Formulation and Evaluation of Sustained Release Tablets of Quinapril HCl

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In present investigation an attempt has been made to design and develop some Quinapril matrix tablets using Hydroxypropyl Methylcellulose K100M, K4M, Guar gum and their combination as release retarding polymers. Quinapril is Anti-hypertensive drug which lowers blood pressure level and has been selected to prepare sustained release dosage forms. Quinapril sustained release matrix tablets were prepared using Hydroxy Propyl Methyl Cellulose K100M, K4M, Guar gum and their combination as base polymer by wet granulation method. FT-IR spectral analysis showed that characteristic peak of Quinapril pure drug was retained in the spectra of all the formulations indicating the intactness of the drug in all the formulations. Quinapril matrix tablets formulated employing HPMC K100M and combination of Guar gum provided slow and controlled release of Quinapril up to 12 hr. Drug release from the matrix tablets formulation containing HPMC K100M and combination of Guar gum follows Zero order drug release with Higuchi diffusion. All the tablet formulation showed compliance with pharmacopoeia standard as the time increases. The dissolution result shows that an increased amount of polymer resulted in reduced drug release. A concentration dependent drug release is evident in case of the polymer i.e., lower concentration of polymers, release is marginally retarded at higher concentration is considerable. Prepared sustained formulation containing HPMC K100M, HPMCK4M and combination of Guar gum (F8) probably showing better release based up to 96.03% drug release within 12 hour.

Keyword: Sustained release, Quinapril, HPMC K100M, HPMC K4M, Guar gum.

1. Introduction

Oral controlled release drug delivery is a drug delivery system that provides the continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either a local or systemic action.

All the pharmaceutical products formulated for systemic delivery via the oral route of administration, irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage form (either solid dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology. Therefore the scientific framework required for the successful development of oral drug delivery systems consists of basic understanding of (i) physicochemical, pharmacokinetic and pharmacodynamic characteristics of the drug (ii) the anatomic and physiologic characteristics of the gastrointestinal tract and (iii) physicochemical characteristics and the drug delivery mode of the dosage form to be designed.
The main areas of potential challenge in the development of oral controlled drug delivery systems are:-

1) Development of a drug delivery system: To develop a viable oral controlled release drug delivery system capable of delivering a drug at a therapeutically effective rate to a desirable site for duration required for optimal treatment.

2) Modulation of gastrointestinal transit time: To modulate the GI transit time so that the drug delivery system developed can be transported to a target site or to the vicinity of an absorption site and reside there for a prolonged period of time to maximize the delivery of a drug dose.

3) Minimization of hepatic first pass elimination: If the drug to be delivered is subjected to extensive hepatic first-pass elimination, preventive measures should be devised to either bypass or minimize the extent of hepatic metabolic effect.

1.1. Sustained Release:
Sustained release tablets allowing a twofold or greater reduction in frequency of administration of a drug in comparison with the frequency required by a conventional dosage form. It is designed to maintain constant levels of a drug in the patient's bloodstream by releasing the drug over an extended period. Maintaining constant blood levels of the drug in the bloodstream increases the therapeutic effectiveness of the drug.

2. Materials and Methods:

2.1. Materials:
Quinalapril Hydrochloride obtained from Spectrum Pharma laboratories Hyderabad, Hydroxyl Propyl Methylcellulose K100M, Hydroxyl Propyl Methylcellulose K4M, Magnesium stearate obtained from SDFL Chemicals Ltd Mumbai. All materials used were of analytical grade procured from commercial sources.

Table 1: Formulation of Quinapril HCl sustained release tablets

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
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<tbody>
<tr>
<td>Quinapril</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
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<td>..</td>
<td>20</td>
<td>..</td>
<td>..</td>
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</tr>
<tr>
<td>Hpmc K4m</td>
<td>..</td>
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<td>..</td>
<td>..</td>
<td>20</td>
<td>..</td>
<td>10</td>
<td>..</td>
</tr>
<tr>
<td>Guar Gum</td>
<td>..</td>
<td>..</td>
<td>10</td>
<td>..</td>
<td>..</td>
<td>20</td>
<td>..</td>
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</tr>
<tr>
<td>Magnesium Stearate</td>
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<td>3</td>
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<tr>
<td>Talc</td>
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<td>2</td>
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<td>2</td>
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<td>2</td>
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<tr>
<td>Mcc</td>
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<td>Starch</td>
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<td>10</td>
<td>10</td>
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<td>10</td>
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<td>Total Weight</td>
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<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

