)	91.00 (± 4.03)	89.71 (± 1.04)	92.44 (± 2.18)	97.26 (± 1.37)	95.25 (± 2.87)	98.41 (± 2.33)
% LOD	2.04 (± 0.53)	2.17 (± 0.19)	1.95 (± 0.02)	2.13 (± 0.21)	2.39 (± 0.05)	2.58 ± 0.33	2.77 (± 0.36)
% Potency	29.11 (± 1.75)	25.09 (± 1.07)	24.22 (± 2.31)	23.11 (± 1.09)	22.72 (± 1.23)	22.09 (± 3.34)	20.52 (± 1.17)
Bulk density (g/cm ³)	0.78 (± 0.02)	0.82 (± 0.01)	0.87 (± 0.02)	0.92 (± 0.01)	0.93 (± 0.04)	0.94 (± 0.01)	0.98 (± 0.02)

LOD: % Loss on drying. Three samples run for each trial

Initially the color of the drug-loaded pellets was white and the size was spherical but after coating with acrylic polymers pellets become off-white but shape remained same (Table II). During beads preparation by powder layering process total yield was found 85.77 % due to some loss of raw materials mainly from adhesion of wet mass with the machine surfaces that should be considered during manufacturing (Table II) but in case of coating the yield was increased gradually which indicates that very few agglomeration or powdering was occurred in the coating process. The LOD value was increased along

with increase in polymer load, which indicates that polymers form stable film around the pellets that inhibits the moisture present in core to expel out through the polymeric membranes. It was also expressed that bulk density of the coated pellets increased harmonically along with polymer load (Table II) which reflects that volume of the pellets might not be increased proportionally along with increase in weight of pellets due to polymer load.

When diclofenac sodium loaded pellets were coated with 5 % to 30 % of the combination

of Eudragit RS 30 D and Eudragit RL 30 D polymers (5:1 ratio), then it was revealed that the polymers have significant release retarding effect of drug in acid media and from all formulations maximum 2.87 % drug was released at first 2 hours (Fig. 2). In the buffer

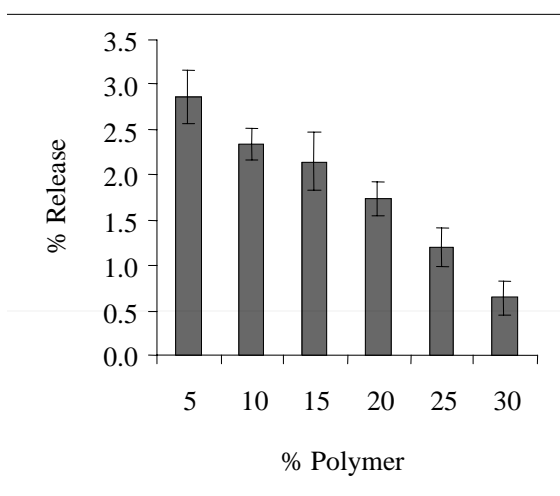


Fig. 2. Release of diclofenac sodium from different percent of Eudragit RS 30 D and Eudragit RL 30 D (5:1) coated pellets at two hours in 0.1N HCl (n=3).

media, it was found that the drug release decreases gradually along with the increase in percent of polymer load and in all cases it was observed that the initial drug release was slower than the terminal drug release which can be governed by the physico-chemical properties of Eudragit RS 30 D (Abmus *et al.* 2001, Kibbe 2000, Lehmann 1996). It was also revealed that when diclofenac sodium pellets was coated with the 5 % polymer load then about 45 % drug was released at first

hour which indicates the burst release of drug but this possibility was decreased gradually from 10 % to 30 % polymer load (Fig. 3). With 10 % polymer load about 28 % drug

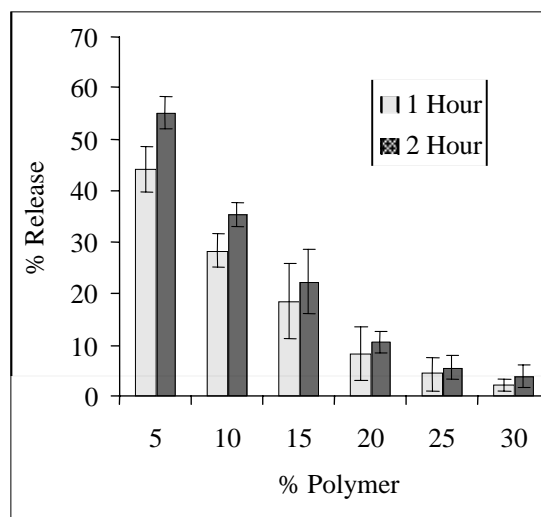


Fig. 3. Burst phase release of diclofenac sodium from coated pellets at 1 hour in pH 6.8 phosphate buffer (n=3).

was released at first hour and about 50 % drug was released at 5th hour but only 65 % drug was released within 10 hours (Fig. 4). Again for higher percent polymer load (15 %) only 18 % drug was released at first hour whereas 45 % drug was released within 10 hours. Simultaneously the drug release was decreased markedly with higher percent of polymer level (Fig. 4). While the percent of polymer increased the low permeability nature of Eudragit RS 30 D (Abmus *et al.* 2001) was increased simultaneously which

