

**FABRICATION OF SUSTAINED RELEASE MATRIX TABLET  
FORMULATION OF METOPROLOL SUCCINATE USING PVAP****Abhijit N. Merekar<sup>1</sup> and Bhanudas S. Kuchekar<sup>2</sup>**

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**ABSTRACT**

The present study was conducted to investigate the effect of PVAP at different concentrations on the release profile of Metoprolol Succinate from matrix tablets. Matrix-based tablet using different concentrations of PVAP was developed using direct compression technique to contain 47.50 mg of Metoprolol Succinate . The pre-compression and post compression parameters were evaluated. Formulations were evaluated for the release of Metoprolol Succinate over a period of 12 h in pH 6.8 phosphate buffer using USP type II dissolution apparatus. Metoprolol Succinate and pure PVAP compatibility interactions was investigated by using Fourier-transform infrared (FTIR) spectroscopy and differential scanning calorimetry (DSC). Formulation was optimized on the basis of acceptable tablet properties and in vitro drug

release. The f2 similarity factor for F5 of 78.65 shows drug release pattern very close to marketed product release profile . The in vivo X-ray studies were carried out to confirm the release pattern in vivo in rabbits, the studies showed that the sustaining activity where achieved by adhering to various sites in the gastrointestinal tract for the period of 12 h. The in vitro release profile and the mathematical models indicate that release of Metoprolol Succinate can be effectively controlled from a single tablet using PVAP matrix system.

**Keywords:** Metoprolol Succinate ,PVAP, Matrix system.

## 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. In this respect, different devices have 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, 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 Metoprolol Succinate was selected as a model drug. Metoprolol succinate is a cardio selective  $\beta$ -blocker used in the treatment of hypertension, angina pectoris and heart failure. It is available commercially in 25 mg, 50 mg strength as immediate release tablets. Its half life is about 3 to 7 hours (6). Its bioavailability is 50% following oral administration. It has been reported that conventional dosage forms increase the plasma concentration of Metoprolol above that achieving the maximum  $\beta_1$  blockage ( $>300$  nM). A therapeutic level of  $\beta$  blockage is achieved when plasma concentration are in the range of 80-300 nM. Higher concentration produces more  $\beta_2$  blockage but little additional  $\beta_1$  blockage. "Lower concentration may result suboptimal  $\beta_1$  blockage". To meet the need for effective and well tolerated  $\beta_1$  blockage an extended release formulation of metoprolol succinate is beneficial to

meet the objective of providing once daily dosing that maintains therapeutic plasma concentration and avoids the extreme peaks and troughs characteristics of metoprolol immediate release formulation (7).

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 (8, 9).

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 Metoprolol Succinate in the form of a matrix tablet by using in vitro dissolution studies and in vivo X-ray studies.

## MATERIALS AND METHODS

### Materials

Metoprolol Succinate was a gift sample from Emcure Pharmaceutical Ltd. (Pune, 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 were obtained as gift samples from Cipla (Kurlumbh, India). All other reagents were of analytical grade.

### Preparation of Metoprolol Succinate matrix tablets

Metoprolol Succinate polymeric matrix tablets were prepared by direct compression method as follows. The formulation of each tablet is shown in Table 1.

**Table 1: Formulation development of Metoprolol Succinate 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
Metoprolol Succinate	47.50	47.50	47.50	47.50	47.50	47.50	47.50	47.50	47.50	47.50
PVAP	189.60	-	-	94.80	94.80	-	126.40	31.60	31.60	63.20
Microcrystalline cellulose	-	189.60	-	94.80	-	94.80	31.60	126.40	31.60	63.20
Dibasic Calcium Phosphate dihydrate	-	-	189.60	-	94.80	94.80	31.60	31.60	126.40	63.20
Colloidal silicon dioxide	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2

Mg.Stearate	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Total weight	239.5	239.5	239.5	239.5	239.5	239.5	239.5	239.5	239.5	239.5

The corresponding amounts of Metoprolol Succinate, 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 239.5 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.

#### **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 (10), friability, uniformity of weight and content uniformity of drug as per IP 2007 (11).

#### **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  $\mu$ m) and the drug content was determined by UV spectroscopy (Evolution 201, UV-visible spectrophotometer, Thermo Fisher Scientific, Shanghai, China) at a wavelength of 275 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 Metoprolol Succinate, PVAP+MCC+DCP and Metoprolol Succinate with PVAP+MCC+DCP were recorded in a FTIR spectrometer (FTIR-4100, Jasco, Japan). The spectra were recorded within 4000–400 $\text{cm}^{-1}$  wave numbers.

### 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 Metoprolol Succinate 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  $37 \pm 0.5^\circ\text{C}$  temperature at 100rpm. 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  $\mu\text{m}$  Whatman filter paper and assayed at 275.7 nm by UV spectrophotometer (Evolution 201, UV-visible spectrophotometer, Thermo Fisher Scientific, Shanghai, China) (12).