2.2. Preparation of the Tablets:
Quinalapril Hydrochloride, polymer and bulking agent MCC, weighed and they were sifted through #40 mesh. Then these are taken in a mortar and pestle, triturated well to ensure proper mixing of drug with the excipients for 15 minutes at fast speed. Starch was dissolved in purified water for binder solution preparation. Added this starch solution to drug and excipients to produce damp mass and then it was passed through # 10 mesh screen to obtain wet granules. The wet granules were loaded into tray drier. The granules were dried at 50 to 60°C till the moisture content is 5 to 3 %. The dried granules were passed through the mesh no. 16 to break the aggregates. The lubricants talc (2%) and magnesium stearate (2%) were passed through the mesh no. 100 onto the dry granules and blended in a closed polyethylene bag. The tablet granules were compressed into tablets on a rotary multi-station
tablet punching machine (Cadmach Machinery Co. Pvt. Ltd., Mumbai) to a hardness of 8 - 10 kg/sq. cm using 9 mm round and flat punches.

3. Pre-Compression Parameters

3.1. Angle of Repose (\(\tan \theta\)):
For determination of angle of repose (\(\tan \theta\)), the blend were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 20 cm above hard surface. The blends were poured till the time when upper tip of the pile surface touched the lower tip of the funnel. The \(\tan^{-1}\) of the (height of the pile/radius of its base) gave the angle of repose.

\[
\tan \theta = \frac{h}{r} \\
\theta = \tan^{-1} \left( \frac{h}{r} \right)
\]

Where, 
\(\theta\) = angle of repose  
\(h\) = height of the heap  
\(r\) = radius of the heap

3.2. Bulk Density (\(D_b\)):
It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve #20) into a measuring cylinder and the initial volume was noted. This initial volume is called the bulk volume. From this, the bulk density is calculated according to the formula mentioned below. It is expressed in g/cc and is given by:

\[
D_b = \frac{m}{V_0}
\]

Where, 
\(m\) = mass of the powder 
\(V_0\) = bulk volume of powder.

3.3. Tapped density (\(D_t\)):
It is the ratio of total mass of powder to the tapped volume of powder. The volume was measured by tapping the powder for 500 times. Then the tapping was done for 750 times and the tapped volume was noted (the difference between these two volumes should be less than 2%). If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. It is expressed in g/cc and is given by:

\[
D_t = \frac{m}{V_i}
\]

Where, 
\(m\) = mass of the powder 
\(V_i\) = tapped volume of powder.

3.4. Compressibility Index (Carr’s Consolidation Index):
The flowability of powder can be evaluated by comparing the bulk density (\(D_b\)) and tapped density (\(D_t\)) of powder and the rate at which it packed down. Compressibility index is calculated by –

\[
\text{Compressibility index (\%)} = \frac{D_t - D_b}{D_t} \times 100
\]

Where, 
\(D_b\) = Bulk density, 
\(D_t\) = Tapped density

3.5. Hausner’s Ratio:
Hausner’s Ratio is an indirect index of ease of powder flow. If the Hausner’s ratio of powder is near to 1.25, indicates better powder flow. It is calculated by the following formula

\[
\text{Hausner’s Ratio} = \frac{D_b}{D_t}
\]

Where, 
\(D_t\) = tapped density of the powder 
\(D_b\) = bulk density of the powder.
Table 2: Pre compression parameters of the various batches of the Quinapril HCl tablet blend Flow properties:

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Angle of repose (degrees)</th>
<th>Bulk density (gm/ml)</th>
<th>Tapped density (gm/ml)</th>
<th>Carr’s index (%)</th>
<th>Hausner’s ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>29.74±0.05</td>
<td>0.429±0.002</td>
<td>0.498±0.003</td>
<td>13.89±0.2</td>
<td>1.16±0.04</td>
</tr>
<tr>
<td>F2</td>
<td>28.43±0.04</td>
<td>0.508±0.003</td>
<td>0.653±0.004</td>
<td>22.21±0.3</td>
<td>1.2±0.02</td>
</tr>
<tr>
<td>F3</td>
<td>31.11±0.06</td>
<td>0.501±0.005</td>
<td>0.601±0.006</td>
<td>16.6±0.3</td>
<td>1.2±0.05</td>
</tr>
<tr>
<td>F4</td>
<td>33.66±0.03</td>
<td>0.469±0.002</td>
<td>0.536±0.005</td>
<td>12.5±0.2</td>
<td>1.14±0.03</td>
</tr>
<tr>
<td>F5</td>
<td>28.43±0.04</td>
<td>0.487±0.003</td>
<td>0.602±0.006</td>
<td>16.6±0.3</td>
<td>1.24±0.05</td>
</tr>
<tr>
<td>F6</td>
<td>30.23±0.04</td>
<td>0.507±0.008</td>
<td>0.512±0.003</td>
<td>13.25±0.24</td>
<td>1.16±0.07</td>
</tr>
<tr>
<td>F7</td>
<td>33.66±0.03</td>
<td>0.469±0.002</td>
<td>0.536±0.005</td>
<td>12.5±0.2</td>
<td>1.14±0.03</td>
</tr>
<tr>
<td>F8</td>
<td>28.43±0.04</td>
<td>0.508±0.003</td>
<td>0.653±0.004</td>
<td>22.21±0.3</td>
<td>1.2±0.02</td>
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<tr>
<td>F9</td>
<td>28.43±0.04</td>
<td>0.487±0.003</td>
<td>0.602±0.006</td>
<td>16.6±0.3</td>
<td>1.24±0.05</td>
</tr>
</tbody>
</table>

