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# Formulation and Evaluation of Release Kinetics of Diltiazem Hydrochloride from Kollicoat SR 30 D Coated Pellets Prepared by Air Suspension Technique

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## Abstract

The purpose of the present study is to investigate the effect of polyvinyl acetate on the release kinetics of diltiazem hydrochloride from coated pellets prepared by solution and suspension layering technique. Kollicoat SR 30 D, an aqueous dispersion of polyvinyl acetate with different weight ratios was chosen to sustain the release of the drug. Drug was loaded with hydroxypropyl methyl cellulose on nonpareil seeds then coated with the Kollicoat SR 30 D. In vitro dissolution studies were carried out using USP dissolution apparatus Type-2. No significant difference was found in drug release from uncoated pellets and the pellets coated with 5% polymer load. With 10% polymer load, the initial release was minimized but from 2nd hour the release was quick-tempered. Better sustaining effect was found from 15-20% polymer loaded pellets. The mean dissolution time was 2.5h and 4h while the polymer load was 15% and 20% respectively. Also these two cases 80% drug was released at 6h and 9h respectively. The physical parameters of the prepared pellets were also compared in this study. The release of drug from the coated pellets appeared to follow Higuchi's release kinetics.

**Key words:** Diltiazem, Pellets, Kollicoat SR 30 D, Aqueous coating, Physical parameters, Release kinetics.

## Introduction

Spherical oral dosage forms such as pills have been used in the pharmaceutical industry for a long time but the full impact of systemically agglomerated spherical units or pellets on oral dosage form design and performance was not realized until the early 1950s (Ghebre-Sellassie, 1989). In 1949 the pharmaceutical scientist at SmithKline and

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French (SK&F, UK) developed sustained-release tiny drug pellets that could be loaded into capsules (Special Delivery, 1986). In 1951, the seeds were prepared utilizing standard coating pans and involved successive layering of powder and binder on sugar granules until spherical seeds of the desired size were obtained (Cimicata, 1951 and Tang *et al*., 2000). Pellets range in size, typically, between 0.5-1.5 mm, though other sizes could be prepared, depending on the processing technologies employed. The most widely used pelletization processes in the pharmaceutical industry are extrusion/spheronization, solution/suspension layering and powder layering (Ghebre-Sellassie, 1989).

The fluidized bed is well suited for producing pellets by layering as well as for applying virtually any type of coating system. Although layering can be conducted by the top spray system, bottom spray and rotary tangential spray are the preferred methods (Ghebre-Sellassie, 1989). A far more common configuration for bottom spray coating is known as the Wurster process (Wurster, 1959). The Wurster process for bottom spray coating has been in use for well over 18 years (Ghebre-Sellassie, 1989). This process is attractive for solution and suspension layering, in part because of its ability to apply high-quality films subsequent to the palletizing operation (Ghebre-Sellassie, 1989). Layering of suspension or solution of drug onto a seed material (generally a coarse crystal or nonpareil) can result in pellets that are uniform in size distribution and generally possess very good surface morphology. These characteristics are especially desirable when the pellets will subsequently be coated for some types of controlled release (Ghebre-Sellassie, 1989). The rate at which the solids are being applied is dependent on several factors: (i) the velocity and density of particles in spray zone, (ii) the thickness of the liquid, (iii) the capacity of air for spraying of the solvent being used, and (iv) the solids concentration of the solution or suspension (Ghebre-Sellassie, 1989). If it is possible to produce an acceptable solution or suspension of drug, there are further considerations for obtaining the desired results. A binder will typically be required to give the strength of the pellets needed for subsequent processing (Ghebre-Sellassie, 1989).