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

Formulations	Correlation coefficient (r^2)		Release rate	
	Zero order	Higuchi	Zero order (mg/Hr)	Higuchi (mg/Hr ^{-1/2})
5 % Polymer level	0.9882	0.9823	6.37	27.72
10 % Polymer level	0.9837	0.9819	3.84	16.55
15 % Polymer level	0.9988	0.9872	2.87	12.18
20 % Polymer level	0.9867	0.9579	1.48	6.14
25 % Polymer level	0.9284	0.9268	1.01	4.17
30 % Polymer level	0.9466	0.9020	0.88	3.65

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 process (Fig. 4). But the low permeability properties of Eudragit RS 30 D as well as the high permeability properties of

Eudragit RL 30 D may lead the drug to release linearly throughout the whole dissolution process in aqueous media at pH 6.8 (Abmus *et al.* 2001, Al-Taani and Tashtoush 2003, Cox *et al.* 1998). And it is also revealed that the combination of Eudragit RS 30 D and Eudragit RL 30 D is much more effective

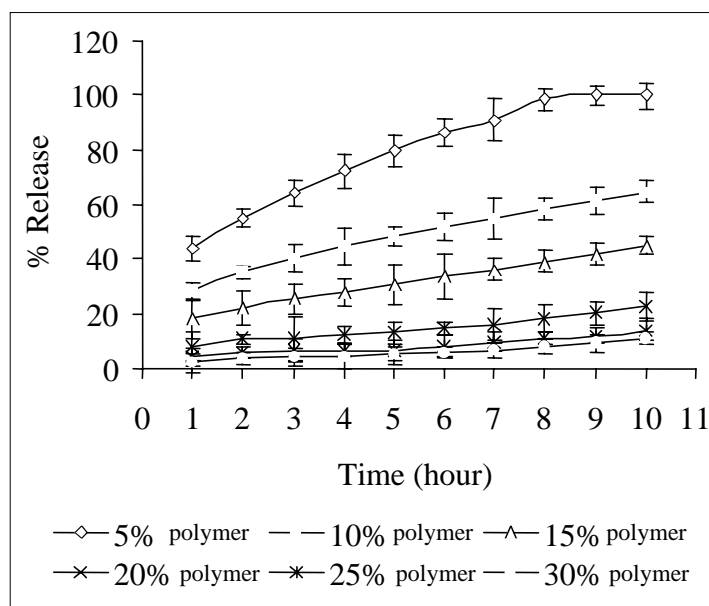


Fig. 4. Mean percent of diclofenac sodium release from Eudragit RS 30 D and Eudragit RL 30 D (5:1) coated pellets in dissolution study at pH 6.8 phosphate buffer (n=3).

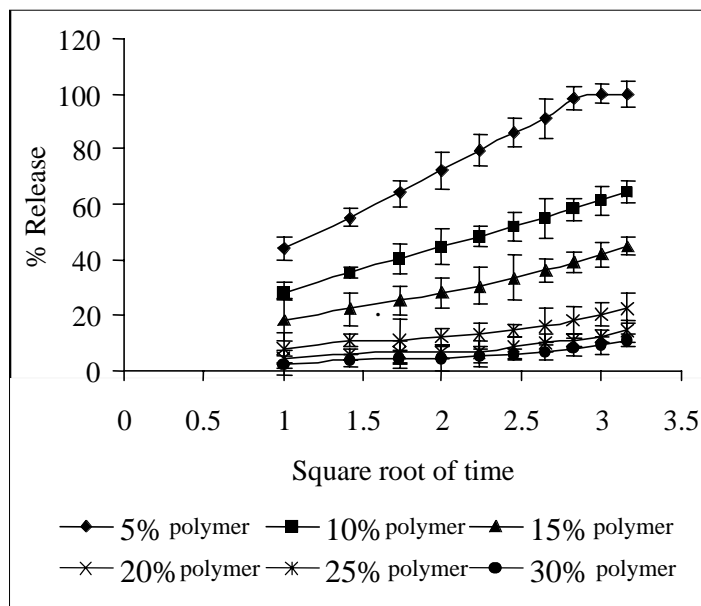


Fig. 5. Effect of polymer level on Higuchi's release rate (% drug release/time^{-1/2}) of diclofenac sodium from Eudragit RS 30 D and Eudragit RL 30 D (5:1) coated pellets in dissolution study at pH 6.8 phosphate buffer (n=3).

to sustain the release of diclofenac sodium from the coated pellets and better sustained effect was found in case of 5 % and 10 % polymer load with a good dissolution profile. Only about 10 % drug was released at 10 hours while the polymer load was 25 % ($r^2 = 0.9284$) and 30 % ($r^2 = 0.9466$).

Conclusion

Diclofenac sodium loaded pellets were prepared by powder layering technology and the in vitro release profile of drug was investigated. The physical properties of pellets influenced by the polymer level. The release profile of drug was found to be a function of

polymer load as well as the physico-chemical nature of the polymeric materials. The combination of two different acrylic polymers showed the better effect on the release kinetics of drug with lower percent of polymer load (5-15 %) to sustain the release of drug over a period of time with better dissolution profile as well as better linearity in drug release kinetics. So it is possible to modify the release profile of drug from diclofenac containing coated pellets by choosing suitable polymeric combinations according to the desired drug concentration at the target site of drug absorption. This process can be applied for commercial manufacturing of

diclofenac sodium sustained release pellets but proper dissolution profile can be adjusted by selecting the proper combination of Eudragit RS 30 D and Eudragit RL 30 D along with appropriate percent of polymer level.

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Received : June 10, 2007;

Accepted : August 15, 2007