Formulation and the *in-vitro* and biopharmaceutical evaluation of sustained release tablet of verapamil HCL using precirol ATO 5 through melt granulation technique

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Sustained release tablet of Verapamil hydrochloride (VPH) was prepared by using Precirol ATO 5 (PREC) by direct compression of matrices prepared by using the melt granulation technique. The effect of different concentrations of PREC on the *in-vitro* drug release of VPH was studied by comparing it with the marketed formulation and percent release given in USP for VPH extended release tablets. Effect of release enhancers such as microcrystalline cellulose (MCC) and lactose on *in-vitro* drug release was also studied. Biopharmaceutical evaluation of the satisfactory formulation was also performed in order to estimate the maximum concentration of drug in plasma (Cₘₐₓ), time required to reach maximum concentration (tₘₐₓ), elimination rate constant (k), elimination rate constant (t₁/₂), area under curve (AUC₀ₐ₀ and AUC₀₋₂ₐ), apparent volume of distribution (Vₐ) and mean residence time. The results showed that PREC can be utilized as the matrix forming agent to sustain the release of VPH. The results of biopharmaceutical evaluation showed that the rate of absorption appeared to be more sustained, resulting in a more uniform plasma concentration profile of VPH. More bioavailability was noted with the sustained release formulation even though the drug has substantial first pass metabolism. The results indicated that it is possible to make once-a-day sustained-release tablet of VPH by using the melt granulation technique.

**Key words:** Biopharmaceutical evaluation, melt granulation, precirol ATO 5, sustained release, verapamil hydrochloride

INTRODUCTION

Verapamil hydrochloride (VPH) is a calcium channel-blocking agent used in the treatment of angina pectoris, hypertension and cardiac arrhythmia. It is completely absorbed from the gastrointestinal tract. Its biological half-life is 4 to 6 h with a usual dose of 40 to 240 mg three times a day. Because of the high frequency of administration and short biological half-life, VPH was considered as an ideal drug for designing sustained release (SR) formulation.[¹,²]

Waxes have been extensively investigated for sustaining the release of drugs. In forming a wax matrix system, different processing methods such as dry blending (direct compression), wet granulation, melt granulation and extrusion spheronization are used.[³,⁴] The sustaining effect by simply incorporating wax into granulation is not sufficient, especially for highly water-soluble drugs. It has been reported that formulation and process variables, including the manufacturing process, influence the physical properties of the blends and granules and affect the resulting dissolution profiles of tablets.[⁵]

Melt granulation is the process in which granulation is obtained through the addition of meltable binder that melts/soften at relatively low temperatures; after melting, the binder acts as binding liquid. There is no need of drying steps because dried granules are obtained by cooling it to room temperature. Moreover, the amount of liquid binder can be controlled precisely, and the production and equipment costs are reduced. This method can be used for granulating water-sensitive materials and producing SR granulation.[⁶,⁷]

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Glyceryl palmitostearate (Precirol ATO 5) is a mixture of mono-, di-, and triglycerides of C₁₆ and C₈ fatty acids, freely soluble in chloroform and dichloromethane and practically insoluble in ethanol (95%), mineral oil, and water. Glyceryl palmitostearate is used in oral solid-dosage pharmaceutical formulations as a lubricant.⁹

Hence, the present study aims towards formulation and the in-vitro and biopharmaceutical evaluation of SR matrix tablet of VPH by melt granulation technique using PREC as meltable binders.

**MATERIALS AND METHODS**

**Materials**
Verapamil hydrochloride (VPH) was obtained as a gift sample from Ranbaxy Research Laboratories, Gurgaon. Precirol ATO 5 was obtained as gift samples from Colorcon Asia Pvt. Ltd., Goa. All other chemicals were of analytical grade.

**Methods**

*Preparation of matrices by melt granulation*

The PREC melted in porcelain dish on a water bath maintained at constant temperature of 75°C. VPH was gradually added to the molten wax with continuous stirring. The molten mixture was allowed to cool and solidify at room temperature. The drug was present in its solid form within the molten mixture. The solidified mass was pulverized in mortar and sieved through a 16-mesh screen.¹⁰ Matrices of different batches F1, F2 and F3 for sustained release tablet of VPH was prepared using 15%, 20% and 25% of PREC, respectively.

**Evaluation of SR matrices**

Granules were evaluated for various parameters such as particle size distribution, angle of repose, bulk density, compressibility index, Hausner’s ratio¹¹,¹² and Kawakita plot.

