Original Research Article

Chronomodulated drug delivery system of urapidil for the treatment of hypertension

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Abstract

Introduction: Hypertension is a disease which shows circadian rhythm in the pattern of two peaks, one in the evening at about 7 pm and other in the early morning between 4 am to 8 am. Conventional therapies are incapable to target those time points when actually the symptoms get worsened. To achieve drug release at two time points, chronomodulated delivery system may offer greater benefits. Materials and methods: The chronomodulated system comprised of dual approach; immediate release granules (IRG) and pulsatile release mini-tablets (PRM) filled in the hard gelatin capsule. The mini-tablets were coated using Eudragit S-100 which provided the lag time. To achieve the desired release, various parameters like coating duration and coat thickness were studied. The immediate release granules were evaluated for micromeritical properties and drug release, while mini-tablets were evaluated for various parameters such as hardness, thickness, friability, weight variation, drug content, and disintegration time and in-vitro drug release. Compatibility of drug-excipient was checked by Fourier transform infrared spectroscopy and Differential scanning calorimetry studies and pellets morphology was done by Scanning electron microscopy studies. Results: The in-vitro release profile suggested that immediate release granules gives drug release within 20 min at the time of evening attack while the programmed pulsatile release was achieved from coated mini-tablets after a lag time of 9 hrs, which was consistent with the demand of drug during early morning hour attack. Pellets found to be spherical in shape with smooth surface. Moreover compatibility studies illustrated no deleterious reaction between drug and polymers used in the study. Conclusions: The dual approach of developed chronomodulated formulation found to be satisfactory in the treatment of hypertension.

Key words: Chronomodulated drug delivery system, immediate release granules, pulsatile release mini-tablets

INTRODUCTION

Circadian rhythm regulates many body functions in humans, such as metabolism, behavior, sleep patterns, and hormone production. Blood pressure also shows circadian rhythm variation and exhibits 2 times peaks of 7 pm in the evening, and 4 am in the morning.[1] The conventional drug delivery systems releases drug immediately and requires to be taken during the peak hours of disease attack and hence it is not feasible to use such systems targeting diseases with the symptoms prevailing during early morning hours. In such cases release of drug is preferred in pulses and these systems are termed as chronomodulated pulsatile drug delivery system.[2] The pulsatile effect, which shows the release of drug as a “pulse” after a predetermined lag time should be designed in such a way that a complete and rapid drug release should follow the lag time.[3] Urapidil is a postsynaptic alpha 1-adrenoceptor antagonist antihypertensive drug, which reduces the blood pressure by decreasing peripheral vascular resistance. Urapidil appears to be well-tolerated, with most adverse events being mild and transient. Urapidil improves myocardial oxygen consumption, systemic vascular resistance, left ventricular function, and cardiac output.[4] The plasma concentration decreases for 10 min and then remains at that level for about 1 h. The short mean serum half-life is 2.7 h. The plasma protein binding is 80%. Two factors modify the pharmacokinetics of Urapidil: Very old age, severe impairment of liver function. [5] There are three different stages of hypertension namely stage 1, stage 2 and severe hypertension. The therapy that is currently used against hypertension includes angiotensin receptor blocker, diuretics, calcium channel blockers, vasodilators and angiotensin converting enzyme inhibitors.[6] Therapy with modified release dosage forms with zero order drug release theoretically leads to controlled and constant levels of drug in plasma throughout the
day. The pulsatile drug delivery system is generally categorized as single unit systems or multiparticulate systems. Multiparticulate drug delivery system are preferred over single unit dosage forms because of the benefits like predictable gastric emptying, lower risk of dose dumping, flexibility in release patterns, increased bioavailability.[7] Minitabs are one such multiparticulate system which are filled in capsule and thus shows the benefit of tabletting within capsule. These minitabscan be scheduled to deliver the drug at different sites of the gastrointestinal tract. Minitabs are available in different sizes that solve the problem of drug loading and generally ranges from 1.5 to 4 mm in diameter. Additional layering can be done on the minitabs for controlling the release at different rates.[8] Qureshi et al. have developed a pulsatile drug delivery system targeting nocturnal asthma by formulating an effervescent core tablet and the coat containing rupturable and swelling polymers.[9] Similarly hollow microspheres of piroxicam pulsatile drug delivery system were formulated by Maghsoodi et al., for treatment of rheumatoid arthritis.[10] To overcome the drawbacks of conventional drug delivery system for treatment of diseases with circadian variation, here hypertension, the chronomodulated drug delivery system was prepared by formulating capsule filled with immediate release granules (IRG) and pulsatile release mini-tablets (PRM) containing pellets. As granules show immediate release so they can be preferred for release during the evening hours when there is mild attack of hypertension while the pulse dose will be released after predetermined lag time from mini-tablets during early morning hours when the attack of hypertension is at its peak. For the preparation of granules, general granulation method was used whereas the pulsatile release pellets were formulated by extrusion-spheronization method and finally compressed in mini-tableting within capsule. These minitabs can be scheduled to be taken around 7 in the evening.

