Design and \textit{In Vitro} Characterization of Dexlansoprazole Controlled Release Tablets

Y. Naveen Kumar$^1$, J. Sreekanth$^2$, P. Vijay Chander Reddy$^3$

$^1$Drugs Control Administration, Hyderabad, Telangana, India, $^2$Progenerics Pharma Pvt. Ltd, Hyderabad, Telangana, India, $^3$Pfizer Pharmaceuticals Pvt. Ltd., Vishakapatnam, Andhra Pradesh, India

Abstract

Aim: This study was to develop a controlled release formulation of various proton pump inhibitor drugs to maintain constant therapeutic levels of the drug over 24 h. \textbf{Settings and Design}: Dexlansoprazole was selected as model drugs. Various formulations were developed with different polymers for each drug molecule. To achieve pH-independent drug release of formulations, pH modifying agents were used. \textbf{Materials and Methods}: The precompression blends of all formulations were subjected to various flow property tests, and all the formulations were passed the tests. Various grades of hydroxypropyl methylcellulose were employed as polymers. \textbf{Statistical Analysis Used}: Absence of probable chemical interactions of Fourier transform infrared between pure drug and polymers. \textbf{Results}: Dexlansoprazole dose was fixed as 30 mg. Total weight of the tablet was considered as 250 mg. Polymers were used in the concentration of 75 and 150 mg concentration. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. \textbf{Conclusions}: Whereas from the dissolution studies it was evident that the formulation (F-2) showed better and desired drug release pattern, i.e. $98.79 \pm 0.48$ in 24 h. It followed zero-order release kinetics mechanism.

\textbf{Key words}: Controlled release, dexlansoprazole, direct compression, hydroxypropyl methylcellulose

INTRODUCTION

An ideal oral drug delivery system should steadily deliver a measurable and reproducible amount of drug to the target site over a prolonged period. Controlled release (CR) delivery system provides a uniform concentration or amount of the drug at the absorption site and thus after absorption allow maintenance of plasma concentrations within a therapeutic range, which minimizes side effects and also reduces the frequency of administration.$^{[1]}$

To overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits.$^{[2]}$

MATERIALS AND METHODS

Dexlansoprazole was an obtained from Aarti Drugs Ltd, Mumbai. A carbopol and hydroxypropyl methylcellulose (HPMC) grades were supplied by Yarrow Chem Products, Mumbai, and sodium carboxymethyl cellulose (CMC), magnesium stearate, aerosil, and microcrystalline cellulose (MCC) were supplied by Signet Chemical Corporation, Mumbai, India.

Methodology

\textbf{Analytical method development}

\textit{Determination of absorption maxima}

A solution of containing the concentration 10 μg/ml was prepared in 0.1 NHCl, phosphate buffer of pH 6.8 and phosphate buffer of pH 7.4, respectively, ultraviolet (UV) spectrum was taken using Double beam UV/visible spectrophotometer. The solution was scanned in the range of 200-400 nm.

Address for correspondence:
Y. Naveen Kumar, Drugs Control Administration, Hyderabad, Telangana, India. Phone: +91-9908335856. E-mail: naveen.yed@gmail.com

Received: 01-12-2016
Revised: 12-12-2016
Accepted: 16-12-2016

Asian Journal of Pharmaceutics • Oct-Dec 2016 (Suppl) • 10 (4) | S770
Preparation calibration curve
10 mg of drug was accurately weighed and dissolved in 10 ml of 0.1 N HCl, phosphate buffer of pH 6.8 and phosphate buffer of pH 7.4 in 10 ml volumetric flask, to make (1000 μg/ml) standard stock solution (1). Then, 1 ml stock solution (1) was taken in another 10 ml volumetric flask to make (100 μg/ml) standard stock solution (2), then again 1 ml of stock solution (2) was taken in another 10 ml volumetric flask and then final concentrations were prepared 2, 4, 5, 10, 15, 20, 25, 30 and 20 μg/ml with 0.1 N HCl, 6.8 pH phosphate buffer, and 7.4 pH phosphate buffer. The absorbance of standard solution was determined using UV/visible spectrophotometer at 273 nm. Linearity of standard curve was assessed from the square of correlation coefficient (r²) which determined by least-square linear regression analysis.

Preformulation parameters
The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Evaluation of flow for pharmaceutical powders

Angle of repose
The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel.