In this study diltiazem hydrochloride, a calcium antagonist is used as a model drug and commercial aqueous polyvinyl acetate dispersion (Kollicoat SR 30 D) is used as modified release polymeric material. Kollicoat SR 30D is an aqueous dispersion composed of 27% polyvinyl acetate (PVAc), 2.5% povidone, and 0.3% sodium lauryl sulfate (BASF Technical Bulletin, 2004; Kolter and Ruchatz, 1999). With adequate plasticizing, the formed PVAc film has been shown to possess unique physical and mechanical properties such as enormous flexibility, rendering the film-coated pellets compressible without rupture (Dashevsky *et al.,* 2000). Additionally, PVAc-based matrix and film-

coated products were demonstrated to release drugs in a pH-independent fashion (Kolter and Ruchatz, 1999; Bodmeier et al., 1999; Ruchatz *et al.*, 1999). The dispersion is suitable for the manufacturing of pH-independent sustained-release pellet dosage form (BASF Technical Bulletin, 2004; Zezhi *et al*., 2002). The minimum film forming temperature (MFT) of the pure dispersion is 18$^{O}$C which can be lowered by the addition of plasticizers. Triethyl citrate, 1,2-propylene glycol, polyethylene glycol, triacetin are the suitable plasticizers or gloss enhancers (BASF Technical Bulletin, 2004). The drug release characteristics of the polymer may be modified by the addition of povidone (Kibbe, 2000), hydroxypropylmethylcellulose (Gohel *et al.*, 2002; Hogan, 1989; Rowe, 1986; Sadeghi *et al.*, 2000) or a plasticizer (Saettone *et al*., 1995). The aim of this study was to investigate the effect of different percent of coating load on the release kinetics of the drug as well as the physical properties of the coated beads prepared by solution and suspension layering technology.

## Materials and Methods

Materials that are used throughout the experiment are Diltiazem hydrochloride (Index Pharma, India), Sucrose (Cerestar, Netherland), Maize Starch (Cerestar, Netherland), Polyethylene Glycol (PEG 6000) (Cell Chemical Co. Korea), Kollidon 30 (BASF, Germany), Kollicoat SR 30 D (BASF, Germany), Hydroxypropylmethylcellulose (HPMC 6 cps) (Shin-etsu, Japan).

### Preparation of diltiazem hydrochloride sustained release pellets

At first nonpareil seeds (NPS) was prepared by powder layering method. These were prepared in Centrifugal Fluidized Coater with sucrose, lactose, maize starch, Kollidon 30 and water. After preparing NPS were dried for 7 hours at 60-70$^{O}$C in hot air oven. To get desired size these were then sieved through 18 and 24 mesh respectively.

The air suspension technique was chosen to prepare the diltiazem hydrochloride sustained release pellets. Different percent of Kollicoat SR 30 D i.e. 5%, 10%, 15% and 20% polymer (%w/w on dry basis) with reference to 300g drug loaded pellets (Table I) was considered to prepare the following samples.

The drug loaded pellet was prepared first. This regard HPMC 6cps, PEG 6000 and diltiazem hydrochloride were dissolved separately in purified water. Then diltiazem hydrochloride solution was added to HPMC solution followed by PEG 6000 solution then mixed well and diluted with purified water to make the final weight of solution according to Table I. Then 210.00 g NPS was loaded onto the bottom spray fluid bed coater (Wurster column) and above solution was sprayed according to Table II. After completion of spraying, the drug loaded pellet was dried at 60$^{O}$C for 5 hours in hot air

**Table I. Core and coating formula of diltiazem hydrochloride sustained release pellets (weights are expressed in g.) [KSRD-0: uncoated pellets, KSRD-5: 5% polymer loaded pellets, KSRD-10: 10% polymer loaded pellets, KSRD-15: 15% polymer loaded pellets, KSRD-20: 20% polymer loaded pellets].**