MATERIALS AND METHODS

Materials

Urapidil was obtained from Lupin Ltd., Mumbai, India as gift samples. Polymers such as Eudragit S100, Eudragit NE 30D and Eudragit L30D 55 were gifted by Evonik Industries, Mumbai, India. Compritol 888 ATO was obtained from Gattefosse, Lyon, France. Avicel PH-101 (VIVAPUR®) was gifted by JRS pharma, Germany. Cross povidone (kollidon® VA64) was gifted by Signet Chemical Corporation Pvt. Ltd., Mumbai, India. Polyvinyl pyrollidone was purchased from Burgoyne Burbidges and corporation, Mumbai, India. Ethanol was purchased from Ureca Consumers Cooperation Stores Ltd., Ahmedabad, India. Sodium starch glycolate (SSG) was purchased from Shital industries, Ahmedabad, India. Microcrystalline cellulose (MCC), lactose, talc and magnesium stearate were purchased from Ahmedabad agency, Ahmedabad, India. Concentrated hydrochloric acid was obtained from Chemdye, Ahmedabad, India. Starch, sodium hydroxide pellets and potassium dihydrogen phosphate were purchased from Suvidhinath Laboratories, Baroda, India. All other chemical reagents and solvents used were of analytical grade.

Methods

Immediate release granules

Screening of excipients for the preparation of immediate release granules

The micromeritical properties describe the particle size, shape and its distribution which ultimately affects the stability, and hence it is an important factor for evaluation of granules.[31] Hence, the excipients like-lactose, MCC, starch paste, polyvinyl pyrollidone, SSG and cross povidone were selected and screened for obtaining desired micromeritical properties.

Preparation of immediate release granules

All the excipients except talc and magnesium stearate were mixed together in a mortar by geometric mixing. The drug was allowed to mix in a binder solution (polyvinylpyrrolidone [PVP] in ethanol). The cohesive mass was formed by adding binder solution to the excipients and was allowed to pass through sieve no. 10. The granules were allowed to dry at room temperature. After which they were again sifted through no. 20 sieve and retained on. 40. In the end talc and magnesium stearate was added to IRG to increase the flow property.

Characterization of immediate release granules

Micromeritical properties of immediate release granules

Prepared IR Granules were evaluated for micromeritical properties like % yield, Hausner’s ratio, Carr’s index, angle of repose and content uniformity for their desirable properties. The batch which showed the best results was selected for further characterization.

Dissolution testing of immediate release granules

100 mg of granules was filled in capsule were introduced in USP Apparatus I (basket) with 900 ml 0.1N HCl buffer (pH 1.2). The apparatus was set in motion for 75 rpm and the temperature was set at 37°C ± 0.5°C with sampling interval at 0, 5, 10, 15, 20, 30, 45 and 60 min. 5 ml aliquot was withdrawn and replaced with fresh 0.1N HCl buffer (pH 1.2) every time. The sample was diluted 10 times and was analyzed ultraviolet (UV)/visible spectrophotometer (Schimadzu Corporation) at 268 nm wavelength.

