Development of Hot Melt Coating Technique for Taste Masking of Chloroquine Phosphate Tablets

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ABSTRACT

In the present study to mask the unpleasant taste of chloroquine phosphate, hot melt coating technique was used as a taste masking tool. Hot melt coating is a solvent free technology grants rapid, additionally economical coating process with reduced risk of dissolving drug during process and provide uniform application rate of coating agent. Precirol ATO 5 was used as hot melt coating material for taste masking. Tablets were prepared by wet granulation method and coated using hot melt coating technique. Coated tablets exhibited good uniformity of drug content. Amount of drug release from all batches were evaluated. Taste evaluation of hot melt coated tablets was done by using electronic tongue. Precirol ATO 5 was found to be a better taste masking agent when used by hot melt coating technique.

Keywords: Precirol ATO 5, Hot melt coating, taste masking.

INTRODUCTION

Coating is one of the effective techniques for taste masking of solid dosage forms. Traditionally sugar coating and various polymers were used to this end. Having some disadvantages i.e. it require longer processing time, use of organic solvents and when aqueous solvent used there is a risk of bacteriological contamination and toxicity as compared to Hot Melt Coating.

An innovative approach, hot melt coating has been reported in order to mask the poor taste of many APIs. In HMC technique, the coating material is applied on the substrate, in a molten state, and no solvent is needed[1], it can reduce coating time (no need for drying/evaporation step), production costs, safety measurements, solvent recovery and disposal processes [2].

HMC is carried out to coat capsules, granules, pellets, spherules and tablets. The coatings, which contain a lipid and an emulsifier, which facilitate the production of coated immediate-release products with a neutral taste [3,4], production of sustained release tablets, pellets, used in controlling the stability and release properties of the dosage form, used for enteric coating, preparation of orally disintegrating taste masked granules, and tablets.

Taste, odour and texture form important consideration in development of oral dosage forms, they ensure better patient compliance and good product quality. Taste masking of bitter drugs has achieved the importance as the most of the drugs are administered orally[5]. Various methods are used for taste masking of unpleasant drugs that include flavour’s and sweeteners[6,7], inhibiting bitterness [8,9], numbing of taste buds [10,11], prodrug, formation of different salts [12,13], complexation approaches, microencapsulation, multiple emulsion[14], using viscosity modifiers [15], vehicles and liposomes coating of drug particle[16] thereby, minimizing the interaction between drug and the taste bud.

The objective of this study is to evaluate effectiveness of hot Melt coating technique as an approach of taste masking by coating. Precirol ATO 5 was used as a HMC material for taste masking of chloroquine phosphate tablets. The bitterness masking of tablets were evaluated using electronic tongue and tablets were found to have taste protected.
MATERIALS AND METHODS:
The materials used for the preparation of tablets were: Chloroquine phosphate (Zim laboratories Kalmeshwar, Nagpur), lactose monohydrate (Loba chemicals, Mumbai), polyvinylpyrrolidone (Anabal fine chemicals, Mumbai), cross povidone (Anabal Fine Chemicals, Mumbai), colloidal silicon dioxide (Evonik), Magnesium stearate (Loba chemicals, Mumbai).

Precirol ATO 5 was received as a gift sample from (Gattefosse, Mumbai), calcium carbonate from (Lobachemicals, Mumbai), PEG 4000 (Lobachemicals, Mumbai) were procured locally.

Analytical method:
Analytical method for estimation of Chloroquine phosphate by UV-Visible Spectrophotometry:
Solution of chloroquine phosphate 1mg/ml was suitably diluted to produce solutions in concentration range of 5-30 μg/ml, the absorbance was noted at wavelength of 342 nm.

Preparation of uncoated chloroquine phosphate tablets (500mg):
Chloroquine phosphate tablets were prepared by wet granulation method, using polyvinyl pyrrolidone in ethanol (2 %) as binder. Wet granulation method was applied for preparation of chloroquine phosphate tablets. The wet mass was screened through 14 mesh, the granules were dried to constant weight hot air oven at 60 °C temperature. Then, the dried granules were passed through 18 mesh and mixed with magnesium stearate, colloidal silicon di-oxide and cross povidone were added. The resultant mix was evaluated for bulk density, angle of repose and Carr’s index and finally compressed using 10 mm concave punches (B tooling). Composition of chloroquine phosphate tablets was given in Table 1.