| Materials | Formulation code | | | | |
|---|---|---|---|---|---|
| | KSRD-0 | KSRD-5 | KSRD-10 | KSRD-15 | KSRD-20 |
| Core Formula | | | | | |
| Nonpareil seeds (NPS) | 210.00 | 210.00 | 210.00 | 210.00 | 210.00 |
| Diltiazem hydrochloride | 73.50 | 73.50 | 73.50 | 73.50 | 73.50 |
| HPMC 6cps | 15.00 | 15.00 | 15.00 | 15.00 | 15.00 |
| PEG 6000 | 1.50 | 1.50 | 1.50 | 1.50 | 1.50 |
| Water upto | 400.00 | 400.00 | 400.00 | 400.00 | 400.00 |
| Coating Formula | | | | | |
| Kollicoat SR 30 D | 0.00 | 50.00 | 100.00 | 150.00 | 200.00 |
| Talc | 0.00 | 0.75 | 1.50 | 2.25 | 3.00 |
| $TiO_2$ | 0.00 | 0.15 | 0.30 | 0.45 | 0.60 |
| Triethyl citrate | 0.00 | 1.50 | 3.00 | 4.50 | 6.00 |
| Water upto | 0.00 | 100.00 | 175.00 | 260.00 | 350.00 |

oven and sieved through 30 mesh to discard the particles.

Then coating suspension was prepared by using 5% (%w/w on dry basis) of Kollicoat SR 30 D, purified talc, titanium dioxide, triethyl citrate and water (Table I). Drug loaded pellets (300 g) was taken in the fluid bed coater and coating suspension was sprayed according to Table II. After completion of spraying, the coated pellet was dried at 60 0C for 5 hours and sieved through 16 and 24 mesh respectively to get the desired size of the diltiazem hydrochloride sustained release pellets (Fig. 1) and the batch is termed as KSRD-5. Same process was applied for 10%, 15% and 20% of Kollicoat SR 30 D load (Table I) and batches are termed as KSRD-10, KSRD-15 and KSRD-20 respectively (Fig. 1).

***In vitro* dissolution study**

The dissolution of diltiazem hydrochloride sustained release pellets was studied by Erweka (Germany) dissolution tester USP (XXVIII) using USP apparatus 2 (Paddle method). Diltiazem hydrochloride sustained release pellets equivalent to 90 mg of diltiazem hydrochloride was used in 900 ml of dissolution medium (purified water) at $37^{O}C$ with a rotation of 100 RPM for 10

**Table II. Machine parameters set up during drug loading and coating of different batches.**

| Machine | Fluid bed coater (Wurster), Umang Pharmatech Ltd. |
|---|---|
| Batch Size | 300 g |
| Inlet air temperature | $60^{O}C$ |
| Outlet air temperature | $37^{O}C$ |
| Product temperature | $35^{O}C$ |
| Chamber Humidity | 55% |
| Air flow | 100 $m^3/h$ |
| Spraying pressure | 1 bar |
| Spraying rate (during drug loading) | 4.0 g/min |
| Spraying rate (during coating) | 5.0 g/min |
| Spraying time (for drug loading) | 88 min |
| Spraying time (for coating) | 20-70 min depending on solution wt. |
| Peristaltic pump rpm | 2 |
| Secondary drying | $50^{O}C$/5 min. |