The dissolution similarity ( $f_2$  similarity factor) was assessed by using FDA recommended approach for comparison of optimized formulation (F05) with marketed formulation (13). 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.

$$f_2 = 50 \log \left\{ \left[ 1 + \frac{1}{n} \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\}$$

Where;

$n$  = number of sample points

$R_t$  = percent of marketed product release profile

$T_t$  = percent of test formulations release observed

FDA has set a public standard of  $f_2$  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. (14) 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 Metoprolol Succinate, excipient as PVAP+ DCP, Metoprolol Succinate +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-C) at a constant scanning speed (10-C/min) in sealed aluminum pans, using nitrogen atmosphere.

### **In vivo X-ray Studies**

In vivo X-ray studies were conducted by X-ray analysis (15) 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/01/448/11-12/24) 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° 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 Metoprolol Succinate 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 5.240 to 6.403%, bulk density 0.434 to 0.477 g/cm<sup>3</sup>.

**Table 2: Pre-compression parameters of Metoprolol Succinate Sustained release matrix tablets using PVAP:-**

FORMULATION	BULK DENSITY (G/CM <sup>3</sup> )	TAPPE DENSITY (G/CM <sup>3</sup> )	COMPRESSI BILITY INDEX (%)	HAUSNER RATIO	ANGLE OF REPOSE (°)*
F1	0.458	0.485	5.567	1.059	19.093±0.020
F2	0.465	0.492	5.488	1.058	23.734±0.014
F3	0.442	0.467	5.353	1.056	24.764±0.010
F4	0.434	0.458	5.240	1.055	26.552±0.013
F5	0.497	0.531	6.403	1.068	23.699±0.013
F6	0.477	0.508	5.731	1.061	24.139±0.022
F7	0.458	0.486	5.761	1.061	24.546±0.011
F8	0.466	0.494	5.668	1.060	25.371±0.023
F9	0.446	0.471	5.307	1.056	26.331±0.024
F10	0.469	0.497	5.633	1.059	27.613±0.030

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



### Evaluation of post-compression parameters

Sustained release tablets were prepared by punching 239.5 mg of the drug-loaded polymer under a pressure of 400 kgf/cm<sup>2</sup> and tablets contained 47.50 mg of Metoprolol Succinate.

The post compression parameters tablet hardness, friability, uniformity of weight and content uniformity of drug in Table 3.

**Table 3: Evaluation of Metoprolol Succinate sustained release matrix Tablets Containing PVAP.**

FORMULATION	HARDNESS <sup>^</sup> (KG/CM <sup>2</sup> )	WEIGHT VARIATION*	FRIABILITY # (%)	CONTENT UNIFORMITY <sup>^</sup> (%)
F01	4.8 ±0.312	239±0.057	0.72 ±0.033	98.70±0.415
F02	4.8 ±0.158	240±0.127	0.71 ±0.041	99.70±0.173
F03	1.8 ±0.315	241±0.066	0.68 ±0.054	99.60±0.173
F04	4.8 ±0.214	240±0.071	0.55 ±0.025	98.90±0.051
F05	4.2 ±0.132	240±0.053	0.81 ±0.028	99.70±0.069
F06	4.4 ±0.156	241±0.045	0.75 ±0.011	99.30±0.051
F07	4.6 ±0.114	241±0.173	0.88 ±0.021	98.80±0.051
F08	4.2 ±0.245	242±0.416	0.82 ±0.032	99.40±0.034
F09	4.4 ±0.112	240±0.174	0.85 ±0.010	99.30±0.069
F010	4.0 ±0.158	240±0.192	0.76 ±0.022	99.20±0.086
Marketed (Meta <sup>XL</sup> 50)	4.8±0.312	285±0.057	0.72 ±0.033	98.80±0.415

\*All values are expressed as mean ±SD (n=20)

<sup>^</sup> All values are expressed as mean ± SD (n=6)

