

THE EFFECT OF THE RATIO OF TWO ACRYLIC POLYMERS ON THE IN VITRO RELEASE KINETICS OF KETOPROFEN FROM PELLETS PREPARED BY EXTRUSION AND SPHERONISATION TECHNIQUE

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ABSTRACT

The aim of this study was to investigate the effect of physico-chemical properties of the polymers on the release profile of ketoprofen from the pellets dosage form. Ammonio Methacrylate Copolymer Type A (Eudragit RL 30 D) & Ammonio Methacrylate Copolymer Type B (Eudragit RS 30 D) were used as release rate retarding polymers. The drug containing core pellets were prepared by extrusion spheronisation technique and subsequently coated with 15% (w/w) polymer load of the combination of Eudragit RL 30 D & Eudragit RS 30 D having ratio 1:0, 4:1, 3:2, 1:1, 2:3, 1:4, 0:1 respectively. Significant differences were found among the drug release profile from different formulations. It was revealed that Eudragit RL 30 D has the effect to increase the initial drug release more significantly where as Eudragit RS 30 D has the effect to minimize the initial drug release but increase the terminal drug release more significantly. In acid media about 50% drug was released from pellets coated only with Eudragit RL 30 D where as only 5% drug was released in case of Eudragit RS 30 D but maximum 10% drug was released from pellets when coated with the combination of Eudragit RL 30 D & Eudragit RS 30 D. In buffer media, evidence of burst release was observed for the pellets coated with Eudragit RL 30 D & Eudragit RS 30 D having ratio of 1:0, 4:1, 3:2 respectively. It was also observed that drug release increases sharply as well as the release best fit to the zero order release kinetics when pellets coated with 1:1 ratio of Eudragit RL 30 D & Eudragit RS and follows Higuchi's release kinetics when ratio was 1:0 & 3:2. The results generated in this study showed that proper selection of polymeric materials based on their physico-chemical properties is important in designing sustained release pellets dosage form with suitable dissolution profile.

Keywords: Eudragit RL 30D, Eudragit RS 30D, Ketoprofen, pellets, sustained release, release kinetics.

INTRODUCTION

Most conventional drug products, such as tablets and capsules, are formulated to release the active drug immediately to obtain rapid and complete systemic absorption of the drug. In recent years, various modified drug products have been developed to release the active drug at a controlled rate. A variety of controlled release drug products designed for different routes of administration based on the physicochemical, pharmacologic and pharmacokinetic properties of the drug (Shargel and Andrew, 1941). 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 (Shargel and Andrew, 1941). The pellet dosage form can be prepared as a capsule or tablet. Some products take advantage of

bead blending to provide two doses of drug in one formulation. Formulation of drug into pellet form may reduce gastric irritation as well as gastrointestinal side effects, because the drug is released slowly over a period of time, therefore avoiding high drug concentration in the stomach. Pellet dosage form also allows drug to be absorbed gradually, therefore reducing the incidence of side effects by preventing high C_{max} (Shargel and Andrew, 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 (Shargel and Andrew, 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 a 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).

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Table 1: Codes & formulation of Ketoprofen sustained release pellets (weights are expressed in g.)

Materials	Formulation codes						
	RLRS-1	RLRS -2	RLRS -3	RLRS -4	RLRS -5	RLRS -6	RLRS -7
Drug loaded pellets (core)	200.0	200.0	200.0	200.0	200.0	200.0	200.0
Eudragit RL 30 D*	100.0	80.0	60.0	50.0	40.0	20.0	0.0
Eudragit RS 30 D*	0.0	20.0	40.0	50.0	60.0	80.0	100.0
Purified Talc	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Titanium Dioxide	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Triethyl Citrate	6.0	6.0	6.0	6.0	6.0	6.0	6.0
Water up to	200.0	200.0	200.0	200.0	200.0	200.0	200.0

*30% dispersion commercial grade used.

Table 2: Correlation coefficient (r^2) data at different ratio of polymer load on Ketoprofen release kinetics from Eudragit RL 30 D & Eudragit RS 30 D coated pellets in phosphate buffer.