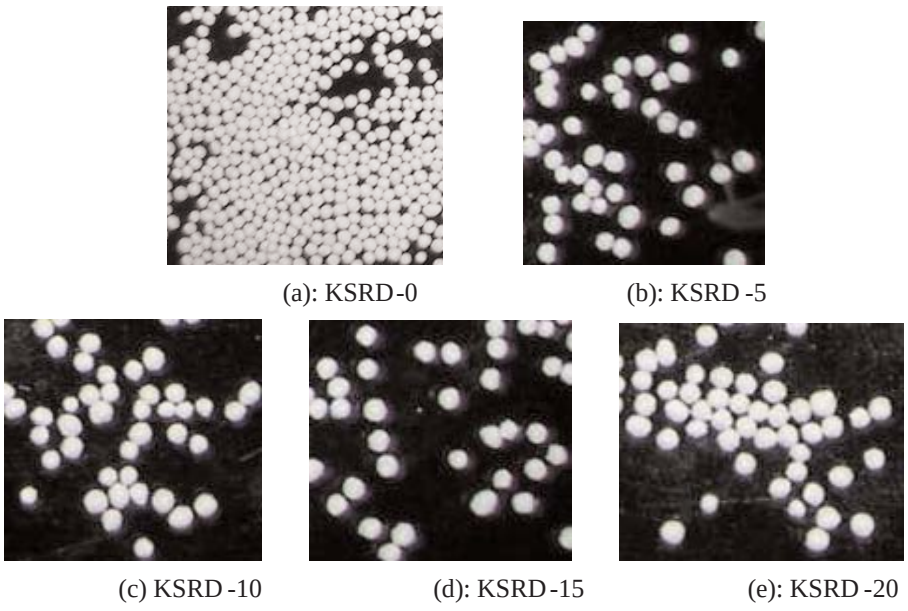


**Fig. 1. Diltiazem hydrochloride sustained release pellets (dried & sieved).[a).KSRD-0: uncoated pellets, b).KSRD-5: 5% polymer loaded pellets, c).KSRD-10: 10% polymer loaded pellets, d).KSRD-15: 15% polymer loaded pellets, e).KSRD-20: 20% polymer loaded pellets].**

hours. Five (5) ml sample was drawn at every one-hour interval and replaced with the fresh medium to maintain the sink condition. After dilution, the drug content was determined spectrophotometrically at 237 nm against a blank by using UV-Visible Spectrophotometer (Shimadzu, Japan). Same process was applied for the drug loaded pellets (KSRD-0) which are uncoated. Drug released in the dissolution media at specified periods was plotted as percent release versus time (hours) curve.

**Results and Discussion**

Diltiazem hydrochloride was loaded with hydroxypropylmethylcellulose onto nonpareil seeds then coated with aqueous dispersion of polyvinyl acetate (Kollicoat SR 30 D) using air suspension technique. The drug release was studied by in vitro dissolution using USP paddle method.

A comparative study was performed among the physical parameters of the prepared pellets of the different formulations. Minor difference was found among moisture content values (%LOD) of the different formulations (Table III). Maximum yield was found during drug loading (KSRD-0) and among the entire coated batches, 20% polymer loaded pellets (KSRD-20) expressed the same. This is because during drug loading (KSRD-0) loss of materials was less as manufacturing was performed by air suspension technique rather than powder layering. As the coating procedure was conducted by spraying coating solution in a fluid bed coater, chance of material loss was high. The 20% polymer loaded pellets (KSRD-20) showed higher yield as the amount of agglomerated pellets was less than those of others. Also 20% polymer loaded pellets showed the least friability value (Table III) which indicates friability decreases along with the increase in

**Table III. Finished product characteristics of different formulations.[KSRD-0: uncoated pellets, KSRD-5: 5% polymer loaded pellets, KSRD-10: 10% polymer loaded pellets, KSRD-15: 15% polymer loaded pellets, KSRD-20: 20% polymer loaded pellets].**

| Parameters | Formulation code | | | | |
|---|---|---|---|---|---|
| | KSRD-0 | KSRD-5 | KSRD-10 | KSRD-15 | KSRD-20 |
| Batch size (g) | 300.00 | 300.00 | 300.00 | 300.00 | 300.00 |
| Yield (%) | 93.37 ± 1.51 | 89.37 ± 1.20 | 88.05 ± 0.32 | 90.07 ± 1.75 | 90.44 ± 2.03 |
| LOD (%) | 1.89 ± 1.01 | 1.78 ± 0.56 | 1.89 ± 0.35 | 1.97 ± 0.44 | 2.01± 0.17 |
| Potency (%) | 23.13 ± 0.72 | 21.07 ± 0.08 | 20.11 ± 0.27 | 21.02 ± 1.12 | 19.75 ± 0.78 |
| Bulk density ($g/cm^3$) | 0.82 ± 0.00 | 0.75 ± 0.01 | 0.75 ± 0.01 | 0.72 ± 0.01 | 0.73 ± 0.00 |
| Friability (%) | 0.85 ± 0.03 | 0.67 ± 0.01 | 0.58 ± 0.00 | 0.56 ± 0.02 | 0.52 ± 0.01 |

LOD: % Loss on drying. (No. of samples for each trial, N=2)

polymer load. The aesthetic view and surface smoothness was found better to all formulations. No twinning or agglomeration problem was faced during drug loading and coating stages.