4. Post Compression Parameters:
4.1. Uniformity of thickness and diameter: The crown thickness of individual tablet may be measured with Vernier calipers, which permits accurate measurements and provides information on the variation between tablets. Other technique employed in production control involves placing 5 or 10 tablets in a holding tray, where their total crown thickness may be measured with a sliding caliper scale. The tablet thickness was measured using Vernier calipers.

4.2. Weight variation: Twenty tablets from each formulation were selected randomly and weighed individually, average weight was determined. Individual tablets were weighed and then they were compared with average weight [39].

4.3. Tablet hardness: The resistance of tablets to shipping or breakage under the conditions of storage, transportations and handling before usage depends on its hardness. The hardness of tablet was measured by Pfizer hardness tester. The hardness was measured in terms of Kg/cm².

4.4. Friability: Friability of the tablets was determined using Roche Friabilator. This device subjects the tablets to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Pre weighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were then de-dusted using a soft muslin cloth and reweighed.

The friability (f) is given by the formula:

\[ \% \text{Friability} = \left( \frac{W_1 - W_2}{W_1} \right) \times 100 \]

Where ‘W1’ is weight of the tablets before the test and ‘W2’ is the weight of the tablet after the test. Limit: It should be not more than 1%.

4.5. Drug content uniformity: Weigh and powder the 20 Quinapril HCl SR tablets. Accurately weigh the powder containing about 20 mg (Theoretical) of Quinapril HCl, transfer it into a 100 ml volumetric flask, add 80 ml of distilled water and shake for 15 minutes.
Make up the volume with distilled water and filter it. Dilute 10 ml of this filtrate to 100 ml with distilled water. Measure the absorbance of the resulting solution at $\lambda_{\text{max}}$ of Quinapril HCl. From absorbance calculate the drug content (Practical). Then calculate the % drug content by the following equation \cite{140}.

$$\text{Percentage drug content} = \frac{\text{Practical drug content}}{\text{Theoretical drug content}} \times 100$$

Limit: The percentage drug content should be 100±15%

4.6. In-vitro dissolution studies:
Drug release from the CR tablets prepared was studied using 6 station dissolution test apparatus (Electro lab) employing a paddle stirrer at 50 rpm and at 37°C. Distilled water (900 ml) used as dissolution fluid. Samples of 5 ml of each were withdrawn at different time intervals over a period of 24 h. Each sample withdrawn was replaced with an equal amount of fresh dissolution medium. Samples were suitably diluted and assayed at 240 nm by using an Elico double beam UV - spectrophotometer. Prepared Diltiazem CR tablets compared with Diltiazem SR and DTM 90 SR Tablets (commercial) were also studied. The drug release experiments were conducted in triplicate. Summary of general in-vitro dissolution conditions employed throughout the study to determine the in-vitro dissolution rate for all the formulation is given in table.

5. Drug Release kinetics:
5.1. Zero order release rate kinetics:
To study the zero–order release kinetics the release rate data are fitted to the following equation.

$$F = K \cdot t$$

$F$ = fraction of drug release, 
$K$ = release rate constant
And $t$ = release time.

5.2. Higuchi release model:
To study the Higuchi release kinetics, the release rate data were fitted to the following equation,

$$K \cdot F = K \cdot t$$

Where,
$F$ = the amount of drug release,
$K$ = the release rate constant, and
$t$ = the release time.

When the data is plotted as a cumulative drug released versus square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to ‘$K$’.