Formulation codes	Ratio of Eudragit RL 30 D & Eudragit RS 30 D	% (w/w) polymer (on dry basis)	Zero Order		Higuchi	
			Release rate ($\pm$ SD), (n=6)	r^2	Release rate ($\pm$ SD), (n=6)	r^2
RLRS-1	1:0	15	2.7665 ($\pm$ 0.0464)	0.9654	10.917 ($\pm$ 0.1023)	0.9893
RLRS-2	4:1	15	3.6671 ($\pm$ 0.0671)	0.9075	14.724 ($\pm$ 0.1502)	0.9628
RLRS-3	3:2	15	4.7696 ($\pm$ 0.0445)	0.9826	18.64 ($\pm$ 0.0145)	0.9877
RLRS-4	1:1	15	6.735 ($\pm$ 0.0542)	0.9877	25.67 ($\pm$ 0.1214)	0.9444
RLRS-5	2:3	15	7.8421 ($\pm$ 0.0487)	0.9700	29.755 ($\pm$ 0.2059)	0.9191
RLRS-6	1:4	15	9.0305 ($\pm$ 0.0018)	0.9697	34.373 ($\pm$ 0.1315)	0.9247
RLRS-7	0:1	15	7.9352 ($\pm$ 0.1479)	0.9642	29.887 ($\pm$ 0.1071)	0.9002

Pelletization is increasingly applied currently for the preparation of solid oral controlled-release dosage forms. The production of the particles, which are regular in shape and size, can be achieved with the application of the proper polymer auxiliary materials and new pharmaceutical technological methods (extrusion, spheronization). Regularity in shape and size, attained by the optimization of several production parameters, can promote the coating procedure. Under optimal conditions, particles were prepared for coating in a high-shear mixer, which is used to produce uniform particles (Fekete *et al.*, 1998; Vergote *et al.*, 2001; Krogars *et al.*, 2000). Using a marketed microcrystalline cellulose (Avicel PH 101) excipient, optimum extrusion and spheronization conditions for less soluble drugs required more water, a longer wet mixing time, and prolonged spheronizing times (Hileman *et al.*, 1997). The successful spheronization of extrudates requires the correct water content. This water content is different for the formulations as well as for the extruders. Pellet sphericity was also strongly dependent on the correct water content of the formulations (Thoma and Ziegler, 1998). The aim of this study was also to prove the importance of the raw

materials composition, mixture and spheronization speed on pellet properties. Extrudates from mixtures of microcrystalline cellulose (Avicel PH 101), lactose and maize starch were prepared with a power-consumption-controlled extruder and spheronizer at different speeds. The spheronization speed had an influence on the size but not on porosity or surface tensile stress of the pellets (Kleinebudde *et al.*, 1999).

Aqueous film-coating dispersions generally consist of polymeric colloidal particles, a plasticizer, a pigment, and an anti-adherent agent (Chuanbin and James, 2001). Polymethacrylates are primarily used in oral capsule and tablet formulations as film coating agents (Okor and Obi, 1990; Lehmann and Dreher, 1973; Lehmann and Dreher, 1981). 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). 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. Film coatings prepared from both polymers give pH-independent release of active substance. Plasticizers are usually added to improve film properties (Kibbe, 2000). For this study ketoprofen was chosen actually to develop ketoprofen sustained release pellets by using two different acrylic polymers.

MATERIALS AND METHODS

Materials that are used throughout the experiment are Ketoprofen (R, S-Ketoprofen from Southwest Synthetic Pharmaceutical Co. Ltd., Chongqing, China), Maize Starch (Cerestar, Sas Van Gent, Netherlands), Lactose (The Lactose Co. of New Zealand Ltd., Hawera, New Zealand), Avicel PH 101 (Maple Biotech Pvt. Ltd., Maharashtra, India), HPMC 6 cps (Shin-etsu, Tokyo, Japan), Purified Talc (Asian Mineral, Saraburi, Thailand), Titanium Dioxide (Warner Jenkinson, Parma, Italy), Triethyl Citrate (Morflex Inc. Greensboro, North Carolina, USA), Eudragit RL 30 D (Rohm Pharma., Darmstadt, Germany), Eudragit RS 30 D (Rohm Pharma., Darmstadt, Germany). All the other chemicals used were of analytical grade where Hydrochloric Acid, Sodium Hydroxide and Potassium Dihydrogen Phosphate were obtained from Merck, Darmstadt, Germany.