Table 1. Composition of uncoated chloroquine phosphate tablets (500mg).

<table>
<thead>
<tr>
<th>Sr.no</th>
<th>Ingredients</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Chloroquine phosphate</td>
<td>30 mg</td>
</tr>
<tr>
<td>2.</td>
<td>Lactose monohydrate</td>
<td>16.9 mg</td>
</tr>
<tr>
<td>3.</td>
<td>Polyvinyl pyrrolidone</td>
<td>5 mg</td>
</tr>
<tr>
<td>4.</td>
<td>Cross povidone</td>
<td>20 mg</td>
</tr>
<tr>
<td>5.</td>
<td>Colloidal silicon dioxide</td>
<td>1 mg</td>
</tr>
<tr>
<td>6.</td>
<td>Mg stearate</td>
<td>5 mg</td>
</tr>
</tbody>
</table>

Coating formula optimization for Hot Melt Coating: The quantity of the coating ingredients were decided after initial trials. The general formula for coating composition was arrived at as given in Table 3.

Table 3. General formula for Hot melt coating composition

<table>
<thead>
<tr>
<th>Sr.no</th>
<th>Ingredients</th>
<th>Quantity (gm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Precirol ATOS</td>
<td>6-8</td>
</tr>
<tr>
<td>2.</td>
<td>PEG 4000</td>
<td>3</td>
</tr>
<tr>
<td>3.</td>
<td>Calcium carbonate</td>
<td>1-3</td>
</tr>
</tbody>
</table>

Substrates were then rolled in the coating pan which was heated to a pan temperature of 60°C. The molten coating mass was then filled in spray gun and spraying was done with controlled rate. After the completion of application of coating solution, the substrates were allowed to roll for further 10 minutes during which the pan temperature was allowed to gradually come down. The substrates were then removed, cured for 5-10 minutes. Process parameters were given in Table 2.

Table 2. Process parameters for Hot Melt coating of tablets

<table>
<thead>
<tr>
<th>Process parameters</th>
<th>Settings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Coating time</td>
<td>30 min</td>
</tr>
<tr>
<td>2. Pan speed</td>
<td>23 rpm</td>
</tr>
<tr>
<td>3. Amount of coating solution</td>
<td>10 gm.</td>
</tr>
<tr>
<td>4. Tablet Bed temperature</td>
<td>60-70°C</td>
</tr>
<tr>
<td>5. Relative humidity</td>
<td>50°C</td>
</tr>
<tr>
<td>6. Atomizing air pressure</td>
<td>0-15 psi.</td>
</tr>
</tbody>
</table>

Experimental design:
A 3² factorial design, was used to optimize the quantities of precirol ATO 5 (wax) and calcium carbonate (release agent) for achieving coating level 10% w/w without adversely affecting the drug release. The factors and levels are given in the Table 4.

Table 4. Factors and Levels of DOE

<table>
<thead>
<tr>
<th>DOE</th>
<th>Factors and levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Precirol</td>
<td>+1 0 -1</td>
</tr>
<tr>
<td>2. Calcium carbonate</td>
<td>3gm 2gm 1gm</td>
</tr>
</tbody>
</table>

Responses | Goal
---|---
Coating level | Maximize
Dissolution (%) | Maximize

Coating level:
Coating level is generally defined as actual percentage weight gain relative to the theoretical 100 %weight gain of coating of tablets would mean no loss in coating.

Coating level = [(Wtg / Wgt) × 100%]

Where, Wgt is the theoretical % weight gain and Wtg is the actual% weight gain.

Coating level was determined by following equation:

% weight gain = [(Wta – Wtb) × Wtb] × 100%

Where, Wta and Wtb are the total batches weight before and after coating, respectively.

Coating level of F1-F9 batch was given in Table 5.

Evaluation parameters of tablets:
The uncoated tablets and coated tablets were evaluated for hardness, friability, uniformity of weight, disintegration and dissolution as per methods described in literature [19,20].