Pulsatile release mini-tablet

Pellets preparation

Screening of excipients for the pellets preparation

The pellets with round shape appearance and good extrudability are desired and hence the excipients such as lactose, Avicel PH-101, starch paste, polyvinyl pyrollidone, SSG, cross povidone, glycine and polyethylene glycol-400 (PEG-400) were screened for pellets preparation. The excipients with which the dumbbell shaped pellets were formed were excluded were excluded from the pellet preparation mass.

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Preparation of pellets
All the excipients except drug were sifted through no. 60 and were geometrically mixed together in a mortar. The drug was dissolved in isopropyl alcohol (IPA) which was used as a binding agent. The cohesive mass was prepared with desired consistency to make the mass extrudable. The cohesive mass was then allowed to pass through extruder and extrudates were formed. The extrudates were allowed to spheronize for 20 min in spheronizer to obtain round pellets. The pellets formed were allowed to dry at room temperature for 24 h.

Characterization of pellets

Micromeritical properties of pellets
The pellets were evaluated for different micromeritical properties such as particle size, % yield, Hausner’s ratio and angle of repose.

Encapsulation efficiency of pellets
Accurately weighed 100 mg of pellets was crushed in mortar and pestle and the powder was dissolved in phosphate buffer solution pH 6.8 (PBS). Necessary dilutions were made, and drug content was detected at 268 nm using UV/visible spectrophotometer. Amount of drug encapsulated and encapsulation efficiency was calculated using following formula:

\[
\text{Amount of drug encapsulated} = \frac{\text{Concentration from std curve} \times \text{dilution factor}}{1000} \tag{1}
\]

\[
\text{Encapsulation efficiency} = \frac{\text{Drug encapsulated/theoretical yield} \times 100}{100} \tag{2}
\]

Friability of pellets
Accurately weighed 6 g pellets were taken and put in DBK Roche friabilator and were subjected to friability for 4 min at 25 rpm. After the testing was done the pellets were reweighed, and friability was found out using DBK Roche friabilator.

Scanning electron microscopy of pellets
Scanning electron microscopy (SEM) studies were conducted because SEM gives the actual strikingly clear images with better magnification capacities and hence are preferred over the traditional microscopes. Characterization of surface morphology of pellets was done using SEM. The SEM studies are done to study the spherical nature and surface of the prepared pellets.

Mini-tablets preparation

Tableting of pellets
The pellets can be filled in capsule but when compressed into the tablet, it offers better advantages associated with it. Thus, pellets were compressed into tablet using cushioning agent Avicel PH-102. The cushioning agent is used to keep the pellets intact in tablets while compressing it into the tablet. The pellets having equivalent weight of 60 mg drug were used to compress into mini-tablets. The mini-tablets to be filled in capsule were calculated according to dose requirement.

Coating of mini-tablets

Screening of coating polymers
The coating with which the lag time of 7 h can be obtained was used as the criteria for screening of coating polymers such as Eudragit S-100, Eudragit NE 30D, Eudragit L 30D 55, Compritol 888 ATO.

Coating levels for coating of mini-tablets
The mini-tablets were coated using 5%, 7% and 10% coating solution of Eudragit S-100 in pan coater for 30-45 min and the coated mini-tablets were dried at 65°C temperature with blower attached with the pan coater itself.

Preparation of the coating solution
Eudragit S-100 was accurately weighed (9.75 g) and was allowed to dissolve in solution mixture of IPA (51.4 g), acetone (31.4 g) and water (4 g) for 30 min at magnetic stirrer. The solution mixture was divided into two equal halves and Eudragit S-100 was dissolved in one-half while in other half talc (0.5 g) and triethyl citrate (0.35 g) were mixed at propeller stirrer for 10 min. The second solution mixture was then incorporated into the first solution with constant stirring.

Postcompression characterization of mini-tablets

Weight variation of mini-tablets
Twenty mini-tablets were randomly selected, and weight variation test was conducted. The average weight and standard deviation were found out and reported.

Diameter and thickness of mini-tablets
Three mini-tablets from all the batches were randomly selected, and their diameter and thickness was measured using Vernier calipers.