**Kawakita plot**

The flowability and compaction behavior of the granules of different batches was studied by using Kawakita plot. The reduction in volume after tapping (using measuring cylinder) was noted. Further, the plot of number of tapping vs the degree of volume reduction was plotted, and the values of “a” and “b” were calculated by using the following equation:¹³

\[ \frac{n}{c} = \frac{n}{a} + \frac{1}{ab} \]

Where, “n” is the number of tapping, “c” is the degree of volume reduction equal to

\[ c = (V_0 - V_\infty) / V_0 \]

Where, \( V_0 \) is initial volume before tapping and \( V_\infty \) is volume after tapping.

**Drug-wax interaction study**

*FTIR*

Pure drug, wax and prepared matrices were subjected to IR spectroscopic study using FTIR spectrophotometer (Shimadzu, 8400S, Japan).¹⁴

**X-ray diffractometry**

The X-ray diffraction patterns of granules were determined using a Phillips PW-3710 X-ray diffractometer. Samples were irradiated with monochromatized Cu Kα radiation (1.542 Å) and analyzed between 2° and 60° (2θ). The range and chart speed were 2 × 10⁻² cycle per second and 10 mm/20, respectively.¹⁵

**Preparation of tablets**

The granules that passed through 16 mesh sieve were mixed with lactose and compressed into a tablet with 10 mm deep concave punch using single punch tablet machine (Cadmach mach. Comp, CMS, H/338/88).

**Evaluation of tablets**

Prepared tablets were evaluated for thickness, weight variation, drug content, hardness, friability and in-vitro release studies.¹⁶

**In-vitro dissolution study**

*In-vitro* drug release study for the prepared matrix tablets was conducted for period of 8 hours by using a six-station USP XXVII type 1 apparatus (Electrolab Tablet dissolution tester USP, TDT-06P) at 37 ± 0.5°C and 100-rpm speed. The dissolution studies were carried out in acid buffer of pH 1.2 for one hour and in Phosphate buffer pH 6.8 for further seven hours under sink condition. At one hour and then 2, 3.5, 5 and 8 h intervals, 5 ml samples were withdrawn from the dissolution medium and replaced with fresh medium to maintain constant volume. After filtration, the sample solution was analyzed at 278 nm for VPH by a UV-spectrophotometer (Shimadzu UV-1700). The amounts of drug present in the samples were calculated with the help of appropriate calibration curve constructed from reference standard. Further, the in-vitro drug release study for the marketed tablets (Calaptin SR 120 mg) was conducted.¹⁷

**Data analysis**

To analyze the mechanism for the release and release rate kinetics of the dosage form, the data obtained was fitted in zero order-, first order-, Higuchi matrix, Korsmeyer-Peppas and Hixson Crowell models. The best-fit model was selected by comparing the R² values obtained.¹⁸

**Scanning electron microscopy**

Tablet samples (batch F2) were removed from the dissolution apparatus at predetermined time intervals and kept in oven at 40°C for some time; these samples were then sectioned through the undisturbed part of tablet. Further, the samples were coated with gold and visualized under a scanning electron microscope (SEM) (JEOL JSM-6360, Japan).
**Biopharmaceutical evaluation**

*In-vivo* study was carried out on batch F2 and marketed formulation to determine some biopharmaceutical parameters such as elimination rate constant (*Slope K*, 1/h), plasma half life (*T1/2*, h), area under curve at last to the last measurable concentration (AUC_{(0-t)}, µg·h/ml) area under curve from zero to infinity (AUC_{(0-∞)}, µg·h/ml), volume of distribution (V, L/Kg), maximum concentration (C_{max}, µg/ml), time required to reach maximum concentration (T_{max}, h) and mean residence time (MRT, h).[19]

Rabbits (New Zealand, White) of either sex weighing (2.5 to 3.0 kg) were divided into 3 groups, each consisting of 3 animals. The first group received a tablet of batch F2. The second group received the marketed SR tablet of VPH, and the third group was kept as control. The tablets were put behind the tongue to avoid their destruction due to biting. Food was withdrawn from the rabbits 12 h before the administration of tablet. All rabbits had free access to water throughout the study. The Institutional Animal Ethical Committee approved the protocol for this study. Blood samples were collected from marginal ear vein at time intervals of 0, 1, 2, 3.5, 5, 8 and 12 h.[20] For determination of drug plasma concentration, the collected blood was centrifuged for 5 min at 5000 rpm (Elektrocraft (India) Pvt. Ltd.). Aliquot portion of 1 ml plasma was transferred into the separating funnel, and drug was estimated by reported extractive spectrophotometric determination.[21]

**RESULTS AND DISCUSSION**

**Preparation of matrices by melt granulation**

It was easy to prepare SR matrices of VPH by the melt granulation technique.