Bulk density
Density is defined as weight per unit volume. Bulk density is defined as the mass of the powder divided by the bulk volume and is expressed as g/cm³. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 g powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting.

Tapped density
After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops/min and this was repeated until difference between succeeding measurement is <2% and then tapped volume, V measured, to the nearest graduated unit.

Measures of powder compressibility
The compressibility index (Carr’s index) is a measure of the propensity of powder to be compressed. It is determined from the bulk and tapped densities in theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of inter particulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value.

Formulation development of tablets
Direct compression method
Different tablets formulations were prepared by direct compression technique. All powders were passed through 60 mesh. Required quantities of drug and polymers were mixed thoroughly magnesium stearate was added as lubricant. Aerosil was used as glidant. MCC was used as diluent. Finally, the powder mix was subjected to compression after mixing uniformly in a polybag. Before compression, the blends were evaluated for several tests [Table 1].

Evaluation of post compression parameters for prepared tablets
The designed formulation compression tablets were studied for their physicochemical properties such as weight variation, hardness, thickness, friability, and drug content.

Weight variation test
To study the weight variation, 20 tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage.

Hardness
Hardness of tablet is defined as the force applied across the diameter of the tablet to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Thickness
Thickness and diameter of tablets were vital for uniformity of tablet size. Thickness and diameter was precise using vernier calipers.
Friability

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Preweighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 min (100 rotations).

Determination of drug content

Dexlansoprazole compression tablets were tested for their drug content. 10 tablets were finely powdered quantities of the powder equivalent to one tablet weight of dexlansoprazole were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with water. The solution was suitably diluted and the absorption was determined by UV-visible spectrophotometer. The drug concentration was calculated from the calibration curve.

In vitro drug release studies

Drug release studies of tablets

The tablets containing 30 mg dexlansoprazole of were tested in (pH 6.8), for their dissolution rates. Dissolution studies were performed using USP paddle Type-II apparatus at 37°C at 50 rpm. Sample of 5 ml was withdrawn and replaced with fresh medium. The samples were analyzed spectrophotometrically at respective 270 nm.

Drug release studies of dexlansoprazole tablets

The release of tablets from compressed tablets was carried out using USP paddle type-II dissolution apparatus at a rotation speed of 50 rpm, and a temperature of 37 ± 0.5°C. For tablets, simulation of gastrointestinal transit conditions was achieved using different dissolution media. Thus, drug release studies were conducted in simulated gastric fluid (SGF, pH 1.2) for the first 2 h as the average gastric emptying time is about 2 h. Then, the dissolution medium was replaced with enzyme-free simulated intestinal fluid (SIF, pH 6.8) and tested for drug release for 8 h, as the average small intestinal transit time is about 8 h, and finally enzyme-free SIF (SIF, pH 7.4) was used up to 14 h.[10,11]

Drug release was measured from compression tablets, added to 900 ml of dissolution medium. 5 ml of sample was withdrawn every time and replaced with fresh medium, samples withdrawn at various time intervals were analyzed spectrophotometrically.

Application of release rate kinetics to dissolution data

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.[12-15]

Zero-order release rate kinetics

To study the zero-order release kinetics the release rate data are fitted to the following equation.

\[ F = K_o t \]

Where, “F” is the drug release at time “t,” and “K_o” is the zero-order release rate constant. The plot of % drug release versus time is linear.

First order release rate kinetics

The release rate data are fitted to the following equation,

\[ \log (100-F) = kt \]

A plot of log cumulative percent of drug remaining to be released versus time is plotted then it gives first order release.