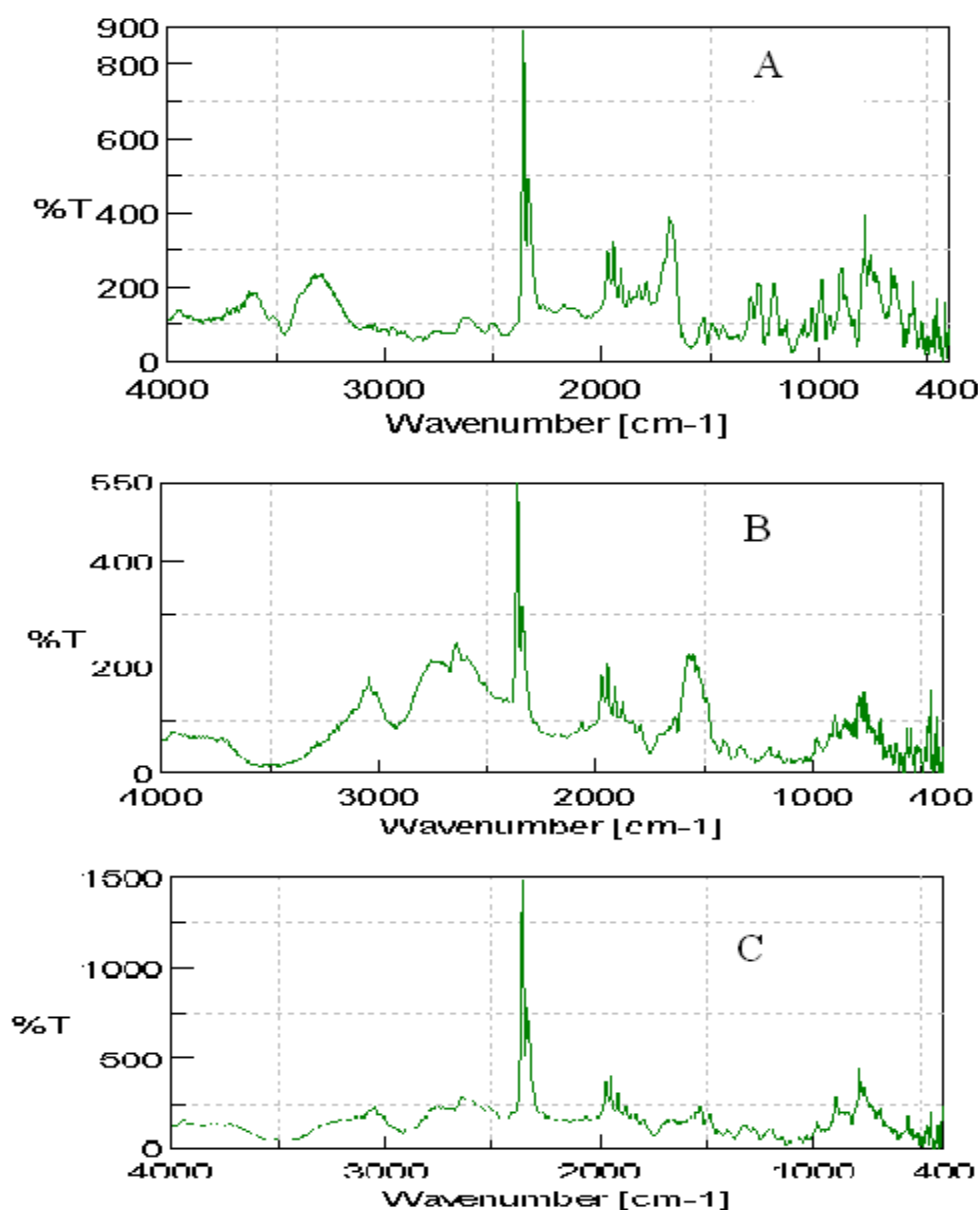
# All values are expressed as mean ± SD (n=6).

Hardness, weight variation, friability and content uniformity for all batches manufactured were tested. The hardness values of Metoprolol Succinate formulations were within range of 1.8 ±0.315 to 4.8 ±0.312. 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 Metoprolol Succinate formulation observed within the range of 0.55 ±0.025 to 0.88 ±0.021. Results showed that the percent of the Metoprolol Succinate in the compressed tablets as within the 98.70±0.415% to 99.70±0.173% of the theoretical label claim.



### FTIR Study

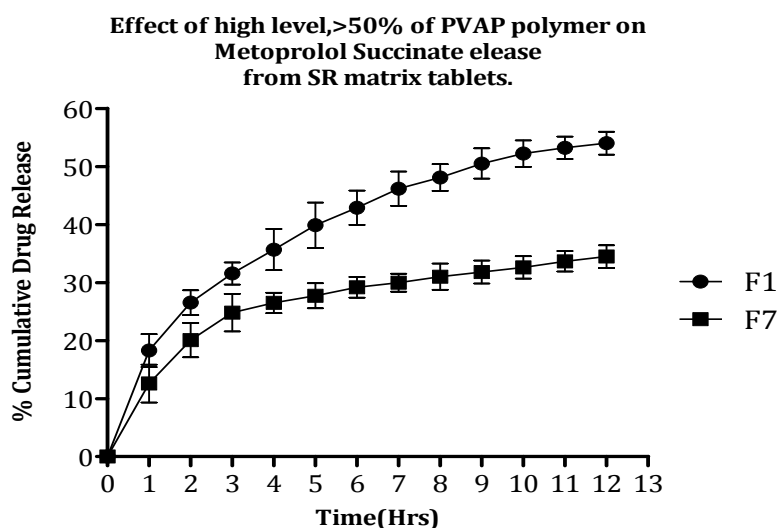
Drug polymer interaction was checked by comparing the FTIR spectra of the physical mixture of drug with the excipients used with the IR spectrum of pure drug. The IR spectrum of Metoprolol Succinate is characterized by the absorption of COOH group at (1760-1670  $\text{cm}^{-1}$ ). Also present in pure drug as well as in combination with other excipients. Frequencies of functional groups of pure drug remained intact in physical mixture containing polymers. Thus, mentioned evidence leads to conclude that changes are not seen as there is no physical interaction between drug & polymer.