**Evaluation of granules**

Result of particle size distribution showed that the amount of fine powder (size <250 µm) and the amount of big lumps (size >1000 µm) were less. The main fraction was 250-1000 µm, and the maximum percentage of granules was present in this range. The angle of repose of matrices of all the batches was found to be in the range of 15.28 ± 0.06 to 17.54 ± 0.03, indicating excellent flow property. The loose bulk density and tapped bulk density for all three batches varied in the range of 0.403 ± 0.02 gm/ml to 0.533 ± 0.04 gm/ml and 0.473 ± 0.04 gm/ml to 0.64 ± 0.03 gm/ml, respectively. The obtained values were within the acceptable range. These results may further influence properties such as compressibility and tablet dissolution. The percent compressibility for all batches were within the range of 14.79 ± 0.04 to 16.71 ± 0.02, and Hausner’s ratio was found to be in the range of 1.17 ± 0.01 to 1.20 ± 0.02, which showed that all batches have high compressibility and good flow properties.

**Kawakita plot**

Kawakita plot is used to analyze the behavior of powder from the bulk density state to the tap density state. The constants “a” and “b” of Kawakita plot were determined from the slope and intercept of graph of n/c versus the number of tapping. The value of a indicated compressibility or densification due to tapping and b indicated the rate of achieving final packing. The small value of a and high value of b indicated high flowability and low cohesiveness.

The studies on Kawakita plot for all batches showed that the value of a was least, and b was the maximum in granules of all three formulations, indicating high flowability, as shown in Table 1 and Figure 1.

**Drug-wax interaction study**

**FTIR**

IR Spectrum of the prepared granules were compared with that of pure drug IR spectra and no significant change was observed in the appearance of characteristic peaks of the pure drug spectra. This indicates that the drug is compatible with the PREC.[22]

**X-ray diffractometry**

To confirm the crystalline nature of VPH in granules, X-ray diffraction (XRD) analysis was performed.[23] Diffractogram (intensity vs 2θ°) of untreated VPH shows that drug is crystalline as demonstrated by numerous sharp and intense peaks. Granules prepared by using VPH and meltable binders showed no potential interaction between drug and wax. However, the XRD pattern of VPH-meltable binder showed most resemblance with the XRD pattern of pure meltable binders. This might be due to efficient coating of meltable binder on VPH particles.[23]

**Table 1: Values of slopes (m, a and b) and coefficient (r) from Kawakita plot**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>m (slope)</th>
<th>a</th>
<th>b</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>F2</td>
<td>4.633</td>
<td>0.2158</td>
<td>0.3414</td>
<td>0.9972</td>
</tr>
<tr>
<td>F5</td>
<td>3.845</td>
<td>0.2600</td>
<td>0.3547</td>
<td>0.9978</td>
</tr>
<tr>
<td>F8</td>
<td>7.797</td>
<td>0.1282</td>
<td>0.4435</td>
<td>0.9971</td>
</tr>
</tbody>
</table>

![Figure 1: Kawakita plot](image-url)
Preparation of tablets
VPH tablets were prepared successfully by melt granulation technique.

Evaluation of tablets
In weight variation test, the pharmacopoeial limit for the percentage of deviation for tablets of more than 250 mg is ±5%. The average percentage deviation of all tablets was found to be within the limit; hence, all formulations passed the weight variation test. The drug content was found to be uniform among all formulations and ranged from 98.10 ± 0.32 to 99.88 ± 0.16%. The hardness of tablets of all formulations were in the range of 5.7 ± 0.31 to 7.2 ± 0.44 kg/cm². As the concentration of lipophilic binder increases, cold welding of the waxes increases in melt granules, thereby increasing the tablet hardness.[23] The friability of tablets of all formulations was in the range of 0.25 ± 0.01 to 0.41 ± 0.02%, i.e., less than 1%. The thickness of tablets ranged from 5.236 ± 0.02 to 5.246 ± 0.04. All formulations showed uniform thickness [Table 2].

In-vitro dissolution study
Effect of different concentrations of PREC on drug release
From the results, it was found that the release of VPH from tablet decreases with an increase in the concentration of PREC [Figure 4]. It may be due to the slower penetration of dissolution medium in matrices due to increased lipophilicity of waxy substances.[24]

Results also showed that release of batch F2 containing 20% of PREC was equivalent to that of the marketed formulation. Hence, F2 formulation was considered as satisfactory and used for further study.