Table 1: Formulations of dexlansoprazole controlled release tablets

<table>
<thead>
<tr>
<th>F. No.</th>
<th>Dexlansoprazole</th>
<th>Carbopol</th>
<th>HPMC K4M</th>
<th>HPMC K15M</th>
<th>Sodium CMC</th>
<th>Magnesium stearate</th>
<th>Aerosil</th>
<th>MCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>F_1</td>
<td>30</td>
<td>150</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5</td>
<td>5</td>
<td>60</td>
</tr>
<tr>
<td>F_2</td>
<td>30</td>
<td>75</td>
<td>75</td>
<td>-</td>
<td>-</td>
<td>5</td>
<td>5</td>
<td>60</td>
</tr>
<tr>
<td>F_3</td>
<td>30</td>
<td>50</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>5</td>
<td>5</td>
<td>60</td>
</tr>
<tr>
<td>F_4</td>
<td>30</td>
<td>100</td>
<td>50</td>
<td>-</td>
<td>-</td>
<td>5</td>
<td>5</td>
<td>60</td>
</tr>
<tr>
<td>F_5</td>
<td>30</td>
<td>75</td>
<td>-</td>
<td>75</td>
<td>-</td>
<td>5</td>
<td>5</td>
<td>60</td>
</tr>
<tr>
<td>F_6</td>
<td>30</td>
<td>50</td>
<td>-</td>
<td>100</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>60</td>
</tr>
<tr>
<td>F_7</td>
<td>30</td>
<td>100</td>
<td>-</td>
<td>50</td>
<td>-</td>
<td>5</td>
<td>5</td>
<td>60</td>
</tr>
<tr>
<td>F_8</td>
<td>30</td>
<td>-</td>
<td>150</td>
<td>-</td>
<td>-</td>
<td>5</td>
<td>5</td>
<td>60</td>
</tr>
<tr>
<td>F_9</td>
<td>30</td>
<td>-</td>
<td>-</td>
<td>150</td>
<td>-</td>
<td>5</td>
<td>5</td>
<td>60</td>
</tr>
<tr>
<td>F_10</td>
<td>30</td>
<td>-</td>
<td>-</td>
<td>75</td>
<td>75</td>
<td>5</td>
<td>5</td>
<td>60</td>
</tr>
<tr>
<td>F_11</td>
<td>30</td>
<td>-</td>
<td>-</td>
<td>50</td>
<td>100</td>
<td>5</td>
<td>5</td>
<td>60</td>
</tr>
<tr>
<td>F_12</td>
<td>30</td>
<td>-</td>
<td>-</td>
<td>100</td>
<td>50</td>
<td>5</td>
<td>5</td>
<td>60</td>
</tr>
</tbody>
</table>

All are expressed in mg. Each tablet weight is 250 mg. HPMC: Hydroxypropyl methylcellulose, CMC: Carboxymethyl cellulose, MCC: Microcrystalline cellulose.
Higuchi release model
To study the Higuchi release kinetics, the release rate data were fitted to the following equation

\[ F = k \sqrt{t} \]

Where, “k” is the Higuchi constant.

In Higuchi model, a plot of % drug release versus square root of time is linear.

Korsmeyer and Peppas release model
The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer-Peppas equation. The exponent “n” indicates the mechanism of drug release calculated through the slope of the straight line.

\[ \frac{M_t}{M_\infty} = k t^n \]

Where, \( M_t/M_\infty \) is fraction of drug released at time “t,” k represents a constant, and “n” is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, \( n = 0.5 \); for zero-order release (case II transport), \( n = 1 \); and for supercase II transport, \( n > 1 \). In this model, a plot of log \( (M_t/M_\infty) \) versus log (time) is linear.

Hixson-Crowell release model

\[ (100 - Q_t)^{1/3} = 100^{1/3} K H C t \]

Where, \( k \) is the Hixson-Crowell rate constant.

Hixson-Crowell model describes the release of drugs from an insoluble matrix through mainly erosion (where there is a change in surface area and diameter of particles or tablets).

RESULTS AND DISCUSSION

This study was aimed to developing CR tablets of dexlansoprazole using various polymers. All the formulations were evaluated for physicochemical properties and in vitro drug release studies.

Analytical method

Graphs of dexlansoprazole were taken in SGF (pH 1.2) and in pH 6.8 phosphate buffer at 238 nm and 234 nm, respectively [Tables 2 and 3, Figures 1 and 2].

Drug-excipient compatibility studies-Fourier transform infrared (IR) spectroscopy

The physical properties of the physical mixture were comparing with those of dexlansoprazole drug. Samples were varied meticulously with 100 mg potassium bromide IR powder and trampled under vacuum at a pressure of concerning 12 psi for 3 min. The ensuing disc was mounted in an appropriate holder in Perkin Elmer IR spectrophotometer and the IR spectrum

**Table 2: Observations for graph of dexlansoprazole in 0.1 N HCl (238 nm)**

<table>
<thead>
<tr>
<th>Concentration (μg/L)</th>
<th>Absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>0.112</td>
</tr>
<tr>
<td>10</td>
<td>0.230</td>
</tr>
<tr>
<td>15</td>
<td>0.336</td>
</tr>
<tr>
<td>20</td>
<td>0.410</td>
</tr>
<tr>
<td>25</td>
<td>0.567</td>
</tr>
<tr>
<td>30</td>
<td>0.645</td>
</tr>
</tbody>
</table>