**Figure 1:** FTIR spectra of Metoprolol Succinate (A), PVAP+MCC+DCP (B), Metoprolol Succinate + PVAP+MCC+DCP (C)

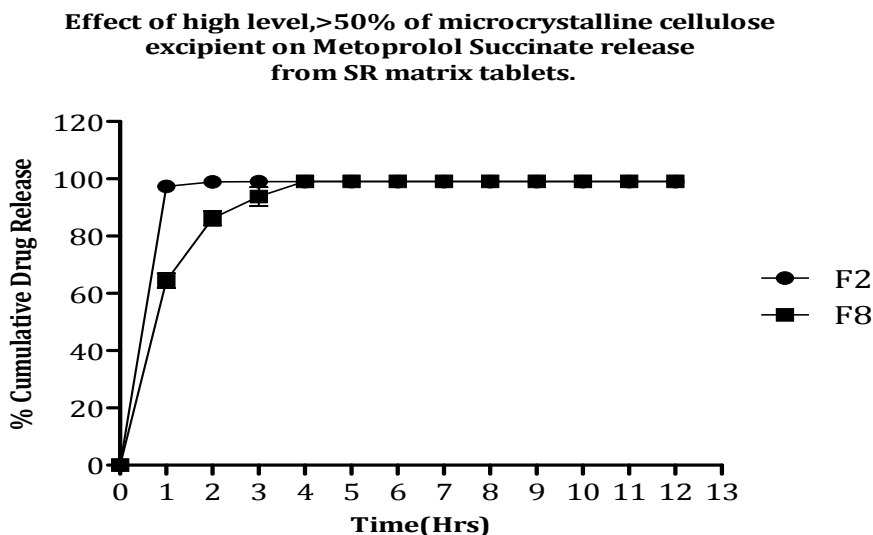
### In vitro Release Studies

The varying concentration of PVAP, MCC, DCP and combination on release profile of Metoprolol Succinate 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 (16). 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 24 and for F07 was 16. So, while F01 and F07 do show an extended release in vitro of the Metoprolol Succinate from the matrix tablets, the similarity factor tells us that these two formulations are not similar to the marketed product.



**Figure 2: Effect of high level, >50%, of PVAP polymer on Metoprolol Succinate release from SR matrix tablet.**

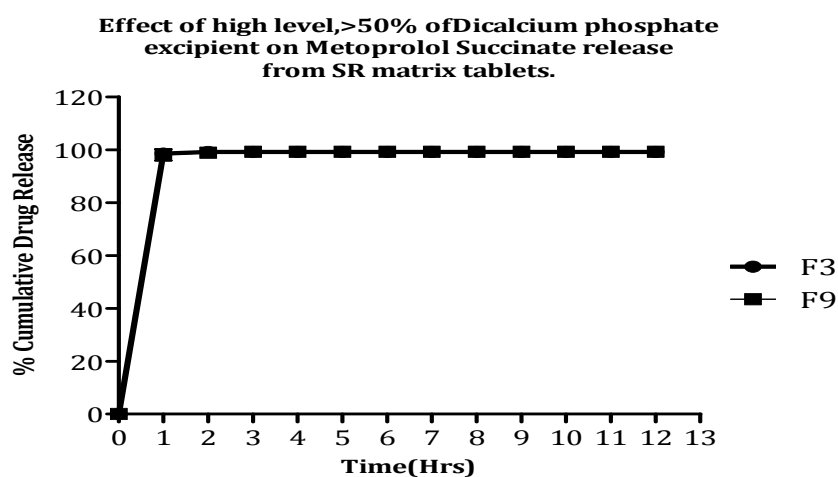
The matrix tablet formulation with high levels, greater than 50%, of microcrystalline cellulose, formulation variable F02 and F08, showed high drug release rate (Figure 3) as the level of PVAP polymer in F02 was 0% while in F08, it was 13.1%.



**Figure 3: Effect of high level, >50% of microcrystalline cellulose excipient on Metoprolol Succinate release from SR matrix tablet.**

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 (17). 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.

