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FORMULATION, *IN-VITRO* AND *IN-VIVO* X-RAY EVALUATION OF KOLLIDON® SR MATRIX TABLETS OF DILTIAZEM HCL.

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ABSTRACT

The present study was conducted to investigate the effect of Kollidon®SR at different concentrations on the release of profile of diltiazem hydrochloride from matrix tablets. Matrix-based tablet using different concentrations of Kollidon®SR was developed using direct compression technique to contain 90 mg of Diltiazem HCl. The pre-compression and post compression parameters were evaluated. Formulations were evaluated for the release of Diltiazem HCl over a period of 12 hrs in PH 6.8 phosphate buffer using USP type II dissolution apparatus. Diltiazem HCl and pure Kollidon®SR compatibility interactions was investigated by using Fourier-transform infrared spectroscopy and differential scanning colorimetry .Pre-Compression Studies Like Bulk Density, Tappe Density, Compressibility Index, Hausner Ratio, Angle of Repose are done.Formulation was optimized on the basis of acceptable tablet properties like Hardness, Weight Variation, Friability, Content Uniformity and in vitro drug release. The F2 similarity factor for F5 of 86.50 shows drug release pattern very close to marketed product release profile Similarity factor(f2) for formulation code F5 is 86.50. The *In-vivo* X-ray studies were carried out to confirm the adherence activity *In-vivo* in rabbits, the studies showed that polymer utilized for the optimization of the formulation showed the sustaining activity in vivo in rabbit by adhering to various sites in the gastrointestinal tract for the period of 12 hr.. The in vitro release profile and the mathematical models indicate that release of Diltiazem HCl can be effectively controlled from a single tablet using Kollidon® SR matrix system.

KEYWORDS: **Diltiazem hydrochloride ,Kollidon® SR, Matrix system.**

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INTRODUCTION

Sustained release dosage forms are prepared in order to achieve a desirable and predictable pharmacodynamic response, appropriate pharmacokinetics parameters, an improved patient compliance, minimization of side effects, and a maximized drug efficacy (1).One of the most commonly used methods of modulating drug release is its inclusion within a matrix system. Matrix systems have achieved extensive importance in controlled drug delivery, thanks to a simple and fast producing technology, low cost and low influence of physiological variables on their release behavior (2). The release mechanism of drug from the matrix systems has been analyzed and explained with the help of different exponential models (3). Based on the features of retarding polymer, matrix systems are usually classified into three main groups: hydrophilic, hydrophobic and plastic (inert). Hydrophilic polymers, based on their solubility in water, could be divided into two types: i) water insoluble polymers including some carbomers and ii) water soluble polymers such as HPMC (4) **.** Plastic polymers, which are capable of forming insoluble or skeleton matrices, have been widely used for controlling the release of drugs due to their inertness and drug embedding ability. Liquid penetration into the matrix is the rate-controlling step in such systems, unless channeling agents are used (5).

Various attempts have been made to develop sustained release dosage forms of Diltiazem. In this respect, different devices has been prepared such as osmotic pumps buccal tablets, microspheres, coated tablets and transdermal patches. Matrix devices have also been formulated using diverse polymeric excipients including a mixture of HPMC and xanthan gum, a combination of HPMC and pectin, guar gum grafted with acrylamide , polyethylene oxide plus carbopol as well as carnuba wax or HPMC (2). In the present study Diltiazem was selected as a model drug. As Diltiazem is a calcium channel blocker widely used for the treatment of angina pectoris, arrhythmia and hypertension. Its short biological half-life (3-5 h) and thus, frequent administration (usually three to four times a day) makes it a good candidate to prepare sustained release matrix tablets (6). Polyvinylacetate/ Povidone (PVAP) based polymer (Kollidon® SR) is a relatively new extended release matrix excipient. It consists of 80% Polyvinylacetate and 19% Povidone in a physical mixture, stabilized with 0.8% sodium lauryl sulfate and 0.2% colloidal silica. It is particularly suitable for direct compression of sustained release matrix tablets (7, 8). In the present study, matrix tablet containing different proportion of various polymers like PVAP (Kollidon® SR), MCC and DCP alone and in combination were evaluated for the oral sustained drug release of water-soluble Diltiazem hydrochloride in the form of a matrix tablet by using in vitro dissolution studies and in vivo X-ray studies.

MATERIALS AND METHODS

Materials

Diltiazem hydrochloride (DTZ) was a gift sample form Wockhardt (Aurangabad,India). PVAP (Kollidon® SR) was gifted by Glenmark (Mumbai,India), Microcrystalline cellulose (Avicel, FMC Type pH-102), Dibasic calcium phosphate dihydrate, Colloidal silicon dioxide and Magnesium Stearate where obtained as gift samples from Cipla (Kurkumbh,India). All other reagents were of analytical grade.

Preparation of Diltiazem HCL matrix tablets

Diltiazem HCL polymeric matrix tablets were prepared by direct compression method as follows. The formulation of each tablet is shown in Table 1. The corresponding amounts of DTZ HCL, PVAP, microcrystalline cellulose, dibasic calcium phosphate dihydrate and colloidal silicon dioxide were accurately weighed. The powders were sieved using screen 60. The screened powders were then transferred into the turbula mixer jar and mixed for 15 minutes. Magnesium stearate was accurately weighed, sieved through screen 60 and added to the turbula jar and mixed for an additional 3 minutes. The powder was then compressed into tablets using a 7 mm round punch on 10 station tablet punching machine (M/s Cadmach Machinaries Pvt Ltd., Ahmedabad, India). In this study, the total

tablet size was fixed at 450 mg. Matrix tablets of each composition were compressed (100 No.) and tested for their hardness,drug content, and drug release characteristics with the required number of tablets for each test. Matrix tablet formulations were coded as F1, F2, F3, F4, F5, F6, F7, F8, F9 and F10. The Matrix systems can be viewed as mixtures of different ingredients, the change in the percentage of the rate controlling polymer indicate a change in the percentage of the other excipients .Thus, the change in the drug release rate coming out as a result is due to the effect of many excipients rather than the rate controlling polymer alone. As such, the simplex-lattice design was used to evaluate the effects of different excipients commonly used in matrix systems on the release from PVAP based tablets. The experimental design was a mixture study based on a three component system made out of the rate controlling PVAP polymer, microcrystalline cellulose and dibasic calcium phosphate dehydrate with a range of 0-79% of the final tablet weight for each of these components. The other components in the test formulations were kept constant: 20% (w/w) Diltiazem Hydrochloride, 0.5% magnesium stearate and, 0.5% colloidal silica.