**Table 3: Observations for graph of dexlansoprazole in pH 6.8 phosphate buffer (234 nm)**

<table>
<thead>
<tr>
<th>Concentration (μg/L)</th>
<th>Absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>0.123</td>
</tr>
<tr>
<td>10</td>
<td>0.210</td>
</tr>
<tr>
<td>15</td>
<td>0.320</td>
</tr>
<tr>
<td>20</td>
<td>0.411</td>
</tr>
<tr>
<td>25</td>
<td>0.501</td>
</tr>
</tbody>
</table>

**Figure 1:** Standard graph of dexlansoprazole in 0.1 N HCl

**Figure 2:** Standard graph of dexlansoprazole pH 6.8 phosphate buffer (234 nm)
was recorded from 3500 cm to 500 cm. The resultant spectrum was compared for any spectrum changes [Figures 3-7].

Preformulation parameters of dexlansoprazole CR powder blend

Tablet powder blend was subjected to various preformulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.34 ± 0.06 to 0.49 ± 0.05 (g/cm³) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.61 ± 0.07 to 0.64 ± 0.07 showing the powder has good flow properties. All the formulations have shown the Hausner’s ratio ranging between 0.6 and 1.3 indicating the powder has good flow properties [Table 4].

Figure 3: Fourier transform infrared spectrum of dexlansoprazole pure drug

Figure 4: Fourier transform infrared spectrum of drug + carbopol

Figure 5: Fourier transform infrared spectrum of drug + hydroxypropyl methylcellulose K4M
Table 4: Preformulation parameters of powder blend

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Angle of repose</th>
<th>Bulk density (g/ml)</th>
<th>Tapped density (g/ml)</th>
<th>Hausner’s ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>27.7±0.61</td>
<td>0.48±0.01</td>
<td>0.59±0.04</td>
<td>1.3</td>
</tr>
<tr>
<td>F2</td>
<td>25.1±0.30</td>
<td>0.35±0.09</td>
<td>0.61±0.07</td>
<td>1.1</td>
</tr>
<tr>
<td>F3</td>
<td>26.2±0.42</td>
<td>0.47±0.07</td>
<td>0.74±0.05</td>
<td>1.13</td>
</tr>
<tr>
<td>F4</td>
<td>25.6±0.18</td>
<td>0.36±0.09</td>
<td>0.69±0.06</td>
<td>1.2</td>
</tr>
<tr>
<td>F5</td>
<td>26.9±1.12</td>
<td>0.42±0.04</td>
<td>0.51±0.02</td>
<td>0.9</td>
</tr>
<tr>
<td>F6</td>
<td>29.7±0.79</td>
<td>0.49±0.05</td>
<td>0.64±0.09</td>
<td>0.97</td>
</tr>
<tr>
<td>F7</td>
<td>30.3±0.65</td>
<td>0.34±0.06</td>
<td>0.55±0.07</td>
<td>0.6</td>
</tr>
<tr>
<td>F8</td>
<td>26.5±0.69</td>
<td>0.42±0.03</td>
<td>0.62±0.04</td>
<td>1.13</td>
</tr>
<tr>
<td>F9</td>
<td>27.5±1.46</td>
<td>0.38±0.08</td>
<td>0.76±0.05</td>
<td>0.89</td>
</tr>
<tr>
<td>F10</td>
<td>28.7±1.20</td>
<td>0.39±0.06</td>
<td>0.52±0.05</td>
<td>0.7</td>
</tr>
<tr>
<td>F11</td>
<td>29.9±0.27</td>
<td>0.46±0.03</td>
<td>0.64±0.07</td>
<td>1.14</td>
</tr>
<tr>
<td>F12</td>
<td>26.5±0.24</td>
<td>0.38±0.02</td>
<td>0.63±0.04</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Figure 6: Fourier transform infrared spectrum of drug + hydroxypropyl methylcellulose K15M

Figure 7: Dissolution profile of dexlansoprazole (F1, F2, F3, F4 formulations)

**Quality control parameters for tablets**

Tablet quality control tests such as weight variation, hardness, friability, thickness, and drug release studies in different media were performed on the compression tablet.

All the parameters such as weight variation, friability, hardness, thickness, and drug content were found to be within limits [Table 5].