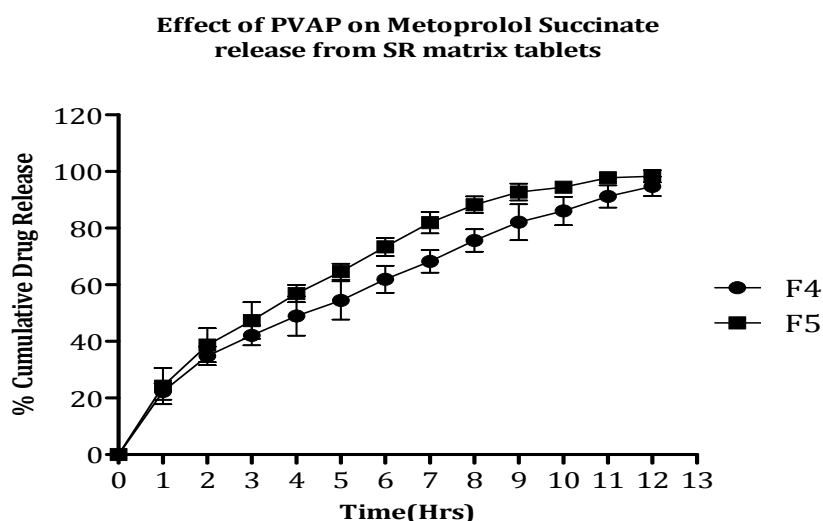
The matrix tablet formulation with high levels, greater than 50%, of dibasic calcium phosphate, formulation variable F03 and F09, showed high drug release rate (Figure 4).



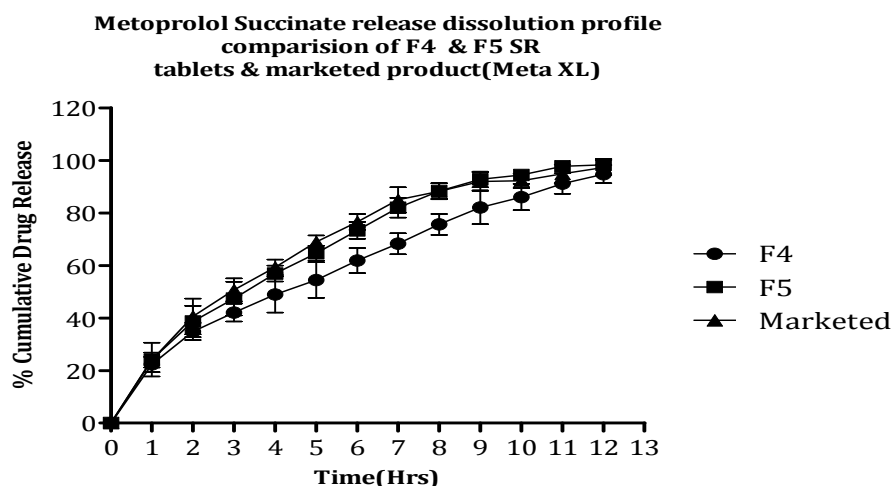
**Figure 4: Effect of high level, >50% of Dicalcium Phosphate excipient on Metoprolol Succinate release from SR matrix tablet.**

This can be explained by the fact that dibasic calcium phosphate on its 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<sup>2</sup> 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.



**Figure 5: Effect of PVAP on Metoprolol Succinate release from SR matrix tablet.**

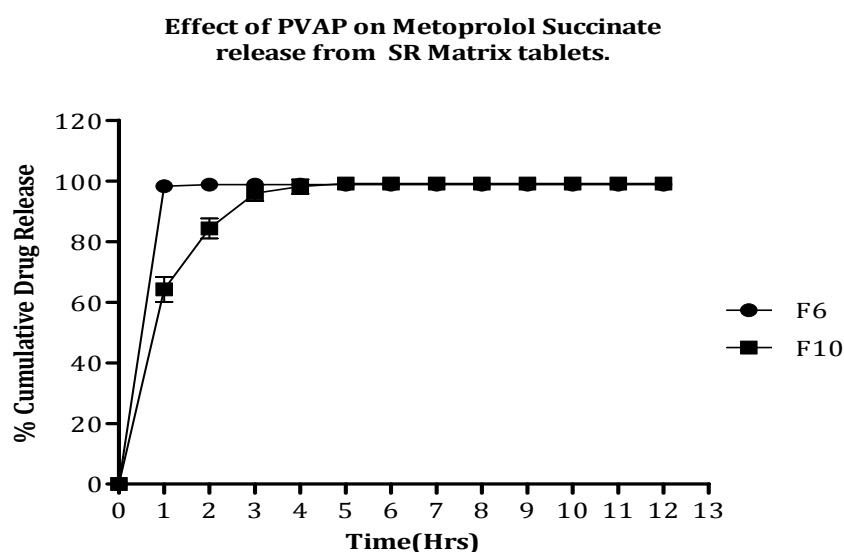


**Figure 6: Metoprolol Succinate release dissolution profile comparison of F4& F5 SR tablet & marketed product.**

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 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  $f_2$  value for F04 is 49.58 when calculated in comparison to the marketed product while the  $f_2$  value for F05 is 78.65 thus suggesting that F05 is similar to the marketed product in Metoprolol Succinate 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 that 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 (16).