Preparation of Ketoprofen SR pellets

Extrusion & Spheronization technology was used to prepare the ketoprofen sustained release (SR) pellets. At first for the preparation of core pellets (nuclei), a wet

mass was prepared with ketoprofen (40.40% w/w), lactose (12.12% w/w), maize starch (6.06% w/w), Avicel PH 101 (37.37% w/w), HPMC 6 cps (4.05% w/w) & purified water. Then the wet mass was passed through 0.8 mm aperture screen (SS) of the screen type Extruder (Extruder 35, Caleva, Dorset, UK) to prepare the extrudes having definite diameter (about 0.8 mm) & variable lengths. Then the extrudes were loaded on the specially designed pan of the Spheronizer (Spheronizer 500, Caleva, Dorset, UK) and the pan was rotated at 550-570 RPM for 2-3 minutes to prepare the spherical pellets. Then all pellets were dried at 60-65°C for 4-5 hours and sieved through the 710 micron and 850 micron screen mesh respectively to get the desired size of the drug loaded pellets (table 1). To prepare the sustained release coating suspension, a paste was prepared by using purified talc, titanium dioxide and purified water. Then the paste was added to Eudragit RL 30 D {15% (w/w) polymer on dry basis} and mixed well. At last Triethyl Citrate was added and diluted with purified water to make the final weight 200.0 g and mixed well properly (table 1). The same process was applied in case of Eudragit RS 30 D {15% (w/w) polymer on dry basis} but in case of Eudragit RL 30 D & Eudragit RS 30 D combinations {15% (w/w) polymer on dry basis and the ratio was 4:1, 3:2, 1:1, 2:3, 1:4 respectively} these two polymers are mixed first, then above process was followed to prepare the coating suspensions. Then 200.0 g drug loaded pellets was loaded in the bottom-spray Lab coater (Wurster Column) and spraying of coating suspension was started by starting the peristaltic pump. After completion of spraying, the coated pellets were dried at 50-60 °C for 5-6 hours to maintain the loss on drying (LOD) not more than

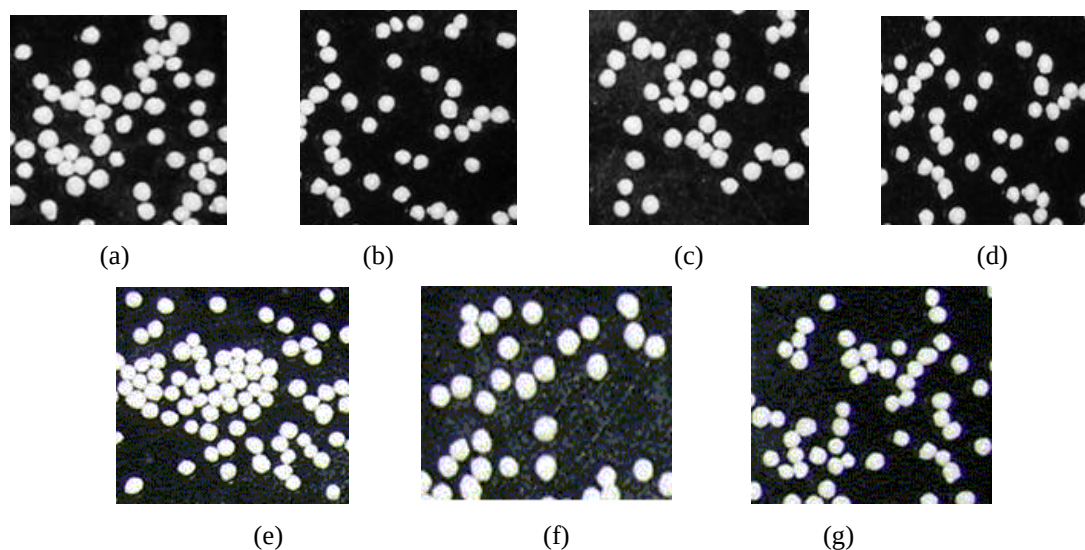


Fig. 1: Ketoprofen SR pellets (dried and sieved) coated with different ratio of Eudragit RL 30 D & Eudragit RS 30 D [(a): Eudragit RL/RS ratio 1:0, (b): Eudragit RL/RS ratio 4:1, (c): Eudragit RL/RS ratio 3:2, (d): Eudragit RL/RS ratio 1:1, (e): Eudragit RL/RS ratio 2:3, (f): Eudragit RL/RS ratio 1:4, (g): Eudragit RL/RS ratio 0:1].