5. Results and Discussion:
5.1. Organoleptic identification
Melting point (M.P):
Melting point of Quinapril HCl was found to be within the range as per literature and readings were given in below table. It is confirmed as pure compound.

5.2. Drug-Excipients Compatibility studies:
FTIR Spectrums of samples were shown in below figures.
Fig 17: FTIR spectrum of Quinapril HCl with HPMC K4M and MCC

Fig 18: FTIR spectrum of Quinapril HCl with HPMC K100M and MCC

Fig 19: FTIR spectrum of Quinapril HCl with Guargum and MCC
Table-14 Drug excipients compatibility results

<table>
<thead>
<tr>
<th>S. No</th>
<th>Drug-Excipients combination</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Quinapril HCl pure</td>
<td>Complies</td>
</tr>
<tr>
<td></td>
<td>API+ HPMC K4M and Microcrystalline cellulose</td>
<td>Compatible</td>
</tr>
<tr>
<td>3</td>
<td>API+ HPMC K100M and Microcrystalline cellulose</td>
<td>Compatible</td>
</tr>
<tr>
<td>4</td>
<td>API+ Guargum and Microcrystalline cellulose</td>
<td>Compatible</td>
</tr>
</tbody>
</table>

Pure drug of Quinapril HCl complies with the reference sample and the combination of API with different excipients show no deviation from pure drug. Hence there was no compatibility problem between API and excipients.

5.3. Angle of repose
The angle of repose of all the developed formulations F1 to F9 was found to be 28.43±0.52 to 33.66 ±0.03 C as indicated in Table. According to USP – if the angle of repose is 25 -35, it shows good flow property. So the present granules are within the limits.

5.4. Bulk and tapped densities
The bulk density of the formulations F1 to F9 was found to vary between 0.43± 0.001to 0.513±0.0005 gm/ml as indicated in the table. Tapped density was found to be 0.511± 0.012 to 0.523±0.0122gm/ml for formulations F1 to F9 as indicated in the table. Both are having low standard deviations.

5.5. Carr’s Compressibility Index
The carr’s index was found to be12.52±0.5 to 22.21±0.3% for formulations F1 to F9 as indicated in the table. These values were found to be within pharmacopoeial limits and having good to possible flow properties. The standard deviation was also very low.

5.6. Hausner’s ratio
Hausner’s ratio was found to be 1.12±0.02 to1.24±0.05 for the formulations F1 to F9 as indicated in the table. These values were found to be within the pharmacopoeial limits and showing fair to good flow properties.

5.7. Tablet thickness
The thicknesses of the tablets were found to be between 2.37±0.25 to 2.50± 0.17 mm for the formulations F1 to F9 as indicated in the table, which is in the acceptable range.

5.8. Tablet Diameter
The diameter of the formulations F1 to F9 was found to be 3.37 ±0.15 to 3.67± 0.23mm respectively as indicated in the table, which is in the acceptable range.

5.9. Weight Variation Test
The weight variation of tablets for all the formulations developed F1 to F9 is 101±2.6 to 99.6±1.52 mg respectively as indicated in the table. According to pharmacopeia tablets weighing between 80-250mg should not exceed a standard deviation of 7.5%. So the standard deviation of all the formulation batches did not exceed a SD of 7.5% hence the tablets comply with standard limits.

5.10. Tablet hardness
The hardness of the tablets of different formulations from F1 to F9 varied between 5.5±0.25 to 6.06±0.37 kg/cm² as indicated in the table. Generally the hardness varies in the range of 5 to 7 for Matrix tablets. So the formulated batches are within the predetermined limits.
5.11. Tablet Friability
The friability of the tablets was found for all the developed formulations from F1 to F9 as 0.16±0.015 to 0.34±0.03% respectively as indicated in the table. Usually more than 1% deviation is not accepted. A very low standard deviation of less than 1% was found in all the formulations. Thus the friability of all the formulations is within the pharmacopoeial limits.

5.12. Drug content of Quinapril HCl Matrix tablets:
The drug content was estimated in the tablets for all the formulations developed from F1 to F9. The drug content uniformity can be estimated. The drug content for the formulations F1 to F9 are 98.4±0.94 to 99.64±1.49 respectively as indicated in the table which is within the limits.