**Figure 7: Effect of PVAP on Metoprolol Succinate release from SR matrix tablet**

### 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

**Table 4: Correlation coefficient [ $r^2$ ] and Diffusion exponent [n] after fitting of dissolution data into various releases kinetic models of all formulation of Metoprolol containing PVPA.**

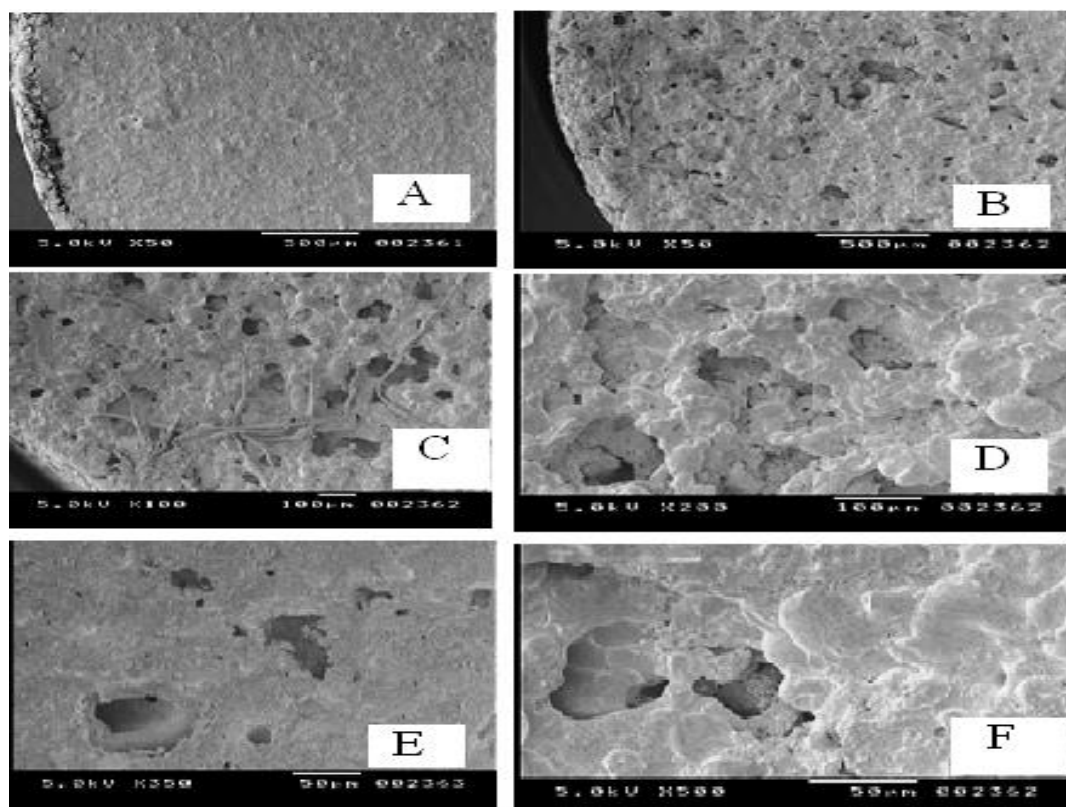
FORMU-LATION	CORRELATION COEFFICIENT [ $r^2$ ]					FOR KROSMEYER-PEPPAS EQUATION
	ZERO ORDER	1ST ORDER	HIGUCHI	HIX. CROW.	KORSMEYER PEPPAS	RELEASE EXPONENT [n]
F1	0.7465	0.8828	0.9856	0.8456	0.9849	0.4393
F2	0.6694	0.8185	0.9122	0.7534	0.7500	0.0165
F3	0.8400	0.8238	0.9578	0.8456	0.3333	0.0092
F4	0.9222	0.9553	0.9881	0.9845	0.9878	0.5832
F5	0.8872	0.9383	0.9902	0.9897	0.9833	0.5881
F6	0.6592	0.7136	0.9078	0.6855	0.6937	0.0053
F7	0.4358	0.6062	0.9369	0.5587	0.9482	0.3691
F8	0.8051	0.9740	0.9781	0.9807	0.9800	0.3132
F9	0.6653	0.7546	0.9103	0.7277	0.4778	0.0115
F10	0.6947	0.9801	0.9566	0.9476	0.9645	0.2795
Marketed	0.8450	0.9535	0.9905	0.9887	0.9871	0.5631

In 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 ( $r^2$ ): 0.9902 and 0.9905 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 0.5881 for F05, and n value of 0.5631 for marketed formulation indicating non-Fickian release suggesting that the transport from these formulations is controlled by diffusion and/or relaxation of the polymer. It is suggested that the main driving force for the drug release in case of water soluble drug like Metoprolol Succinate 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 polyvinylacetate, which is a very plastic material, produces a coherent matrix, sustaining the drug release from the tablet matrix.