2.0%. In this way all lots of pellets were coated according to the formula for RLRS-1 to RLRS-7 (Table 1). Then the coated pellets was sieved through the 710 micron & 1.00 mm screen mesh respectively to get the desired size of ketoprofen sustained release (SR) pellets (Fig. 1).

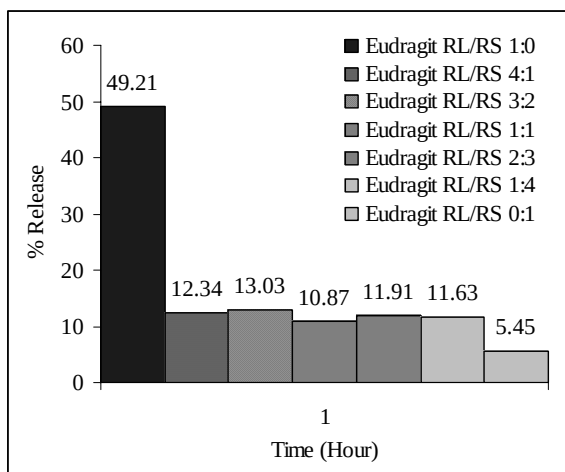


Fig. 2: Release of ketoprofen from Eudragit RL 30 D and Eudragit RS 30 D coated pellets in 0.1N HCl (pH 1.2).

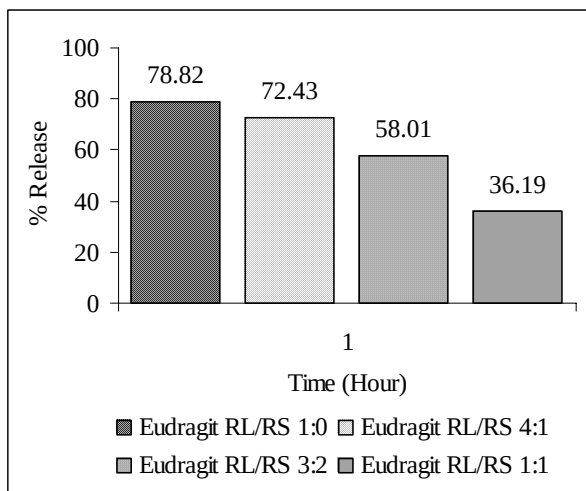


Fig. 3: Burst phase release of ketoprofen from coated pellets at 1 hour in phosphate buffer (pH 7.2).

In vitro dissolution study

The dissolution of the prepared ketoprofen sustained release (SR) Pellets was studied by Erweka (Heusenstamm, Germany) dissolution tester USP (XXVIII) using USP apparatus I (Basket method). An appropriate amount of ketoprofen SR pellets containing 100 mg of ketoprofen in total was used in 900 ml of dissolution medium (0.1 N Hydrochloric acid) at 37 °C with a rotation of 100 RPM for 1 hour. At the end of 1 hour, drug content of the sample solution i.e. the quantity of the drug release was determined by spectrophotometric

analysis and the absorbance measured at 260 nm by using Shimadzu (Kyoto, Japan) UV-Visible Spectrophotometer using the mixture of 900ml 0.1N HCl & 20ml 5N NaOH as blank. Then by replacing the acid media after 1 hour, 900 ml dissolution media (KH₂PO₄ buffer, pH 7.2) was added in each vessel. Then again ran the machine at a rotation of 100 rpm at 37 °C for next 8 hours. At every one-hour interval two (2) ml sample was withdrawn from each vessel and replaced with the fresh medium to maintain the volume constant. After appropriate dilution, the drug content of the collected samples i.e. the quantity of the drug release was determined by spectrophotometric analysis and the absorbance measured at 260 nm by using UV-Visible Spectrophotometer (Shimadzu, Japan) where the same buffer was used as blank. The amount of drug present in the samples was calculated with the help of appropriate calibration curve constructed from the reference standard of the respective drug. Drug dissolved at specified periods was plotted as percent release versus time (hours) curve. A minimum of three replicates was performed for each batch of pellets.