Table 3: Post compression parameters of the various batches of the Quinapril HCl tablets

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Thickness (mm)</th>
<th>Diameter (mm)</th>
<th>Weight variation (mg)</th>
<th>Hardness (kg/cm²)</th>
<th>Friability (%)</th>
<th>Drug content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>2.4±0.4</td>
<td>3.4±0.3</td>
<td>101±2.64</td>
<td>5.5±0.25</td>
<td>0.16±0.01</td>
<td>98.4±0.94</td>
</tr>
<tr>
<td>F2</td>
<td>2.5±0.17</td>
<td>3.33±0.2</td>
<td>97.3±2.51</td>
<td>6.6±0.3</td>
<td>0.33±0.03</td>
<td>95.5±2.91</td>
</tr>
<tr>
<td>F3</td>
<td>2.3±0.25</td>
<td>3.36±0.3</td>
<td>101±3.51</td>
<td>6.4±0.35</td>
<td>0.15±0.01</td>
<td>92.9±3.31</td>
</tr>
<tr>
<td>F4</td>
<td>2.5±0.35</td>
<td>3.56±0.3</td>
<td>99.3±3.05</td>
<td>5.5±0.2</td>
<td>0.26±0.02</td>
<td>100±0.88</td>
</tr>
<tr>
<td>F5</td>
<td>2.4±0.30</td>
<td>3.46±0.2</td>
<td>99.3±1</td>
<td>6.3±0.3</td>
<td>0.3±0.03</td>
<td>97.7±0.94</td>
</tr>
<tr>
<td>F6</td>
<td>2.4±0.15</td>
<td>3.6±0.2</td>
<td>99.6±1.52</td>
<td>6±0.3</td>
<td>0.34±0.03</td>
<td>99.6±1.49</td>
</tr>
<tr>
<td>F7</td>
<td>2.5±0.17</td>
<td>3.33±0.2</td>
<td>97.3±2.51</td>
<td>6.6±0.3</td>
<td>0.33±0.03</td>
<td>95.5±2.91</td>
</tr>
<tr>
<td>F8</td>
<td>2.3±0.25</td>
<td>3.36±0.3</td>
<td>101±3.51</td>
<td>6.4±0.35</td>
<td>0.15±0.01</td>
<td>92.9±3.31</td>
</tr>
<tr>
<td>F9</td>
<td>2.5±0.35</td>
<td>3.56±0.3</td>
<td>99.3±3.05</td>
<td>5.5±0.2</td>
<td>0.26±0.02</td>
<td>100±0.88</td>
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Fig 1: Thickness of quinapril sustained release tablets
Fig 2: Diameter of quinapril sustained release tablets

Fig 3: Weight variation of quinapril sustained release tablets

Fig 4: Hardness of quinapril sustained release tablets
5.13. *In-vitro drug release studies*

The drug dissolution studies were performed for all the formulations developed from F1 to F9. F8 Formulation was shown best in-vitro drug release profile (96.03% in 12 hrs) compare to other formulations.

**Table 4:** Percentage drug release of formulations

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>F1 (%)</th>
<th>F2 (%)</th>
<th>F3 (%)</th>
<th>F4 (%)</th>
<th>F5 (%)</th>
<th>F6 (%)</th>
<th>F7 (%)</th>
<th>F8 (%)</th>
<th>F9 (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>15.59</td>
<td>13.58</td>
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<td>10.56</td>
<td>11.56</td>
<td>17.09</td>
<td>9.55</td>
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<td>29.66</td>
<td>31.17</td>
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<td>28.66</td>
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<td>17.59</td>
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<td>25.64</td>
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Fig 7: *In-vitro* drug release study of F1, F2 and F3 formulations

Fig 8: *In-vitro* drug release study of F4, F5 and F6 formulations

Fig 9: *In-vitro* drug release study of F7, F8 and F9 formulations
The drug release kinetics explains the release pattern of all the formulations developed. The best formulation F8 follows Zero order kinetic and follows Higuchi mechanism.
6. Conclusion
The present investigation was concerned with the development of the sustained release tablets, which were designed to prolong the duration of action by oral administration. Various formulations were developed by using release rate controlling and gel forming polymers like HPMC K100M, HPMC K4M & Guar gum by wet granulation method. Different proportion of HPMCK 100M and guargum mucilage was associated with decrease in the overall cumulative drug release rate. Thus, we concluded that among all the developed formulations, F8 formulation extended the drug release longer period of time over 12 hrs when compare to other formulations. F8 was selected as the best formulation. From the result, it is evident that combination of HPMC K100M & Guargum mucilage (10% each) by forming a matrix, retards the release rate of drug and comparison with other formulations. These matrix tablets provided slow and complete release of Quinapril 12 hrs. Thus, the objective of the work was formulation of sustained release dosage form of Quinapril by using HPMC and Guarg gum as release rate controlling and gel forming agents has been achieved with success

7. References