### 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 Metoprolol Succinate from formulated matrix tablets.



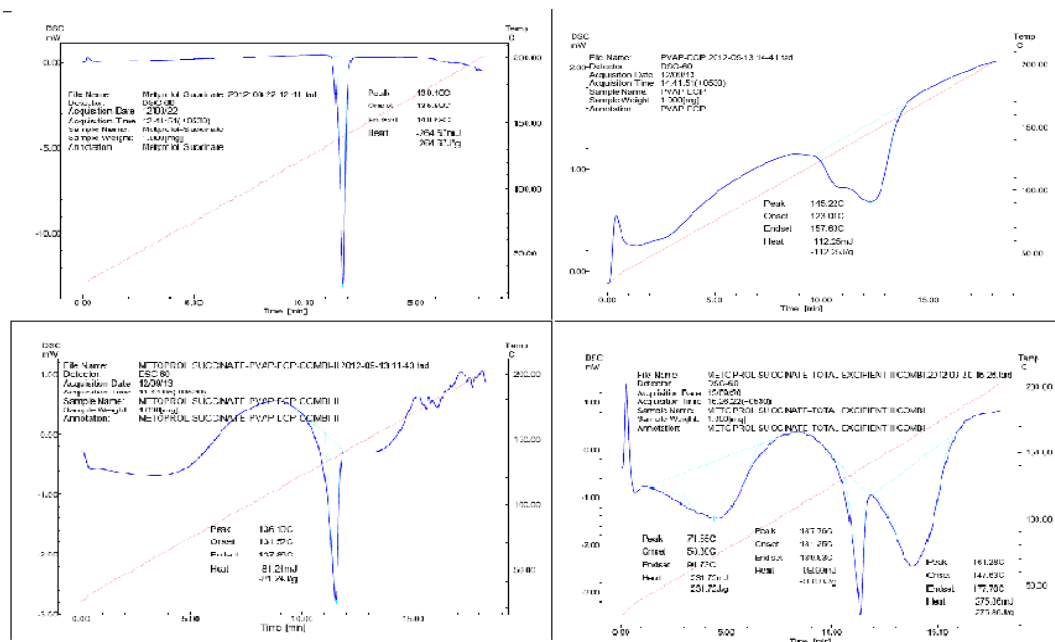
**Figure 7:** SEM photomicrographs of optimized matrix tablet (batch F5) showing surface morphology after 0 hours (A, 500×), 1 hours (B, 500×), 3 hours (C, 500×), 6 hours (D, 500×), 9 hours (E, 500×), and 12 hours (F, 500×) of dissolution study.

#### 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 Metoprolol Succinate, PVAP+ DCP, Metoprolol Succinate+ PVAP+ DCP & Optimized Formulation 05 (F05) are shown in figure 8. A sharp endotherm was observed for Metoprolol Succinate at



139.10°C and Metoprolol Succinate + PVAP+ DCP (Figure 8C) at 136.10°C. In formulation F05 (Figure 8D) melting endotherm at 137.76°C was observed. This confirmed that the presence of other excipients did not affect the drug nature which shows absence of any drug polymer interaction. It indicates that the drug is in crystalline form without undergoing any degradation and that polymer could be considerable compatible with Metoprolol Succinate.



**Figure 8: DSC Thermograms of Metoprolol Succinate (A), PVAP+ DCP (B), Metoprolol Succinate+PVAP+ DCP (C) & Formulation 05 (F05) (D)**

### Stability studies

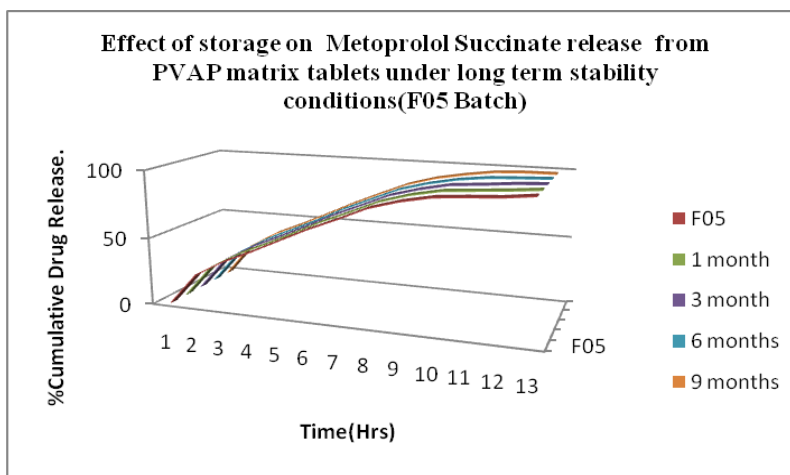
The F05 SR Matrix batch were observed for changes in physical properties (Table No: 5).