Table 1
Formulation development of Diltiazem HCl Sustained release matrix tablets using PVAP

Ingredients (mg)	All batches' quantity in mg/tablet's									
	F01	F02	F03	F04	F05	F06	F07	F08	F09	F010
Diltiazem Hydrochloride	90	90	90	90	90	90	90	90	90	90
PVAP	355.50	-	-	177.75	177.75	-	237	59.25	59.25	118.50
Microcrystalline cellulose	-	355.50	-	177.75	-	177.75	59.25	237	59.25	118.50
Dibasic Calcium Phosphate dihydrate	-	-	355.50	-	177.75	177.75	59.25	59.25	237	118.50
Colloidal silicon dioxide	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25
Mg.Stearate	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25
Total weight	450	450	450	450	450	450	450	450	450	450

Evaluation of the prepared tablets
Tablets were evaluated for both its pre-compression parameters like bulk density, tapped density, Carr's index, Hausner's ratio, angle of repose as well as their post compression parameters tablet hardness (9), friability, uniformity of weight and content uniformity of drug as per IP 2007 (10).

Tablet weight variation
Twenty matrix tablets were randomly selected and accurately weighed using an electronic balance (Shimadzu Corporation, Japan). The results are expressed as mean values of 20 determinations.

Tablet hardness
The hardness of the matrix tablets was determined by using a Monsanto hardness tester.

Drug content uniformity
Ten tablets were weighed individually, crushed and the drug was extracted in water. The solution was filtered through a cellulose acetate membrane (0.45 µm) and the drug content was determined by UV spectroscopy (Evolution201, UV-visible spectrophotometer, Thermo Fisher Scientific, Shanghai, China) at a wavelength of 237 nm after a suitable dilution.

Tablet friability
The friability of tablets was determined using Roche friabilator. It is expressed in percentage (%). 20 tablets were initially weighed (W_0) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 min or run up to 100 revolutions. The tablets were weighed again (W_f). The % friability was then calculated by

$$\% \text{ Friability} = (1-W_f / W_0) \times 100$$

Where, W_0 -Weight of tablet before test,
W_f -Weight of tablet after test.

Fourier-transform infrared (FTIR) spectroscopy
FTIR spectra of DTZ, PVAP+MCC+DCP and DTZ with PVAP+MCC+DCP were recorded in a FTIR spectrometer (FTIR-4100, Jasco, Japan). The spectra were recorded within 4000–400cm−1 wave numbers(Figure 1)

FTIR study of Diltiazem hydrochloride with excipients

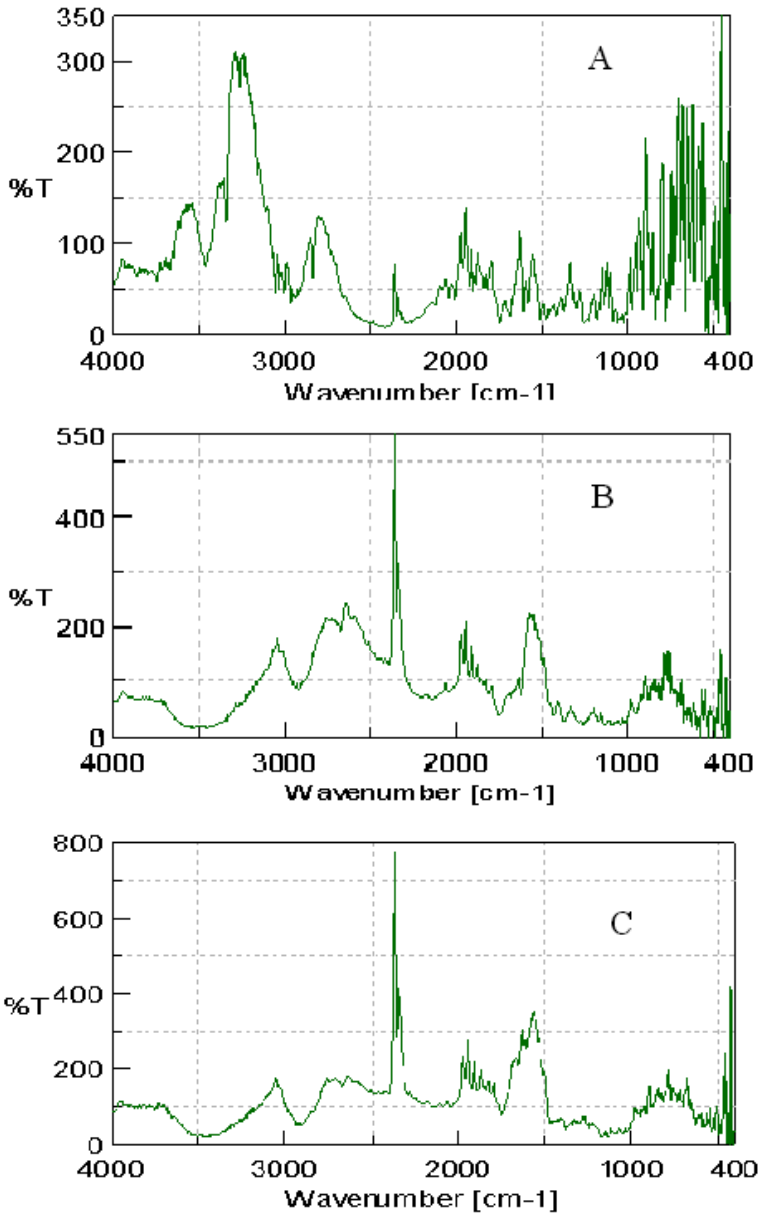


Figure 1
FTIR spectra of Diltiazem HCl (A), PVAP+MCC+DCP (B), Diltiazem HCl + PVAP+MCC+DCP

In vitro drug release from the matrix tablets
To understand the release profiles of the drug from the tablets, dissolution experiments were performed in simulated gastric (0.1 N HCl, i.e., pH 1.2) and intestinal (pH 7.4) conditions. The release of Diltiazem hydrochloride from the tablet was studied using USP XXIII paddle apparatus (Electrolab, Bangalore). Drug release profile was carried out in 750 ml of 0.1N HCl for 2h and then in 900ml of phosphate buffer solution (PBS) pH 7.4 maintained at 37 ± 0.5˚C temperature at100rpm.Ten ml of samples were withdrawn at predetermined time intervals of every 1 h up to 12 h. The samples were replaced by its equivalent volume of dissolution medium and were filtered through 0.45 µm Whatman filter paper and assayed at 237 nm by UV spectrophotometer (Evolution 201, UV-visible spectrophotometer, Thermo Fisher Scientific, Shanghai, China). The dissolution similarity (f2 similarity factor) was assessed by using FDA recommended approach for comparison of optimized formulation (F05) with marketed

formulation (11). The similarity factor is a logarithmic, reciprocal square root transformation of the sum of squared errors, and it serves as a measure of the similarity of two respective dissolution profiles.

$$f2 = 50\log\left\{\left[1+\frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} x100\right\}$$

Where;
n = number of sample points
Rt = percent of marketed product release profile
Tt = percent of test formulations release observed
FDA has set a public standard of f2 value between 50-100 to indicate similarity between two dissolution profiles.