The release of drug in the dissolution media was found to be a function of the percent of polymer load as well as the physico-chemical nature of the polymeric materials. From all formulations it was observed that the drug release was decreased with gradual increase in polyvinyl acetate load (Fig. 2). When dissolution was performed with uncoated pellets (KSRD-0), near about 90% drug was released at 1st hour which indicates the burst release of drug (Fig. 4). It was also revealed that when drug loaded pellet was coated with the 5% polymer load, it fails to show suitable sustained action and about 84% drug was released at 1st hour, the behavior is very close to uncoated pellets (Fig. 4). It indicates that 5% polymer load is not enough to form barrier coat around the pellets uniformly to provide sustained effect. Again as the drug is highly water soluble and present at the surface not in the core of the pellets and so it comes in contact with the dissolution media easily from the very beginning and these phenomena may facilitate to cause the instant release of the drug. So from these formulations the release of drug was very high throughout the dissolution process (Fig. 2). But in case of 10% to 20% polymer load it

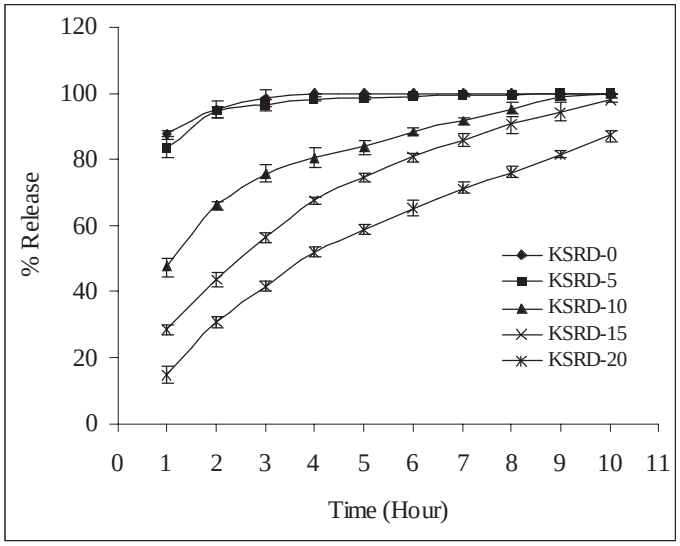


**Fig. 2. Zero order release of diltiazem hydrochloride from different percent polymer coated pellets. [KSRD-0: uncoated pellets, KSRD-5: 5% polymer loaded pellets, KSRD-10: 10% polymer loaded pellets, KSRD-15: 15% polymer loaded pellets, KSRD-20: 20% polymer loaded pellets].**

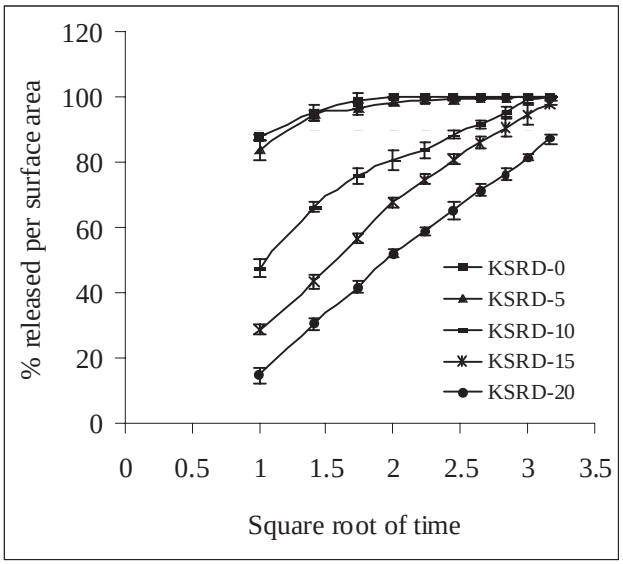


**Fig. 3. Higuchi's release of diltiazem hydrochloride from different percent polymer coated pellets. [KSRD-0: uncoated pellets, KSRD-5: 5% polymer loaded pellets, KSRD-10: 10% polymer loaded pellets, KSRD-15: 15% polymer loaded pellets, KSRD-20: 20% polymer loaded pellets].**