Hardness of mini-tablets
Monsanto apparatus was used to measure the crushing strength or hardness of mini-tablets. Five mini-tablets were subjected to test, and their mean was calculated and reported.

Friability of mini-tablets
Ten mini-tablets were selected and subjected to friability using Roche friabilator.

Content uniformity test of mini-tablets
Three mini-tablets were crushed in mortar and pestle, and the powder was dissolved in 100 ml PBS pH 7.4. The samples were filtered, diluted and measured at λmax 268 nm for urapidil content. The drug content equivalent to the dose filled in capsule was calculated and compared with label claim.

In vitro dissolution study of mini-tablets
Mini-tablets (3) filled in capsule were placed in 900 ml 0.1N HCl, PBS pH 6.8 and PBS pH 7.4 as a dissolution medium for time period 3 h, 4 h and 3 h respectively and was maintained at temperature 37°C ± 0.5°C. Drug release was performed using USP type I apparatus (basket) at 100 rpm for 9-10 h. Aliquots
of 5 ml were withdrawn at specific time intervals, and fresh buffer was replenished every time. Samples were filtered, and absorbance was measured at $\lambda_{\text{max}}$ 268 nm after suitable dilutions. % drug release was calculated for each sample collected.

**Stability study of the optimized formulation**
The optimized formulation containing IRG and PRM filled in the hard gelatin capsule was kept in glass bottle fitted with metal screw cap was placed instability chamber at accelerated conditions at 40°C and 75% RH to determine shelf life.

**Drug excipient compatibility using Fourier transform infrared**
The drug-excipient interaction were studied using Fourier transform infrared (FT-IR 8400S, Schimadzu). IR spectra for drug and powdered tablets were recorded in an FT-IR spectrophotometer with KBr pellets. The spectra were scanned over 3600-400 cm$^{-1}$ range.

**Differential scanning calorimetry study**
A differential scanning calorimeter (DSC) analysis of pure drug and best formulation were carried out using Shimadzu DSC 60. The analysis was performed at a rate 10°C/min ranging from 20°C to 400°C temperature.

**Analysis of urapidil**

**Determination of ultraviolet maxima**
The $\lambda_{\text{max}}$ of urapidil is reported at 268 nm in literature so UV maxima were determined in water and $\lambda_{\text{max}}$ was found out 268 nm.

**Calibration curve plot of urapidil**
Calibration curve of urapidil was taken in 0.1NHCl buffer (pH1.2), PBS (pH6.8) and PBS (pH7.4).

**RESULTS AND DISCUSSION**

**Immediate release granules**

**Screening of immediate release granules based on micromeritical properties**
Uniform particle size distribution, shape and size were obtained for granules preparation by using excipients-MCC, PVP in ethanol and Cross povidone from the list of excipients to be screened. The two batches were prepared batch B1 and B2, using excipients lactose, starch and SSG for B1 and MCC, PVP in ethanol and Cross povidone for B2. Granules made using excipients lactose, starch paste showed poor flow properties, while using SSG as a disintegrant the disintegration time taken was >15 min. Based upon the results such as % yield (93.8%), Hausner’s ratio (1.36), Carr’s index (16.20) and angle of repose (23.70) indicating good flow property; batch B2 was selected as optimized formulation batch. Based on the optimized formulation further three different batches were made with varying concentration of diluent: Disintegrant and were evaluated for different testing. The final formulation of IRG is shown in Table 1.

**Table 1: Final formulation of IRG**

<table>
<thead>
<tr>
<th>Category</th>
<th>Drug/excipients</th>
<th>Amount (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>API</td>
<td>Urapidil</td>
<td>30</td>
</tr>
<tr>
<td>Diluent</td>
<td>MCC</td>
<td>58.33</td>
</tr>
<tr>
<td>Binder</td>
<td>PVP in ethanol</td>
<td>6.66</td>
</tr>
<tr>
<td>Disintegrant</td>
<td>Cross povidone</td>
<td>5</td>
</tr>
</tbody>
</table>

IRG: Immediate release granules, MCC: Microcrystalline cellulose, PVP: Polyvinylpyrrolidone, API: Active pharmaceutical ingredient

**Characterization and selection of batches**
From the above mentioned three batches, batch F3 was selected as the optimized batch as it showed the best result among all others. % Yield was found to be 87.23%, Hausner’s ratio 0.891, Carr’s index 18.45, Angle of repose 23.22 and content uniformity was reported 85.8%. These values indicated good flow properties as Hausner’s ratio was <1.25 which indicated good flowability. Carr’s index was within range of 16-20 which indicated fair flow property and angle of repose values showed excellent flowability.$^{[16]}$ The characterization of granules was done and is shown in Table 2.