Kinetics of Drug Release

The in vitro release data were treated according to zero order, first order, Higuchi's, Hixson-and Crowell cube root law to find out whether the drug release from the formulations was providing a constant drug release. The data were also fitted to the model developed by Korsmeyer et al. (12) in order to find out the drug release mechanism from the formulations. The correlation coefficients were calculated and used to find the fitness of the data.

Scanning electron microscope studies

The optimized formulation (Batch F05) was removed from the dissolution apparatus at predetermined time intervals and sectioned through an undisturbed portion of the gel formed at the flat face of the tablet. The specimen was then positioned on the sample holder so as to present a cross-section of the tablet to the microscope. Samples were coated with gold and visualized under scanning electron microscope (SEM) (DSM 950, Zeiss, Germany) at suitable magnifications using a voltage of 10 kV. Processing parameters were optimized to obtain the best possible micrographs.

Differential Scanning Calorimetry (DSC)

The stability of the drug in the formulation was confirmed by Differential Scanning Calorimetry (DSC) thermograms. DSC thermograms of the drug DTZ, excipient as PVAP+ DCP, DTZ +PVAP+ DCP and optimized formulation (F05) were derived from a DSC-60 (Shimadzu, Kyoto, Japan) with a thermal analysis data station system, computer, and plotter interface. The instrument was calibrated with an indium standard. The samples of (1mg) were heated (20-300-^{0}C) at a constant scanning speed (10^0C/min) in sealed aluminum pans, using nitrogen atmosphere.

In vivo X-ray Studies

In vivo X-ray studies were conducted by X-ray analysis (13) to study the behavior of the optimized formulation in New Zealand rabbits. The drug was replaced with barium sulfate and other ingredients were kept constant. The F05 formulation was used for X-ray examination. After overnight fasting, healthy New Zealand rabbits weighing 1.5–2 kg was fed with a little low calorie food given some water. The matrix tablets were administered by oral route through a stomach tube and flushing 15ml of water from the syringe through the tube. The animals were held on a board. Radiographs were obtained at 0h (control), 1h, 3 h, 6h, 9h and up to 12 h. The X-ray parameters were kept constant throughout. The movements of the matrix tablet was identified and observed. Permission was obtained from the Animal Ethics Committee (CPCSEA/C/01/448/11-12/22) for the use of experimental animals prior to the experiment.

Stability Studies

Stability studies were carried out as per ICH (Q1A (R2), 2003) guidelines. The long term stability was carried out on optimized matrix tablets at temperature and relative humidity (RH) conditions (30^o C and 75 % RH) in stability chambers (Thermo lab, Mumbai, India) for 3 months. Test samples were withdrawn every month and subjected to various tests like weight, hardness, effect of

storage on Diltiazem Hydrochloride release from PVAP (Kollidon@ SR) matrix tablets for F05 batch.

RESULTS AND DISCUSSION

Evaluation of the prepared tablets

Evaluation of pre-compression parameters

All formulation batches were evaluated for pre-compression parameters like bulk density, tapped density, compressibility index, Hausner ratio and angle of repose (Table 2). The Compressibility Index for all formulation was in range of 5.19 to 13.20%, bulk density 0.490 to 0.526 g/cm^3.

Table 2
Pre-compression parameters of Diltiazem Hydrochloride Sustained release matrix tablets using PVAP

FORMULATION	BULK DENSITY (G/CM^3)	TAPPE DENSITY (G/CM^3)	COMPRESSI BILITY INDEX (%)	HAUSNER RATIO	ANGLE OF REPOSE (^{O})*
F1	0.526	0.555	5.19	0.95	22.46 ± 0.21
F2	0.490	0.565	13.20	0.87	23.76 ± 0.10
F3	0.516	0.567	8.89	0.91	25.26 ± 1.20
F4	0.526	0.572	8.07	0.92	24.29 ± 0.32
F5	0.513	0.575	10.68	0.89	22.84 ± 0.62
F6	0.513	0.575	10.68	0.89	22.84 ± 0.62
F7	0.521	0.564	7.52	0.92	25.64 ± 0.21
F8	0.500	0.553	9.57	0.90	21.58 ± 0.15
F9	0.526	0.555	5.19	0.95	22.46 ± 0.21
F10	0.490	0.565	13.20	0.87	23.76 ± 0.10

All values are expressed as mean ±SD(n=5)

Evaluation of post-compression parameters

Sustained release tablets were prepared by punching 450 mg of the drug-loaded polymer under a pressure of 400 kg/cm^2 and tablets contained 90 mg of Diltiazem hydrochloride. The post compression parameters tablet hardness, friability, uniformity of weight and content uniformity of drug in Table 3.

Table 3
Evaluation of Diltiazem hydrochloride sustained release matrix Tablets Containing PVAP.

FORMULATION	HARDNESS^ (KG/CM^2)	WEIGHT VARIATION*	FRIABILITY # (%)	CONTENT UNIFORMITY^ (%)
F01	5.2 ± 0.04472	441 ± 2.5808	0.45 ± 0.0190	98.1 ± 0.0134
F02	4.8 ± 0.04472	440 ± 2.3004	0.30 ± 0.0348	99.4 ± 0.0219
F03	2.2 ± 0.08366	431 ± 2.5808	All Capped	99.4 ± 0.0219
F04	5.4 ± 0.08944	449 ± 2.5726	0.28 ± 0.0185	99.4 ± 0.0219
F05	5.4 ± 0.08944	449 ± 2.5808	0.28 ± 0.0185	99.4 ± 0.0219
F06	4.6 ± 0.04472	449 ± 2.5726	0.80 ± 0.0265	99.4 ± 0.0219
F07	5.0 ± 0.04472	449± 2.2820	0.51 ± 0.0399	97.7 ± 0.0326
F08	5.2 ± 0.05477	448 ± 3.5703	0.43 ± 0.0268	99.4 ± 0.0219
F09	2.8 ± 0.07368	446 ± 2.3951	0.42 ± 0.0378	99.4 ± 0.0219
F010	4.8 ± 0.05477	430 ± 2.1343	0.38 ± 0.0089	99.2 ± 0.0326
Marketed DILZEM SR	5.0 ± 0.08944	188 ± 2.5726	0.28 ± 0.0185	99.4 ± 0.0219

All values are expressed as mean ±SD (n=3)
^ All values are expressed as mean ± SD (n=5)
 # All values are expressed as mean ± SD (n=3).