Drug content estimation: five tablets were weighed and powdered in a dry mortar. Powder equivalent to 500 mg of chloroquine phosphate was added and mixed thoroughly; the contents of the flask were heated while mixing on a hot water bath to dissolve drug. The solution was made up to volume with 0.1 N HCl and assayed chloroquine present in...
each test of tablet and was calculated using calibration curve.

**In-vitro Dissolution studies:**

In vitro dissolution testing was conducted to investigate the release rate of chloroquine phosphate hot melt coated tablets in comparison with marketed tablets in 900 mL of 0.1N HCl for 45 minutes. The temperature of the dissolution medium and the rate of agitation were maintained at 37 ± 0.50 °C and 100 rpm respectively. And 10 mL of dissolution medium was withdrawn at specific time interval and the volume replaced by fresh dissolution medium, pre warmed to 37 ± 0.50°C. The amount of drug dissolved was determined spectrophotometrically using UV spectrophotometer.

**Surface roughness:**

Surface roughness was measured visually and was graded 1 - 10 from better to best.

**Scanning electron microscopy:** Scanning electron microscopy of a coated tablet surface was taken, tablet surface was kept on double adhesive tape which kept on a stub, latter stub containing sample was placed in scanning electron microscope chamber. The scanning electron photo microgram was taken at accelerate voltage of 30KV, chamber pressure of 0.7 Torr at 500x and 1.00kxmagnifications. Make – carl Zeiss and Model No: Supra 5.

**Evaluation of taste masking by using electronic tongue:**

The electronic tongue developed by Analytical instrumentation laboratory, Pune. Provided valuable information about the evaluation of bitterness intensity as function of time. The instrument consisted of working electrode, reference electrode and auxiliary electrode.

**RESULT AND DISCUSSION:**

**Calibration curve of chloroquine phosphate drug:**

![Calibration curve of chloroquine phosphate in distilled water](image)

The standard calibration curve of chloroquine phosphate was established at 342 nm and the Beers law was found to be obeyed in concentration range of 5 - 30 µg/mL as indicated by 

\[ R^2 = 0.9946 \]

The equation line was found to be: 

\[ y = 0.0301x + 0.0031 \]

**Preparation of uncoated chloroquine phosphate tablets:**

Chloroquine has bulk density 0.43gm/ml and angle of repose 31.02°hence wet granulation was done to improve compression and flow properties. The precompression characteristics of prepared granules were bulk density 0.54 gm/ml, Carr’s index 11.94%, and angle of repose 26° show that the granules exhibited improvement in compression as well as flow properties.

The average weight of tablets was 0.537 gm, and all the tablets were within ±5% of it. Thus, the batches compiled uniformity of weight test. Also the hardness of tablets was in acceptable range 259.6-280.1 Newton, the friability was 0.119 % and a disintegration time was noted at 5 min 30 sec. hence core tablets was prepared for coating.

**Coating formula optimization for hot melt coating:**

For taste masking by HMC technique, precirol ATO 5 was selected, it is partial glyceride used as coating agent for taste masking, modified release of the dosage form. It has M.P.50-60°C, insoluble in water, and one of the effective solvent free alternative for Hot Melt Coating technique. The viscosity of molten precirol ATO 5 estimated at 65 °C at 33.5mPas obtained at shear rate 94.8 S⁻¹, which make it good partial glyceride for Hot Melt Coating. PEG 4000 which was used as a polymer, added in pharmaceutical coating formulations as plasticizer to reduce brittleness and increase the flexibility of the resulting film, and it play an important role for the weight gain of dosage form.[17]

**Procedure for Coating of chloroquine phosphate tablets by hot melt coating Technique in a coating pan:**

Waxes and excipients (le precirol ATO 5, PEG4000, Calcium carbonate) were melted in a separate container. Then, raised the temperature of molten mass slightly above the M.P. of coating agent. Preweighed the tablets (13.0294gm,) and then was rolled in the coating pan which was heated until the pan temperature of 60°C was attained. The molten wax sprayed over the tumbling tablet in a small installment with a constant rotation of pan(23rpm). Spraying was done withspary nozzle at controlled rate. After the completion of application of coating solution, the substrates were allowed to roll further for 10 minutes during which the temperature was allowed to gradually come down. The substrates were then removed and cured for 5-10 minutes. The coating level was determined by frequently taking weights of coated tablets to achieve desired coating level.