**Table 2: Evaluation of IRG based on micromeritical properties**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>F1 (mean ± SD)*</th>
<th>F2 (mean ± SD)*</th>
<th>F3 (mean ± SD)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micromeritical properties</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% yield</td>
<td>77.05±0.30</td>
<td>87.20±0.22</td>
<td>87.13±0.11</td>
</tr>
<tr>
<td>Hausners ratio</td>
<td>0.85±0.01</td>
<td>0.81±0.009</td>
<td>0.87±0.01</td>
</tr>
<tr>
<td>Carrs index</td>
<td>17.04±0.12</td>
<td>23.26±0.30</td>
<td>18.42±0.02</td>
</tr>
<tr>
<td>Angle repose</td>
<td>26.98±0.12</td>
<td>23.07±0.18</td>
<td>23.15±0.08</td>
</tr>
<tr>
<td>Content</td>
<td>45.02±0.12</td>
<td>55.05±0.31</td>
<td>85.60±0.10</td>
</tr>
</tbody>
</table>

*(Mean ± SD) is done with n = 6 for all the batches F1, F2 and F3. SD: Standard deviation, IRG: Immediate release granules

**In vitro-dissolution of immediate release granules**
Batch F3 showed around 98% ± 0.005% (n = 6) drug release in 15 min in comparison to batch F1 and F2 with 50% ± 0.01% (n = 6) and 119% ± 0.01% (n = 6) that is, below and above the range.

**Pulsatile release mini-tablets**

**Pellets characterization**

**Screening of excipients for pellets**
Round pellets with good appearance were formed using excipients Avicel PH-101 (diluent), PVP (binder), IPA, water. The pellets with dumbbell shape were formed using excipients lactose, starch paste and hence these excipients were excluded. PEG-400 showed better elasticity than glycerine and disintegration of pellets was faster in cross povidone. Hence, the optimized formulation was selected for further analysis.
of pellets consisted of excipients Avicel PH-101, PVP, Cross povidone, IPA, water and PEG-400. The final formulation of pellets is shown in Table 3. From the above mentioned formula three different batches of pellets P1, P2, and P3 based on varying ratio of diluent and binder 75:7.5% for P1, 85:2.5% for P2 and 80:5% for P3 were prepared.

**Characterization and selection of batches of pellets**

Three batches were evaluated using different parameters and batch B3 was selected as the optimized batch as shown in Table 4. Particle size analysis (sieve analysis method) showed that pellets of P3 were 0.914 μm in size, Hausner’s ratio 1.16, Angle of repose 22.49, Friability 0.83% and encapsulation efficiency was 89.50 ± 0.67%.

**Characterization of pellets based on scanning electron microscopy studies**

The surface morphology of pellets was studied using SEM. The Figure 1 suggested that the surface of pellets was smooth.

**Mini-tablets formulation**

**Polymer selection**

From the listed polymers Eudragit S-100 was selected as the coating polymer at 10% coating level. Eudragit S-100 gave predetermined lag time of 9 h with burst release of 98% within 1 h.

**Coating of mini-tablet**

The coated mini-tablet was of pinkish orange color and round in shape with no color defect. The tablet was free from chipping, picking or capping with shows the integrity of tablet. The weight gain after coating was about 7-8% and the final tablet weight was noted as 70 mg.