Hardness, weight variation, friability and content uniformity for all batches manufactured were tested. The hardness values of DTZ formulations were within range of 2.2 ± 0.08366 to 5.4 ± 0.08944. It was observed that hardness was strongly influenced by the type of polymer. The hardness of tablets containing PVAP was higher than that of tablets

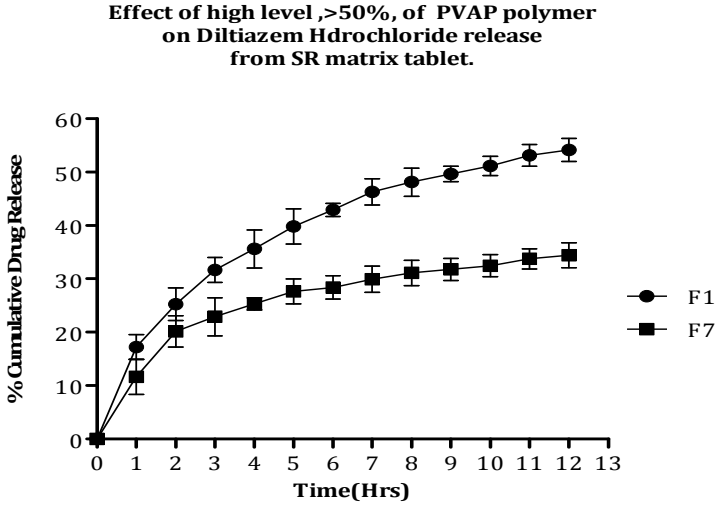
containing only MCC and DCP. This is due to combination of the very plastic polyvinyl acetate and strongly binding povidone in PVAP. The friability of DTZ formulation observed within the range of 0.28 ± 0.0185- 0.80 ± 0.0265. Results showed that the percent of the DTZ in the compressed tablets as within the 97.7 ± 0.0326%- 99.4 ± 0.0219% of the theoretical label claim.

FTIR Study

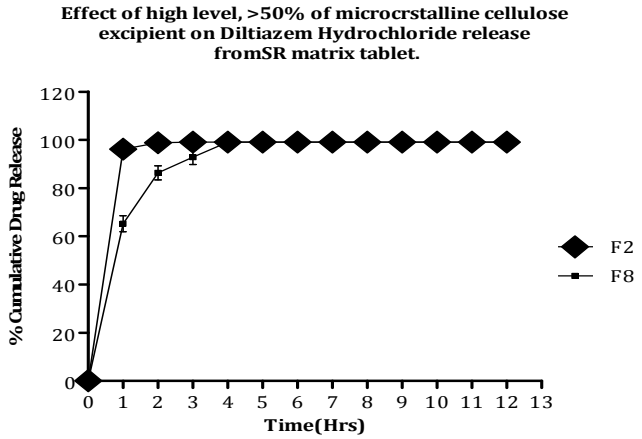
Drug polymer interaction was checked by comparing the FTIR spectra of the physical mixture of drug with the excipients used with the IR spectrum of pure drug. IR Spectra of Diltiazem hydrochloride shows two carbonyl (C=0) peaks in the region of 1679-1745 cm^{-1}. It also shows peak for C-N-stretch (2260-2220cm^{-1}), N-H(s) (3500-3300cm^{-1}), C-O(s)(1260-1000cm^{-1}) were present in pure drug as well as in combination with other excipients. Frequencies of functional groups of pure drug remained intact in physical mixture containing polymers. So it was concluded FTIR spectra obtained indicated no change in chemical identity of the drug and polymers.

In vitro Release Studies

The varying concentration of PVAP, MCC, DCP and combination on release profile of DTZ was studied. The matrix tablet formulation with high levels, greater than 50% of polyvinyl acetate/povidone polymer, formulation variable F01 and F07, showed a low drug release (Figure 2). This confirms the findings by Draganoiu et. al. (2001) where it was found that the higher the percent polymer level in the tablet matrix, the slower the drug release rate. This slowed drug diffusion can be explained by the reduction in the porosity and higher tortuosity of matrix(14). Thus PVAP, which is a very plastic material, produces a coherent matrix, sustaining the drug release from the matrix tablet. The matrix remained intact during the dissolution test due to the water-insoluble polyvinyl acetate. The F2 similarity number when compared to the marketed product for F01 was 23 and for F07 was 15. So, while F01 and F07 do show an extended release in vitro of the DTZ from the matrix tablets, the similarity factor tells us that these two formulations are not similar to the marketed product.



The matrix tablet formulation with high levels, greater than 50%, of microcrystalline cellulose, formulation variable F02 and F08, showed high drug release rate (Figure 3) as the level of PVAP polymer in F02 was 0% while in F08, it was 13.1%. Microcrystalline cellulose allows water to enter the tablet matrix by means of capillary pores, resulting in a disruption of the hydrogen bonding between adjacent bundles of the cellulose microcrystals (15). Therefore, at a higher rate of incorporation, 79% for F02 and 52.67% for F08, microcrystalline cellulose acted as a disintegrant, destroying matrix cohesion, and in essence, producing an immediate release tablet.



The matrix tablet formulation with high levels, greater than 50%, of dibasic calcium phosphate, formulation variable F03 and F09, showed high drug release rate (Figure 4). This can be explained by the fact that dibasic calcium phosphate on it's own at high levels of 79% w/w of tablet does not compress well, as was the case for F03, and produced a tablet whose hardness was only 2.2kg/cm^2 and which when tested by the friability test failed miserably as all tablets capped. F09 also showed a very fast in vitro drug release.