**In vitro drug release studies**

*In vitro* drug release studies revealed that the release of dexlansoprazole from different formulations varies with characteristics and composition of matrix forming polymers as shown in Tables 6-8 and Figures 8-10. The release rate of dexlansoprazole decreased with increasing concentration of HPMC K4M and HPMC K15 M in F3 and F5-F6 and F8-F9, respectively. These findings are in compliance with the ability of HPMC to form complex matrix network which leads to delay in release of drug from the device. Carbopol is more hydrophilic than HPMC; it can swell rapidly, therefore, decrease of carbopol content delays the drug release in F3 and F5-F6. Drug release rate was increased with increasing amount of hydrophilic polymer. The maximum cumulative percent release of dexlansoprazole from formulation F1 could be attributed due to ionization of carbopol at pH environment of the dissolution medium. Ionization of carbopol leads to the development of negative charges along the backbone of the polymer. Repulsion of like charges uncoils the polymer into an extended structure. The counter ion diffusion inside the gel creates an additional osmotic pressure difference across the gel leading to the high water uptake. This water...
uptake leads to the considerable swelling of the polymer. The continued swelling of polymer matrix causes the drug to diffuse out from the formulation at a faster rate. Formulations F10, F11 showed relatively high rate of release of dexlansoprazole which is due to rapid swelling and erosion of sodium CMC. Further, the increase in rate of drug release could be explained by the ability of the hydrophilic polymers to absorb water, thereby promoting the dissolution, and hence the release, of the highly water soluble drug. Moreover, the hydrophilic polymers would leach out and hence, create more pores and channels for the drug to diffuse out of the device. Formulation F12 which contains high amounts of sodium CMC gets eroded during dissolution study before stipulated study period. Thus higher concentration of sodium CMC cannot be incorporated into such formulations for sustaining the release.

The combination of F2 formulation was a carbopol and HPMC K4M equal concentration (75 mg) of polymers was achieved good retarded polymers. Hence, F2 formulation shows the good drug release up to 24 h compared to other formulation.

### Release kinetics for optimized formulation F2

Table 9 enlists various dissolution parameters computed for all the CR tablets. To examine further the release mechanism of dexlansoprazole from tablets, the results were analyzed according to the equation, 

\[ \frac{M_t}{M_\infty} = K_t^n \]

proposed by Peppas and Korsmeyer 40. The obtained values of release rate exponent (n), lie between 0.5901 and 0.8257 in all formulations for the release of dexlansoprazole. In general,
the released pattern found to be non-Fickian tending to approach first order.

Several kinetic models describing drug release from immediate and modified released dosage forms. The model that best fits the release data was evaluated by correlation coefficient (r). The correlation coefficient (r) value was used as criteria to choose the best model to describe the drug release from the CR tablets. The “r” value in various models is in Table 9. The “r” values obtained for fitting the drug release data to first order, indicating that the drug release mechanism follows first order kinetics. From Higuchi’s equation, the high values of correlation coefficient “r” indicating that the drug release mechanism from these tablets was diffusion controlled. The values of “n” in Peppas model indicated the drug release follows non-Fickian diffusion.

From the above results, it is concluded that the drug release from the formulated CR tablets of dexlansoprazole followed zero-order kinetics.

**DSC studies**

Differential scanning calorimetry studies were carried out to determine the compatibility between drug and excipients in
optimized formulation. From the studies it was evident that there was no prominent change in the melting point of pure drug alone and its melting point when it was combined with other excipients in optimized formulation.

**CONCLUSION**

This study was to develop a CR formulation of various proton pump inhibitor to maintain constant therapeutic levels of the drug for over 24 h. Dexlansoprazole was selected as model drugs. Various formulations were developed with different polymers for each drug molecule. To achieve pH-independent drug release of formulations, pH modifying agents (buffering agents) were used. The precompression blend of all formulations was subjected to various flow property tests, and all the formulations were passed the tests. Various grades of HPMC were employed as polymers. Dexlansoprazole dose was fixed as 30 mg. Total weight of the tablet was considered as 250 mg. Polymers were used in the concentration of 75 and 150 mg concentration. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (F-2) showed better and desired drug release pattern, i.e. 98.79 ± 0.48% in 24 h. It followed zero-order release kinetics mechanism.

**REFERENCES**

6. Venkateshwarlu P. Formulation and in-vitro evaluation

---

**Figure 10:** (a-e) Release kinetics for optimized formulation F-2

Source of Support: Nil. Conflict of Interest: None declared.