**Postcompression characterization of mini-tablet**

The pellets and the cushioning agent used for compression of tablets showed good flow property and hence the tablets obtained were of uniform weight [17]. The mean weight of mini-tablet was 70.34 ± 0.57 mg (n = 20). The USP specification is ±10% for tablets weighing 130 mg or less, this shows that mini-tablets passed the weight variation test. The mean diameter of mini-tablet was found to be 6.0 ± 0.0 mm and thickness was 3.64 ± 0.29 mm (n = 6) (mean ± standard deviation [SD]). Mean hardness was found to be 3.75 ± 0.27 kg/cm² (where n = 6) indicating that mini-tablets are of sufficient strength to withstand the physical attrition and impact. The % friability was <1% which suggests good mechanical resistance. The drug content was 91.65 ± 0.69% (mean ± SD, where n = 6).[18]

**In vitro dissolution study of mini-tablets**

Level mini-tablets showed lag time of 6 h that was also undesirable which is shown in Figure 2.

**Results of stability studies**

The stability study of capsule containing IRG and PRM was kept at accelerated conditions (40°C and 75% RH) for the period of 1-month. [19] The evaluation was done using parameters such as appearance of capsule, while drug content and drug release of

![Figure 1: Scanning electron microscopy image of pellets](image1)

![Figure 2: Dissolution profile of mini-tablets](image2)
IRG and mini-tablets were checked. The Figures 3, 4 and Table 5 showed that the formulation remained stable throughout the period of 1-month.

**Drug compatibility study by Fourier transform infrared spectroscopy**

The FT-IR spectra of drug + excipients shows that there were no changes in the peak of drug which suggests that there was no interaction between drug and excipients as shown in Figure 5 (Peak a-FT-IR spectra of physical mixture (Drug + excipients) overlapped with the FT-IR spectra Peak b of pure drug).

**Differential scanning calorimeter study of urapidil and Eudragit S-100**

The DSC study indicated that there was no endothermic reaction between drug and polymer (Eugragit S-100) used in the study as no shift of peak is observed as shown in Figure 6 (Peak [a]-DSC image of pure drug overlapped with DSC image of Peak [b]-urapidil + Eudragit S-100).

**Table 5: Stability study of optimized formulation**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Initial</th>
<th>After 1-month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance of capsule</td>
<td>Good</td>
<td>Good</td>
</tr>
<tr>
<td>Drug content of granules (%)</td>
<td>85.6±0.24*</td>
<td>84.56±0.28*</td>
</tr>
<tr>
<td>Drug release from granules (%)</td>
<td>99.02±0.022*</td>
<td>96.04±0.017*</td>
</tr>
<tr>
<td>Hardness of mini-tablets (kg/cm²)</td>
<td>4.25±0.21*</td>
<td>4.50±0.76*</td>
</tr>
<tr>
<td>Friability of mini-tablets (%)</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Drug content of mini-tablets (%)</td>
<td>89.89±0.21*</td>
<td>87.34±0.31*</td>
</tr>
<tr>
<td>Drug release from mini-tablets (%)</td>
<td>98.43±0.012*</td>
<td>96.11±0.016*</td>
</tr>
</tbody>
</table>

*(Mean ± SD) is done with n = 6 for all the **marked parameters, SD: Standard deviation

**Analysis of urapidil**

**Ultraviolet absorption maxima**

During scanning with the 100 μg/ml of sample urapidil exhibited UV absorption maxima at 268 nm.

**Calibration curve of urapidil**

The calibration curve of Urapidil was taken in three media:

1. HCl buffer pH 1.2,
2. PBS pH 6.8 and
3. PBS pH 7.4. The linearity range was between 5 and 14 μg/ml for the entire buffer media as the solubility of urapidil is pH independent.

**CONCLUSION**

Till now for Urapidil several pharmacokinetic related articles have been described in the public domain. However, to the best of our knowledge related to formulation of Urapidil is not yet reported in India. Chronomodulated therapy using Urapidil reduces blood pressure without altering heart rate. The oral formulation is an effective choice in patients with hypertension and concomitant dyslipidaemia or type 2 diabetes mellitus, in whom the drug does not adversely affect and may improve lipid profiles and glucose metabolism. Moreover, extension of
this work is carried out with animal study that supports the effectiveness of urapidil in hypertension. Thus, urapidil may be a useful alternative to currently available antihypertensive agents.

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