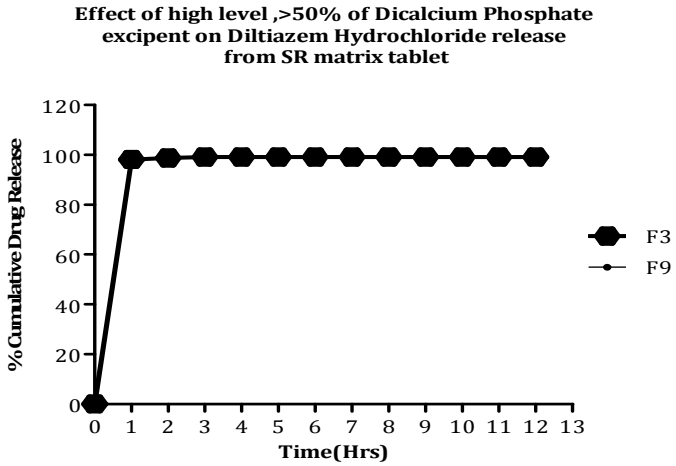
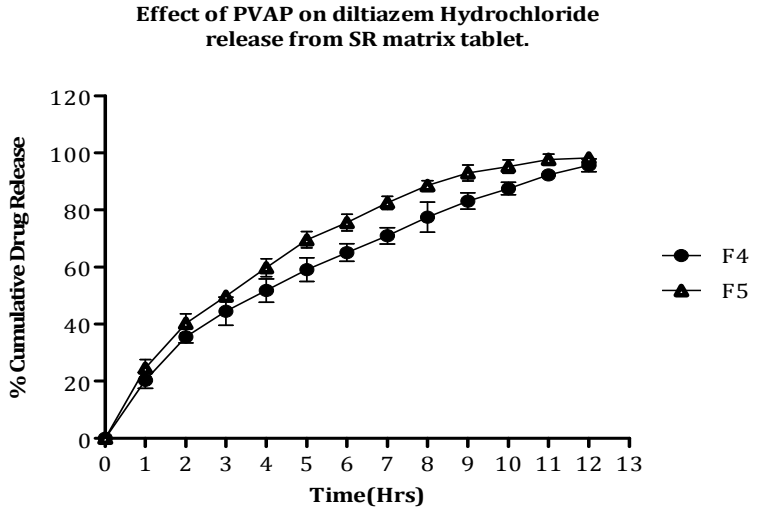


Figure 5, 6 shows the drug release profiles of the formulation variables, F04 and F05 and comparison to the marketed product. F04 and F05 both have a high level (39.5%) of PVAP in their formulations and as such exhibit low drug release in vitro. F04 has a high level of microcrystalline cellulose which as we have seen can act as a disintegrant. In this instance however, the level of PVAP overrides this property, hence the extended release of the drug in vitro. F05 has a high level of dibasic calcium phosphate which combines well with the PVAP to give an extended release of drug in vitro. The f2 value for F04 is 53 when calculated in comparison to the marketed product while the f2 value for F05 is 87 thus suggesting that F05 is similar to the marketed product in DTZ release over 12 hours.



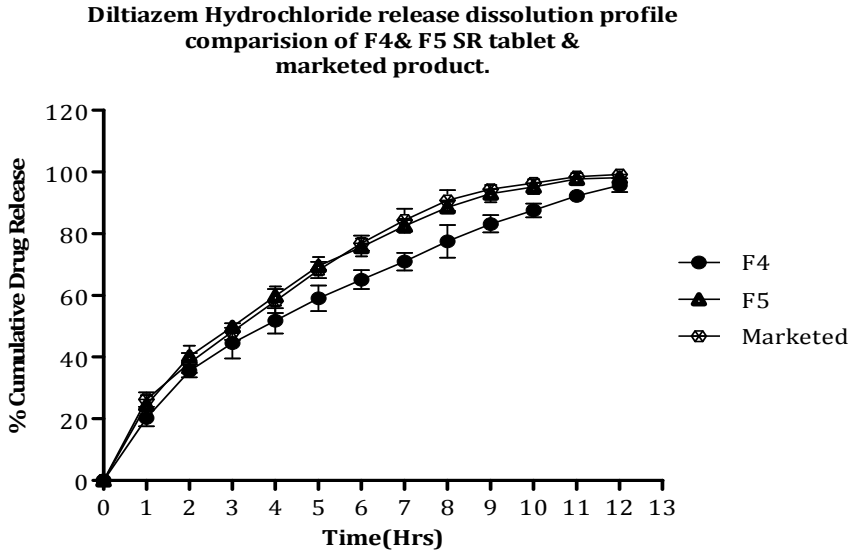
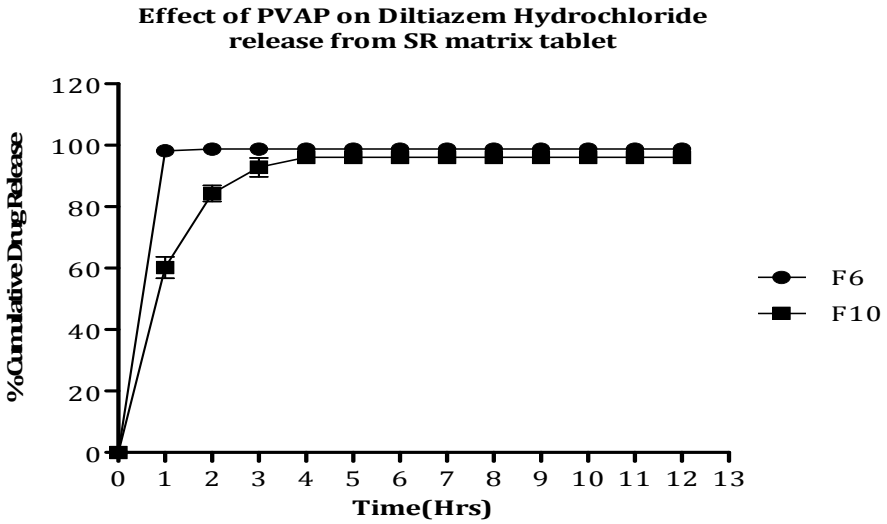


Figure 7 shows the drug release profiles of the formulation variables, F06 and F10. F06 has no PVAP polymer incorporated into the formulation and the in vitro drug release results show a tablet the behaved like an immediate release. F10 had PVAP levels of 26.3% and as has been reported by Draganoiu et. al. 2001, PVAP has minimum drug retarding properties unless it is in levels of greater than 40% in a tablet matrix (14,16).