**Table 5: Effect of long term stability storage on the physical properties of Metoprolol Succinate sustained release tablet containing PVAP (F5 Batch)**

Physical Property	Initial	1 month	3 months	6 months	9 months
Weight	240±0.053	239±0.057	240±0.071	241±0.045	241±0.173
Hardness	4.2 ±0.132	4.8 ±0.156	5.4 ±0.114	6 ±0.214*	6.8 ±0.158*

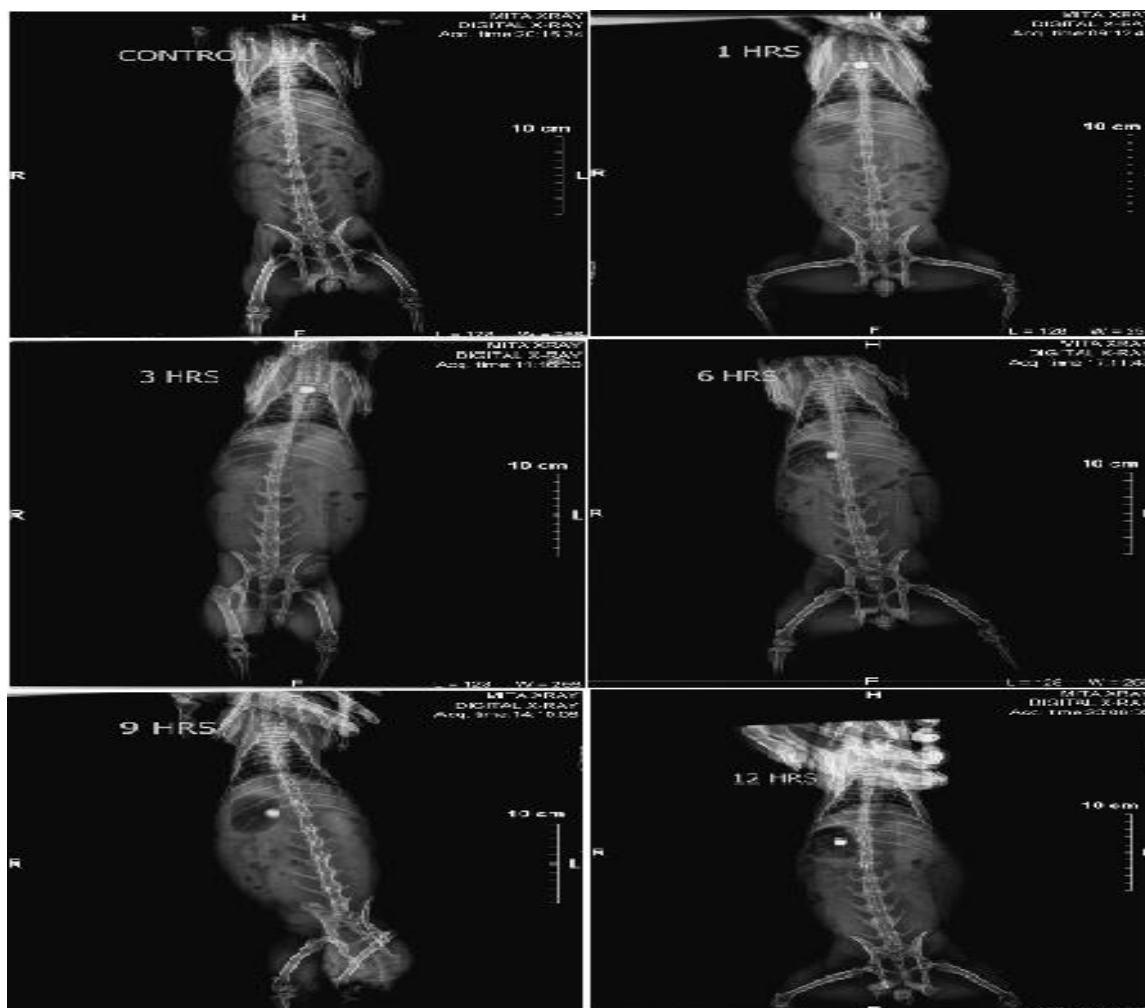
(\*) significantly different from initial at 0.05 level

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.



**Figure 9: Effect of storage on Metoprolol Succinate release from PVAP matrix tablets under long term stability conditions (F05 Batch)**

### In vivo X-ray studies



**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)**

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 h as shown in Figure 10.

## CONCLUSION

The data shows as expected that the PVAP alone exerts a retarding effect on the release of Metoprolol Succinate. Microcrystalline cellulose and dibasic calcium phosphate alone promote the release of Metoprolol Succinate. The present study demonstrated that, PVAP in combination with microcrystalline cellulose and dibasic calcium phosphate shows an even higher retardation of Metoprolol Succinate 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 Metoprolol Succinate 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 Metoprolol Succinate 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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