**Experimental Design:** A 3² design which revealed the effect of process materials on the responses as well as any interaction within was selected, Table 5.

<table>
<thead>
<tr>
<th>Sr.No</th>
<th>Precirol ATO 5(gm)</th>
<th>Calcium Carbonate(gm)</th>
<th>Coating level (%)</th>
<th>Drug Release (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>7</td>
<td>2</td>
<td>9.97</td>
<td>94</td>
</tr>
<tr>
<td>F2</td>
<td>6</td>
<td>2</td>
<td>9.8</td>
<td>93</td>
</tr>
<tr>
<td>F3</td>
<td>6</td>
<td>3</td>
<td>10.3</td>
<td>95</td>
</tr>
<tr>
<td>F4</td>
<td>8</td>
<td>2</td>
<td>10.13</td>
<td>91</td>
</tr>
<tr>
<td>F5</td>
<td>8</td>
<td>3</td>
<td>10.75</td>
<td>85</td>
</tr>
<tr>
<td>F6</td>
<td>8</td>
<td>1</td>
<td>10.44</td>
<td>89</td>
</tr>
<tr>
<td>F7</td>
<td>6</td>
<td>1</td>
<td>10.11</td>
<td>85</td>
</tr>
<tr>
<td>F8</td>
<td>7</td>
<td>1</td>
<td>10.47</td>
<td>83</td>
</tr>
<tr>
<td>F9</td>
<td>7</td>
<td>3</td>
<td>10.62</td>
<td>95</td>
</tr>
</tbody>
</table>
Optimization of Precirol ATO 5 (coating polymer) and Calcium carbonate (release compound): For taste masking of tablets, a taste masking layer prepared by conventional Hot Melt Coating Process, in which coating composition consists of a wax and one of the release agent. If the concentration of precirol ATO 5 increases, so there is an increase in coating level and eventually percentage of drug release decreases. The increase in quantity of release agent increases coating level and drug release. The factorial designs are very good tools to optimize quantities of formulation ingredients to achieve desired performance characteristics to the formulation. It also reveals the interactions within the two factors.

By using 3^2 factorial design, nine batches of hot melt coated tablets were prepared, varying two independent variables Precirol ATO 5 and calcium carbonate. The cumulative % drug release at 45 minutes and coating level (%) were taken as dependent variables and were determined.

The coating level was seen to be affected more significantly by calcium carbonate. Equation (1). However, at higher levels of calcium carbonate, the coating level declined which may be due to non-adhesion of added calcium carbonate. The precirol however had similar effects in high or low levels of calcium carbonate. fig. 2

The drug release increases with increasing concentration of Calcium carbonate, but it can be observed from 3D plot (fig. 3), that drug release is dependent more on releasing agent and precirol and had a very insignificant effect. Equation (2).

**Equation for coating level:**

\[
\text{Coating level} = +10.03 + 0.1850 \times A + 0.1083 \times B + 0.0300 \times AB - 0.0938 \times A^2 + 0.4817 \times B^2 \ldots (1)
\]

**Equation for % of drug release:**

\[
\% \text{ of drug release} = +93.44 + 0.3333 \times A + 5.50 \times B - 0.2500 \times AB - 0.6667 \times A^2 - 3.17 \times B^2 \ldots (2)
\]

Using desirability function, the numerical optimization was done and concentration for optimized batch selected was 7gm of precirol ATO 5 and 2gm of calcium carbonate (desirability=1.000). The optimized batch was prepared and evaluated which showed very less difference between predicted and observed values. Percentage predicted error of coating level was 0.9775% and drug release was 0.6847%. Thus, the model was established.