Drug Release Kinetics

To describe the drug release kinetics in the 10 formulations and marketed formulation, the in vitro release data were treated according to zero order, first order, Higuchi's, Hixson-Crowell cube root law and Korsmeyer et al's. The release rate kinetic data for all the models can be seen in Table 4. In the present study, the in vitro release profiles of drug from F05 and Marketed formulation could be best expressed by Higuchi's equation, as correlation coefficient value (r^2): 0.9928 and 0.9911 shows high linearity respectively. The high correlation coefficient (above 0.99) obtained indicates a square root of time dependent release kinetics. Thus, as the data fitted the Higuchi model, it confirmed a diffusion drug release mechanism. To confirm the diffusion mechanism, the data were fit into Korsmeyer equation. The n value of 0.5651 for F05, and n value of 0.5675 for marketed formulation shows a coupling of diffusion and erosion mechanisms so-called anomalous (non-fickian) diffusion. It is suggested that the main driving force for the drug release in case of water soluble drug like DTZ from the matrix tablets is the infiltration of release medium. As the tablet is introduced into the medium, water penetrates into the matrix and povidone leaches out to form pores through which the drug may diffuse out. Also, as observed in, as the polymer level in the formulation is increased, drug diffusion is slowed due to the lower porosity and higher tortuosity of the matrix. Thus polyvinyl acetate, which is a very plastic material, produces a coherent matrix, sustaining the drug release from the tablet matrix.

Table 4

Correlation coefficient [r^2] and Diffusion exponent [n] after fitting of dissolution data into various releases kinetic models of all formulation of Diltiazem containing PVPA.

FORMU-LATION	CORRELATION COEFFICIENT [r^2]					FOR KROSMEYER-PEPPAS EQUATION
	ZERO ORDER	1ST ORDER	HIGUCHI	HIX. CROW.	KORSMEYER PEPPAS	RELEASE EXPONENT [n]
F1	0.7385	0.8725	0.9825	0.8360	0.9875	0.4587
F2	0.6806	0.9073	0.9171	0.7991	0.9617	0.0293
F3	0.6633	0.7893	0.9095	0.7219	0.8830	0.0093
F4	0.9165	0.9630	0.9931	0.9914	0.9927	0.6072
F5	0.8627	0.9651	0.9928	0.9927	0.9891	0.5651
F6	0.6602	0.7683	0.9081	0.7033	0.9339	0.0060
F7	0.5494	0.6870	0.9560	0.6472	0.9641	0.3988
F8	0.7977	0.9611	0.9762	0.9782	0.9811	0.3014
F9	0.6638	0.8053	0.9097	0.7281	0.9453	0.0098
F10	0.7239	0.9842	0.9635	0.9589	0.9609	0.3084
Marketed	0.8763	0.9126	0.9910	0.9888	0.9901	0.5675

Scanning electron microscope studies

SEM photomicrograph of the matrix tablet taken at different time intervals after the dissolution experiment showed that matrix was intact and pores had formed throughout the matrix (Figure 7C-F). SEM study confirmed both diffusion and erosion mechanisms to be operative during drug release from the optimized batch of matrix tablet. The tablet containing PVAP shows erosion after 1 hour on their surface early in the process, so the active agent placed in this area is immediately released to dissolution medium (Figure 7B). SEM photomicrographs of tablet surface at different time intervals also showed that erosion of matrix increased with respect to time. SEM photomicrograph of the surface of fresh tablet (Figure 7A) did not show any pores. Photomicrographs at 3, 6, 9 and 12 hours revealed pores with increasing diameter. Hence, the formation of both pores on tablet surface indicates the involvement of both erosion and diffusion mechanisms to be responsible for sustaining the release of DTZ from formulated matrix tablets.