Data analysis
The mechanism of drug release from wax matrices has been a matter of controversy since wax systems tend to be a crude and more heterogeneous than other classes of polymeric systems.[25]

From the results, it was observed that for the marketed preparation, the best fitting linear parameter was that of the Higuchi matrix model. This indicates that the drug release is controlled by the diffusion of the drug through the pores. It was also observed that batches F1, F2 and F3 were best fitted in Hixson-Crowell, first order- and Korsmeyer-Peppas models, respectively [Table 3].

Effect of release enhancers such as microcrystalline cellulose and lactose
From results, it was found that the release of VPH increases with the concentration of microcrystalline cellulose (MCC) and

<table>
<thead>
<tr>
<th>Batch code</th>
<th>Thickness (mm)</th>
<th>Hardness (kg/cm²)</th>
<th>Friability (%)</th>
<th>Drug content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>5.246 ± 0.04</td>
<td>5.7 ± 0.31</td>
<td>0.41 ± 0.02</td>
<td>98.10 ± 0.32</td>
</tr>
<tr>
<td>F2</td>
<td>5.236 ± 0.02</td>
<td>6.8 ± 0.57</td>
<td>0.35 ± 0.03</td>
<td>99.88 ± 0.16</td>
</tr>
<tr>
<td>F3</td>
<td>5.239 ± 0.03</td>
<td>7.2 ± 0.44</td>
<td>0.25 ± 0.01</td>
<td>98.77 ± 0.76</td>
</tr>
</tbody>
</table>

*All values represent mean ± standard deviation (n = 3)*

Figure 2: IR spectra of VPH, PREC and melt granules of VPH:PREC

Table 2: Evaluation of tablet parameters

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lactose. Results also showed that lactose produces a higher release of drug compared to MCC. It was because of the rapid solubility of lactose and its tendency to form pores in matrix; this allows the dissolution medium to penetrate the matrix and dissolve the drug.\cite{26}

### Scanning electron microscopy

SEM photomicrograph of the tablet of batch F2 taken

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**Table 3: Model fitting for sustained release tablet of Verapamil hydrochloride**

<table>
<thead>
<tr>
<th>Batch code</th>
<th>Best fit model</th>
<th>n</th>
<th>k</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marked</td>
<td>Matrix</td>
<td>0.5452</td>
<td>2.4960</td>
<td>0.9834</td>
</tr>
<tr>
<td>F1</td>
<td>Hixson-crowell</td>
<td>0.3326</td>
<td>44.558</td>
<td>0.9990</td>
</tr>
<tr>
<td>F2</td>
<td>First order</td>
<td>0.1106</td>
<td>52.199</td>
<td>0.9993</td>
</tr>
<tr>
<td>F3</td>
<td>Korsmeyer-peppas</td>
<td>0.8066</td>
<td>13.4395</td>
<td>0.9921</td>
</tr>
</tbody>
</table>

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**Figure 3:** XRD patterns of VPH, PREC and melt granules of VPH:PREC

**Figure 4:** Dissolution profile of formulations F1, F2, and F3 and the marketed product (M)

**Figure 5:** XRD profiles of VPH, PREC, and VPH:PREC melt granules.
at different time intervals after dissolution experiment showed that matrix was intact and pores were formed throughout the matrix [Figure 5]. SEM photomicrograph of the surface of fresh tablet (at 0 h) did not show any pores. In photomicrographs at 1, 2, 3.5 and 8 h, the arrows indicated the pores with increasing diameter. Hence, the formation of pores on tablet surface indicates that erosion mechanisms are responsible for sustaining the release of VPH from formulated melt granulation tablet.

**Biopharmaceutical evaluation**

Plasma concentration and biopharmaceutical parameters after oral administration of the formulated tablet of batch F2 and marketed SR tablet are summarized in Figures 6 and 7 and Table 4.

**CONCLUSION**

Among all the three batches, batch F2 containing 20% of PREC showed *in-vitro* drug release of 86.496 ± 0.094%, which was equivalent to the marketed preparation. Therefore, it is considered as the most promising formulation. From the effect of release enhancers such as MCC and lactose, it can be concluded that the control of these factors can be successfully
used to modulate the release rate from matrices. Hence, it was confirmed in this study that PREC is an appropriate waxy material that can utilized as the matrix forming agent in melt granulation technique in order to sustain the release of water-soluble drugs such as VPH.

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