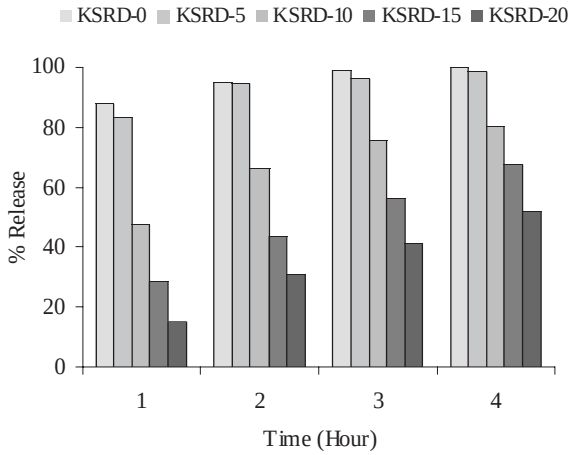


**Fig. 4. Burst phase release of diltiazem hydrochloride from coated pellets. [KSRD-0: uncoated pellets, KSRD-5: 5% polymer loaded pellets, KSRD-10: 10% polymer loaded pellets, KSRD-15: 15% polymer loaded pellets, KSRD-20: 20% polymer loaded pellets].**

was found that the release of the drug was decreased gradually along with the increase in polymer content (Fig. 2).

In case of 10% polymer load (KSRD-10) the initial drug release was very low (47% drug was released) as compared to 5% polymer load (KSRD-5) but within 4 hours about 80% drug was released which also facilitates the burst release of the drug after a certain period. Also it was observed that there was a sharp rise in drug release from 1st hour to 2nd hour (Fig. 2) and for the next dissolution period drug was released linearly ($r^2$=0.8866). Better release retarding effect was found when pellet was coated with 15-20% polymer and Fig. 2 indicates that this range of polymer is sufficient enough to form barrier coat around the pellets. For 15% polymer load (KSRD-15) about 29% drug was released at first hour and for 50% drug release about 2.5 hours required whereas about 80% drug was released at 6 hours. Also it was observed that there was a sharp rise in drug release from 1st hour to 3rd hour Fig. 2 and then a linear drug release was observed throughout the next period ($r^2$=0.9367) and seemed to be much more effective to sustain the release of drug. But in case of 20% polymer load (KSRD-20) the initial drug release was very low and mean dissolution time was found to be 4 hours. About 80% drug was released within 9 hours. Here a linear drug release was also