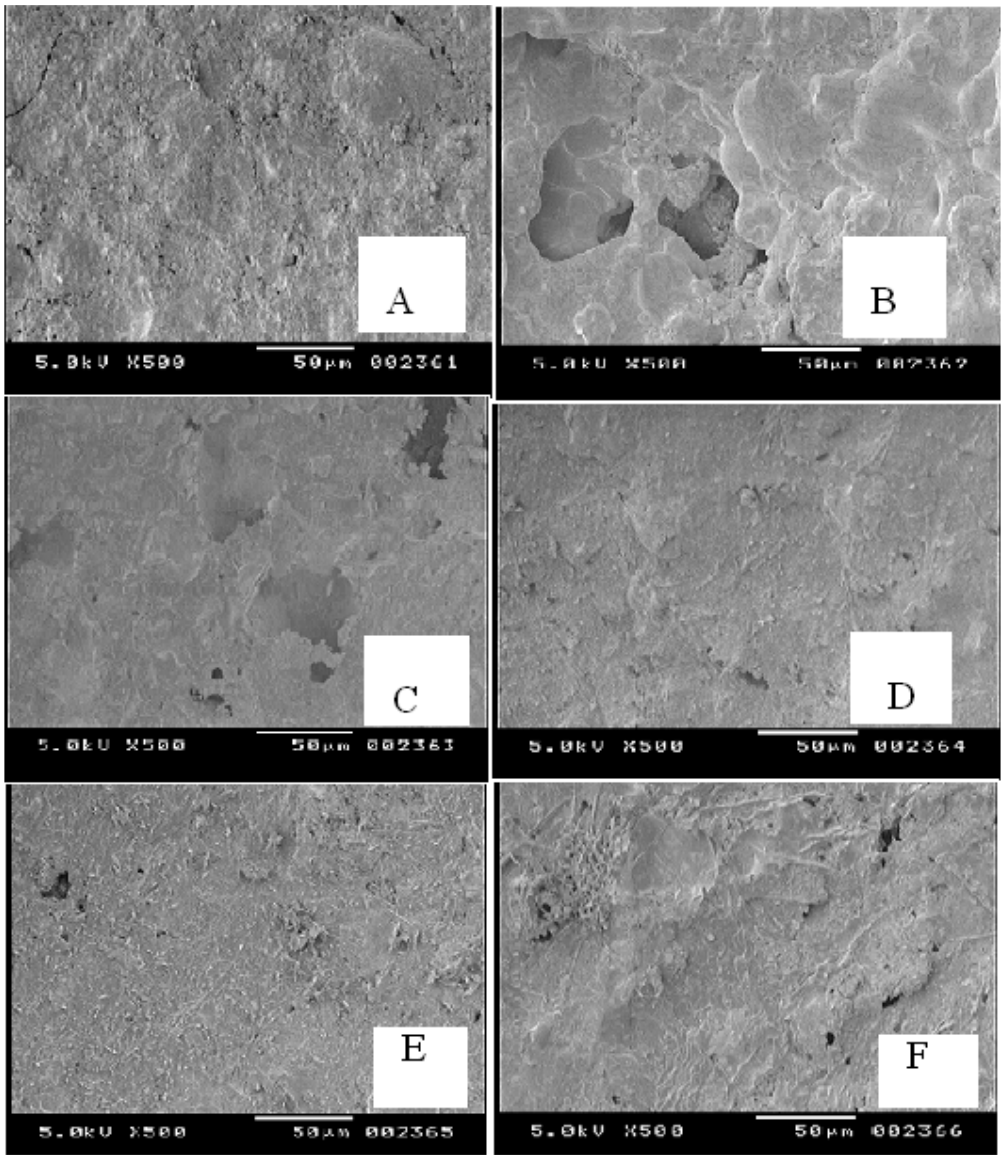


Figure 7

SEM photomicrographs of optimized matrix tablet (batch F5) showing surface morphology after 0 hour (A, 500×), 1 hour (B, 500×), 3 hours (C, 500×), 6 hours (D, 500×), 9 hours (E, 500×), and 12 hours (F, 500×) of dissolution study.

Differential Scanning Calorimetry (DSC)

The DSC study confirmed that the presence of other excipients did not affect the drug nature and it was well maintained in the selected formulation. Thermograms of the DTZ, PVAP+ DCP, Diltiazem HCL+PVAP+DCP & Optimized Formulation 05 (F05) are shown in figure 8. A sharp endotherm was observed for Diltiazem HCL + PVAP+ DCP (Figure 8C) at 147.54 °C. In formulation F05 (Figure 8D) melting endotherm at 139.77°C was observed. This confirmed that the presence of other excipients did not affect the drug nature. This indicates the absence of any drug polymer interaction.

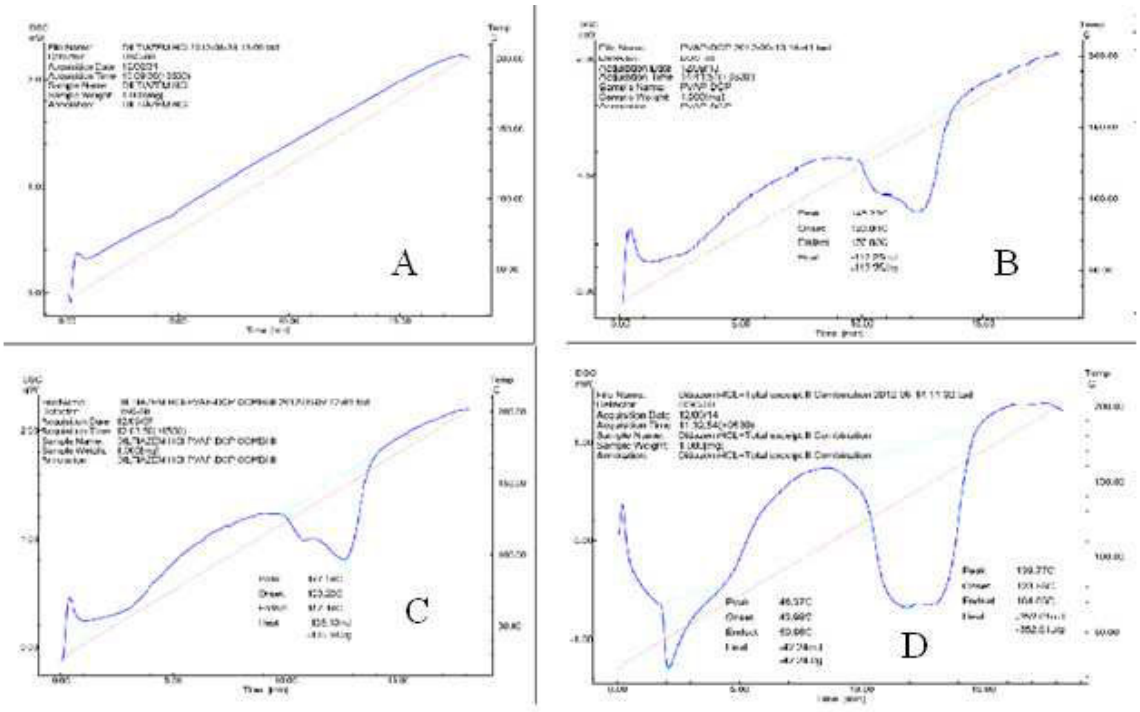


Figure 8
DSC Thermograms of Diltiazem HCL (A), PVAP+ DCP (B), Diltiazem HCL + PVAP+ DCP (C) & Optimized Formulation 05 (F05) (D)

Stability studies

The F05 SR Matrix batch were observed for changes in physical properties (Table No: 5). The long term stability results show a significant change in hardness at the 3 month, 6 month and 9 month period. However, there was no significant change in the dissolution profile (Figure 9) for tablets stored under long term stability conditions for up to 9 months.

Table 5
Effect of long term stability storage on the physical properties of PVAP tablets (F5 Batch)

Physical Property	Initial	1 month	3 months	6 months	9 months
Weight	449 ± 2.5808	449 ± 2.5726	450 ± 2.5726	450± 3.5703	450 ± 2.2820
Hardness	5.4 ± 0.08944	5.6 ± 0.0894	6.2 ± 0.0836	6.8± 0.0447	7.4 ± 0.0894

(*) significantly different from initial at 0.05 level

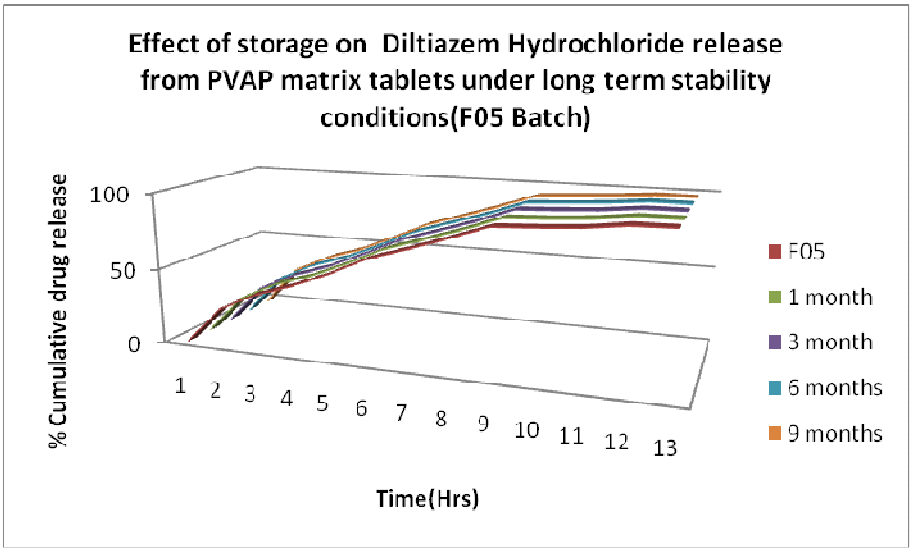


Figure 9
Effect of storage on Diltiazem Hydrochloride release from PVAP matrix tablets under long term stability conditions (F05 Batch)