The formulations prepared as per the experimental design were evaluated and the analysis of experimental results was done by using Stat-Ease Design Expert. The ANOVA, P-value and Model F-value for coating level and drug release were obtained. Table 6.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Outcomes</th>
<th>Coating level</th>
<th>% of drug release</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Models</td>
<td>Quadratic</td>
<td>Quadratic</td>
</tr>
<tr>
<td>2.</td>
<td>Sum of squares</td>
<td>0.7627</td>
<td>203.36</td>
</tr>
<tr>
<td>3.</td>
<td>Diff</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>4.</td>
<td>Mean square</td>
<td>0.1525</td>
<td>40.67</td>
</tr>
<tr>
<td>5.</td>
<td>( R^2 ) VALUE</td>
<td>0.9829</td>
<td>0.9829</td>
</tr>
<tr>
<td>6.</td>
<td>F – VALUE</td>
<td>34.55</td>
<td>34.59</td>
</tr>
<tr>
<td>7.</td>
<td>P – VALUE</td>
<td>0.0075</td>
<td>0.0074</td>
</tr>
<tr>
<td>8.</td>
<td>ADEQUATE PRECISION</td>
<td>18.2484</td>
<td>13.8354</td>
</tr>
</tbody>
</table>

The Model F-value of all models implies the both models were significant. In coating level, the Model F-value of 34.55 implies the model is significant, there is only a 0.75% chance that an F-value this large could occur due to noise. In drug release, Model 1 has 0.74% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate both model terms are significant. If Values greater than 0.1000 indicate the model terms are not significant.

Higher \( R^2 \) value indicated good agreement between formulations variables and response parameters. Adequate Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Ratios of a coating level and % drug release indicate an adequate signal. Thus, models can be used to predict the values of the response parameters at selected values of formulation variables within the design space.
Evaluation of coated tablets with optimized parameters:
The average weight of tablets was 0.575gmandall the tablets were within ±9% of it, thus the batches complied uniformity of weight test. Also the hardness of tablets was in acceptable range 269.2– 280.1 Newton, the friability was0.19% and a disintegration time was noted at 26min.

Drug content estimation: The drug content uniformity of optimization batch was found to be the value ranged from 96.9±0.76 to 98.6±0.94, which was within acceptable limit.

In-vitro dissolution studies: Results of the dissolution studies of the hot melt coated tablet batches (F1-F9) which are given in the fig 4) dissolution studies of all batches were done. So it was found that F1 is a optimized batch. F1 batch shows more drug release as compared to marketed tablets.
Scanning electron microscopy:
The surface morphology of chloroquine phosphate wax coated tablet was studied by SEM. The morphology of tablets was observed uniform as shown in fig.5 and fig.6).

Evaluation of taste masking by using electronic tongue:
The e-Tongue distinguishes tastes based on specific interactions like hydrogen bonds and vander Waal’s interactions between samples at membrane interface which are detected by electrodes and converted into electrical signals. PCA compresses voltage into two principal components (PCA1 and PCA 2) which accounts for maximum variance and minimum correlation within data. Three solutions were prepared 2 mM, 8mM and 20mM, i.e low,Medium and at High concentrations. at each concentration drug show bitterness. and specifically at a very low concentration drug also shows bitterness; so it means that chloroquine phosphate bitter in nature and threshold bitterness concentration was found at 2mM concentration.

PCA analysis was performed on acquired data. it compresses the acquired data point in two principal component which has maximum variance and minimum co-relation with acquired data. The principal components were plotted. More the distance between PCA values, more is the difference in their bitterness intensity so as shown in fig.7 concluded that, as the concentration of drug increases its bitterness intensity also increases. PCA graph of wax coating formulation was shown in fig.8). Initially bitterness has not seen at 20sec, it was seen at 40 sec and 60sec 40 sec is near to bitter threshold of 2mM. So bitterness was seen at 40 sec, so we can put tablet on mouth upto 40 sec.

Fig.4) Cumulative percentage drug release of F1-F9 batches.

Fig.5) SEM Images at 500X magnification of precirol ATO 5 (wax) coated tablet surface.

Fig.6) SEM Images at 500X magnification of precirol ATO 5 (wax) coated tablet surface.

Fig.7) PCA graph of Drug (chloroquine phosphate) in comparison with bitter standard (quinine).
CONCLUSION

From the present study it was concluded that, coating agent precirol AT05 is efficient in masking of bitter taste of drug by Hot melt coating. The coating level of 10% W/W is require to mask complete bitter taste of drug as indicated by study. Thus, hot melt coating is effective, less time consuming, eco friendly for taste masking applications of solid oral dosage formand it was seen that dissolution rate of wax coated tablets was more as compared to marketed tablets.

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REFERENCES