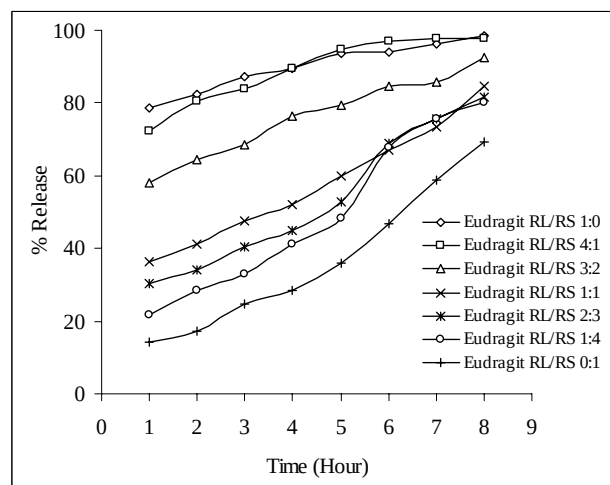


Fig. 4: Zero order release profile of ketoprofen from Eudragit RL 30 D & Eudragit RS 30 D coated pellets in phosphate buffer (pH 7.2).

RESULTS AND DISCUSSION

The physico-chemical nature of the polymeric materials influenced the release of ketoprofen from the coated pellets. The release profiles of the drug from different polymers coated pellets in different dissolution media was plotted in different fashions in figs. 2-6. From all formulations it was found that the drug release was increased in different fashions with the passing of time. It was revealed that Eudragit RS 30 D has a significant drug release lowering effect in acidic media. In 0.1N HCl media about 50% drug was released when ketoprofen-containing pellets were coated only with Eudragit RL 30 D (RLRS-1) but when Eudragit RS 30 D was added to the

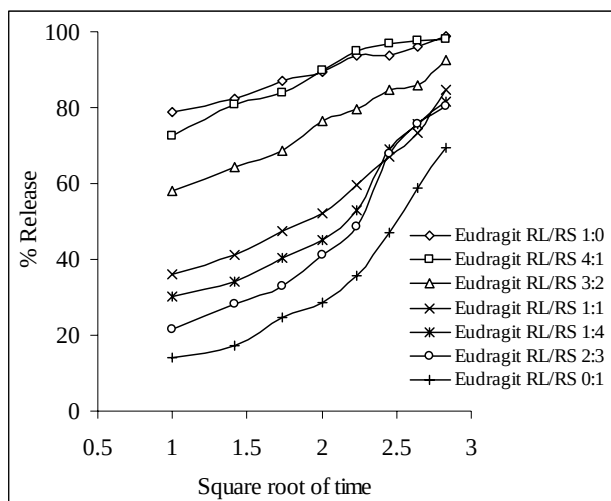


Fig. 5: Higuchi's release profile of ketoprofen from Eudragit RL 30 D & Eudragit RS 30 D coated pellets in phosphate buffer (pH 7.2).

coating formulations (RLRS-2 to RLRS-6) the drug release decreases more dramatically from 50% to 10% and this effect is more significant in case of the pellets when coated only with Eudragit RS 30 D (RLRS-7) where only 5% drug was released in acid media (fig. 2). From all formulations it was also revealed that in buffer media Eudragit RL 30 D increases the initial drug release more significantly where as Eudragit RS 30 D has shown the reverse effect and it increases the drug release sharply as a function of time. It was also observed that the drug release was decreased with the passes of time when the amount of Eudragit RS 30 D was increased gradually (fig. 4). A burst release was demonstrated at first hour in buffer media for the formulations of pellets coated with 15% w/w polymer load (on dry basis) of Eudragit RL 30 D alone (RLRS-1), 4:1 ratio (RLRS-2) of Eudragit RL 30 D & Eudragit RS 30 D and 3:2 ratio (RLRS-3) of Eudragit RL 30 D & Eudragit RS 30 D (fig. 3). The tendency of burst release was decreased with the decrease of Eudragit RL 30 D. This phenomenon can be attributed due to high permeability nature and more drug diffusive properties of Eudragit RL 30 D.