In vivo X-ray studies

The in vivo X-ray studies were carried out in New Zealand rabbit using soft X-ray analysis. The polymer utilized for the optimization of the formulation showed the sustaining activity in vivo in rabbit by adhering to various sites in the gastrointestinal tract. F05 formulation showed sustaining effect for 12 hrs as shown in Figure 10.

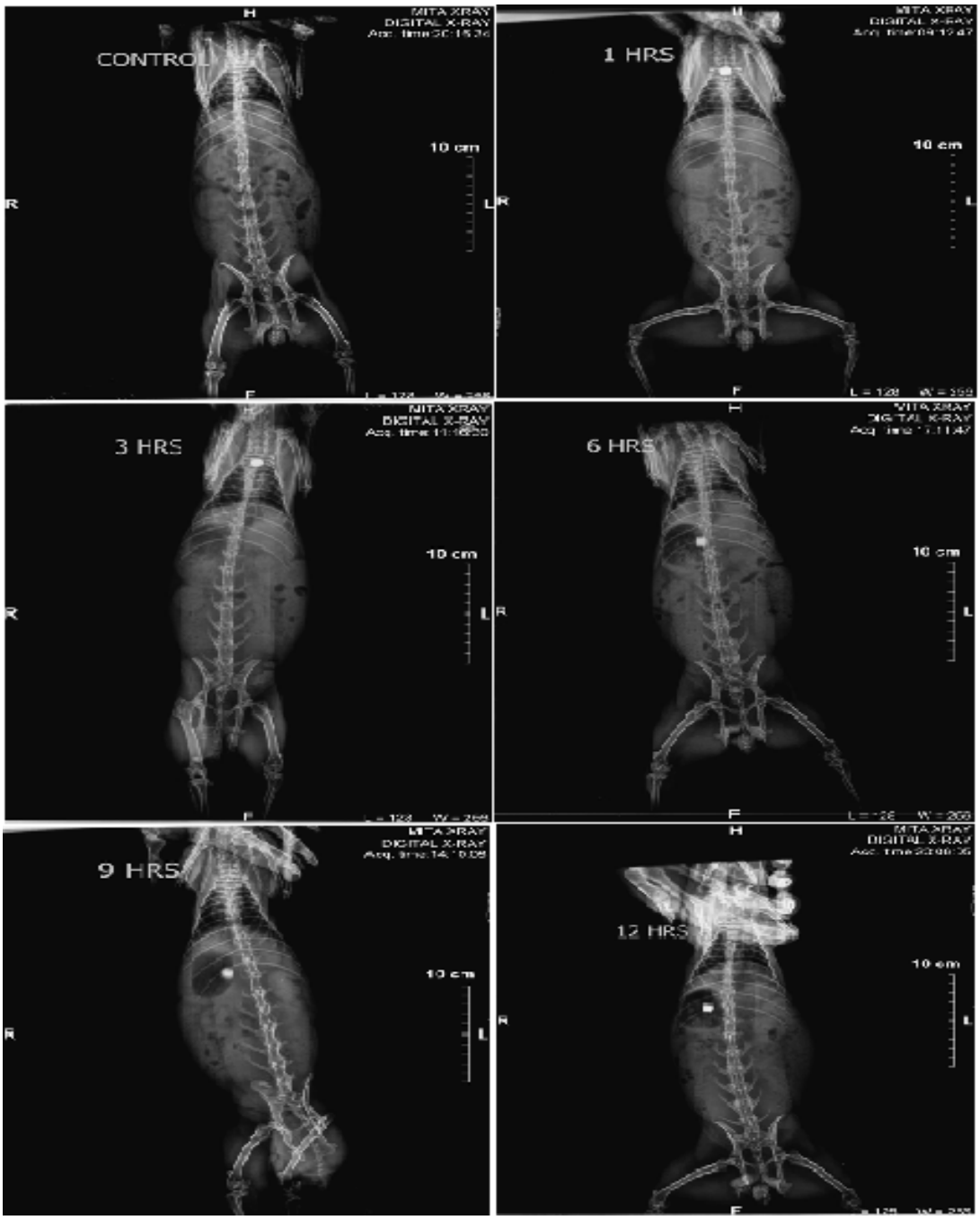


Figure 10

X-rays indicating the position of the barium sulfate-labeled matrix tablets in the gastrointestinal tract of New Zealand rabbits at different time periods X-ray taken at 1 h, 3 h, 6 h, 9 h and 12 h (Arrow indicates the position of tablets)

CONCLUSION

The data shows as expected that the PVAP alone exerts a retarding effect on the release of DTZ. Microcrystalline cellulose and dibasic calcium phosphate alone promote the release of DTZ. The present study demonstrated that, PVAP in combination with microcrystalline cellulose and dibasic calcium phosphate shows an even higher retardation of DTZ than with PVAP alone. For the PVAP SR matrix tablet, while the F04 formula was closer to the marketed product in vitro drug release constant, the KSR04

formula was not similar as per the f2 similarity factor. As such for the PVAP ER matrix tablets, the F05 formula was selected. The investigated sustained-release matrix tablet was capable of maintaining constant DTZ concentration through 12 hours. The high correlation coefficient of drug release for optimized formulation F05 and for marketed formulation (above 0.99) obtained indicates a square root of time dependent release kinetics. Thus, as the data fitted the Higuchi model, it confirmed a diffusion drug release mechanism. This can be expected to reduce the frequency of administration and decrease the dose-dependent side effects associated with repeated administration of conventional DTZ tablets. Based on the above, it is concluded that Kollidon® SR (PVAP) is a potentially useful excipient for the production of sustained release matrix tablets.

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DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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