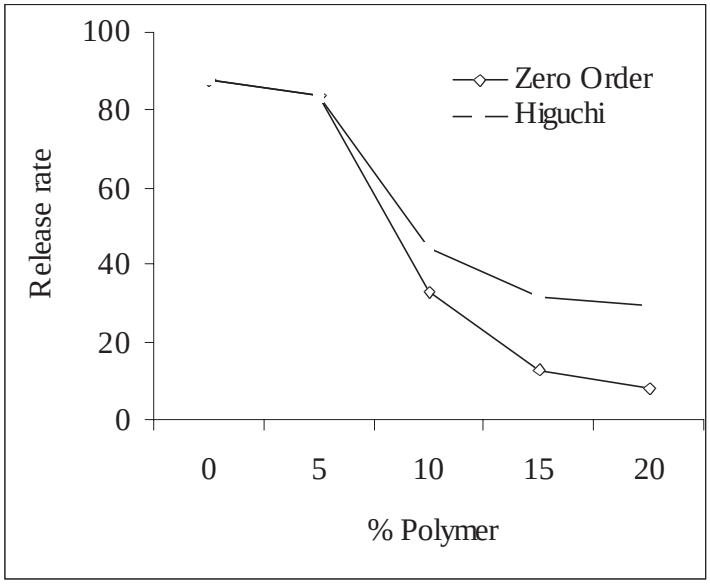


**Fig. 5. Zero order release rate (%/time) and Higuchi's release rate (%/time$^{-1/2}$) of diltiazem hydrochloride release kinetics from coated pellets**

observed throughout the whole dissolution process ($r^2$=0.9615). It was also revealed that when the polymer load was 0-15% (KSRD-0, KSRD-5, KSRD-10 & KSRD-15), about 100% drug was released within 10 hours but in case of 20% polymer load (KSRD-20) more time will be required for total amount of drug release (Fig. 2). From all formulations with 10-20% polymer load it was found that the initial drug release was low but the terminal drug release was comparatively high, which might be due to the presence of sucrose, Kollidon 30, PEG 6000 and HPMC 6cps in the core. As these are water soluble so with the passes of time they will be dissolved while come in contact with the dissolution media & may act as channel formers which may lead to change the drug release characteristics of polyvinyl acetate and play role to increase the terminal drug release rate (Gohel *et al.*, 2002; Hogan, 1989; Kibbe, 2000; Rowe, 1986; Sadeghi *et al.*, 2000; Saettone *et al.*, 1995). The drug release rate was decreased along with the increase in polymer load (Fig. 5). From uncoated as well as 5% polymer loaded pellets the Higuchi's release rate was 87.45%/hr-$^{1/2}$ and 83.51%/hr-$^{1/2}$ respectively (Table IV). Drug release rate was decreased drastically in case of 10% polymer load (44.49%/hr-$^{1/2}$). For 15% and 20% polymer loaded pellets the release rate was decreased accordingly but seemed to be very close. Also in case of 10%, 15% and 20% polymer load, the correlation coefficient value for Higuchi's release was $r^2$>0.95, $r^2$>0.98 and $r^2$>0.99 respectively (Table IV). So it was revealed that the release kinetics of diltiazem hydrochloride from the coated pellets appeared to follow Higuchi's release kinetics (Fig. 3).

**Table IV. Kinetic parameters of diltiazem hydrochloride release from different polymer coated pellets. [KSRD-0: uncoated pellets, KSRD-5: 5% polymer loaded pellets, KSRD-10: 10% polymer loaded pellets, KSRD-15: 15% polymer loaded pellets, KSRD-20: 20% polymer loaded pellets]**

| Formulation codes | % (w/w) polymer load (on dry basis) | Zero Order | | Higuchi | |
|---|---|---|---|---|---|
| | | Release rate | $r^2$ | Release rate | $r^2$ |
| KSRD-0 | 0 | 87.45 | 0.4875 | 87.45 | 0.6258 |
| KSRD-5 | 5 | 83.51 | 0.5745 | 83.51 | 0.7031 |
| KSRD-10 | 10 | 33.01 | 0.8866 | 44.49 | 0.9574 |
| KSRD-15 | 15 | 12.77 | 0.9367 | 32.13 | 0.9880 |
| KSRD-20 | 20 | 8.27 | 0.9615 | 29.21 | 0.9971 |

## Conclusions

*In vitro* dissolution study of drug release from the pellets was performed in purified water and the effect of different percent of polyvinyl acetate load was examined. When pellet was coated with 5% poly vinyl acetate it was revealed that there was eventually no sustained effect of polymer content and in case of 10% polymer load the initial drug release was decreased markedly but with the passes of time the release was not sustained. Better sustaining effect was found when drug loaded pellet was coated with 15% to 20% polyvinyl acetate load. The release kinetics of diltiazem hydrochloride from the coated pellets appeared to follow Higuchi's release kinetics.

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