It was also observed that when ketoprofen-containing pellets coated with the combination of maximum amount of Eudragit RL 30 D and minimum amount of Eudragit RS 30 D (3:2 ratio; RLRS-3), the release kinetics of drug tends to follow zero order release kinetics ($r^2=0.9826$). But when the drug-containing pellets were coated with the equal amount of Eudragit RL 30 D & Eudragit RS 30 D (1:1 ratio; RLRS-4), drug release was increased linearly throughout the whole dissolution process and about 85% of drug was released up to 8-hours which might be due to the combined effect of the high permeability or high drug diffusion nature of the Eudragit RL 30 D and low

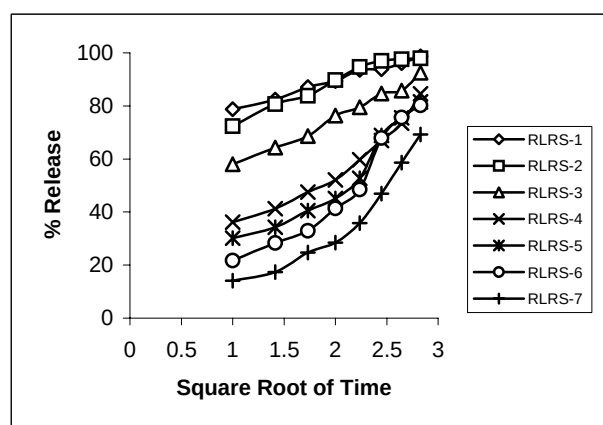


Fig. 6: Higuchi's release profile of ketoprofen from Eudragit RL 30 D & Eudragit RS 30 D coated pellets in phosphate buffer.

permeability or low drug diffusion properties of the Eudragit RS 30 D. As Eudragit RL 30 D shows the initial burst release of drug and on the contrary Eudragit RS 30 D shows the initial lowest release of drug but the terminal significant release of drug and these equal combined effects play an important role to keep the drug release curve much linear as compared to others. Also the release kinetics of drug best fit to follow zero order release kinetics ($r^2=0.9877$) (fig. 4 and table 2). This indicates that the release of drug from the coated pellets does not depend on the dose of the active in the dosage form. When core pellets were coated with the combination of minimum amount of Eudragit RL 30 D & maximum amount of Eudragit RS 30 D (2:3 & 1:4 ratio; RLRS-5 & RLRS-6 respectively), the release of drug increases sharply up to the dissolution period of 5-hours. But from 5th hour the release of drug increased drastically which may be due to the terminal drug release increasing nature of Eudragit RS 30 D. When the pellets were coated with the 15% w/w polymer load (on dry basis) of Eudragit RS 30 D it was found that the initial drug release was so less and also the drug release increased slowly up to the dissolution period of 4-hours and then release of drug increased linearly from 4th hour to 8th hour (fig. 4). This phenomenon can be attributed due to low permeability nature and less drug diffusive properties of Eudragit RS 30 D. From table 2 it was expressed that the release rate of drug was increased gradually in case of zero order & Higuchi's release for each formulation and the variation was within the limit of $\pm 5\%$ and S.D. was found as little as 0.0018 for zero order release kinetics and 0.0145 for Higuchi release kinetics which indicates that the values were much more closure to each other. It was also expressed that in case of Eudragit RL 30 D as well as the combination of Eudragit RL 30 D & Eudragit RS 30 D

(RLRS-1 & RLRS-3), when pellets were coated with 15% polymer load the release kinetics of drug tends to follow Higuchi's release fashion, $r^2=0.9893$ & $r^2=0.9877$ respectively (fig. 5) which indicates that higher percentage of Eudragit RL 30 D leads the drug to follow Higuchi's release kinetics that might be governed by high permeability properties of the polymer.

CONCLUSION

Ketoprofen loaded pellets were prepared by Extrusion-Spheronization technology and the *in vitro* release profile of drug was investigated. 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 than any individual polymer coated pellets 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 ketoprofen containing coated pellets by choosing suitable polymeric materials according to the desired drug concentration at the target site of drug absorption.

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