Design and Optimization of Directly Compressible Matrix Tablets Of Recrystallized Metformin HCL Using Full Factorial Design

Adimoolam Senthil, Prasanthi Sri, Ahmad bin Mahmud and Natesan Gopal

Abstract—Metformin HCl is an oral anti-hyperglycemic agent used in the treatment of non-insulin dependent diabetes mellitus. Metformin HCl is highly water soluble (>300 mg/ml at 25°C), hygroscopic and presents stability problems. Consequently, there is a need to provide a free-flowing and cohesive metformin HCl capable of being directly compressed into strong tablets with an acceptable in vitro dissolution profile. The objective is to prepare metformin HCl tablets by direct compression. Different types of directly compressible excipients (diluents and binders) were evaluated to find the maximum amount of metformin HCl to be loaded in tablet for direct compression. An approach to further increase metformin HCl loading in tablets was designed by employing recrystallization technique such as anti-solvent method. Metformin HCl was recrystallized in the presence of different concentration of PVP K30 for different recrystallization time. A 3^2 full factorial design was employed to get the optimum processing conditions. The optimized batch was selected, where the recrystallization time was 4 h and PVP K30 concentration was 2% w/v. Kawakita, Kuno and Heckel analysis revealed that the packability and compressibility of recrystallized metformin HCl. Recrystallized metformin HCl was explored for the preparation of sustained release tablet using hydroxypropylmethylcellulose K15 M as matrix forming polymer. The release profiles adopted the Weibull model.

Keywords— Metformin HCl, Recrystallization technique, Hydroxypropylmethylcellulose

I. INTRODUCTION

Metformin HCl is an oral anti-hyperglycemic agent used in the treatment of non-insulin dependent diabetes mellitus. It has an absolute oral bioavailability of 40 to 60 % and gastrointestinal absorption is apparently complete within 6 h of ingestion.

Plasma half-life of metformin HCl is 1.5 - 4.9 h. A direct compression method was reported for the preparation of metformin HCl 500 mg extended-release tablet but on a commercial scale, this may create problems of powder flow down the hopper which would lead to weight variation, as well as poor content uniformity, hardness and friability due to its poor compressibility of metformin HCl.

II. MATERIALS AND METHODS

1. Development of directly compressible metformin HCl

   a. Evaluation of flow property and compressibility profile of metformin HCl.
   b. Preliminary studies on Silicified Microcrystalline Cellulose (SMCC) and Di-calcium Phosphate Dihydrate (DCPD) to find out their dilution potential.
   c. Optimization of the process parameters to get the recrystallized metformin HCl with best flow property and compressibility profile (3^2 factorial designs).
   d. Preparation and evaluation of metformin HCl tablet prepared by direct compression.
   e. Characterization of recrystallized metformin HCl by DSC, FTIR spectroscopy & SEM.

2. Exploration of directly compressible metformin HCl in development of sustained release tablets.

III. RESULT AND DISCUSSION

Metformin HCL as such exhibits poor flow property and compressibility profile. To improve flow property and compressibility profile, directly compressible diluents were incorporated in the formulation with an objective to compress more than 90% of the drug directly. Metformin HCl with SMCC and DCPD were tried in various ratios to form tablets. From the two DC diluents used, SMCC yields to be more promising as it has greater dilution potential. Kawakita, Kuno and Heckel analysis revealed that the packability and compressibility of recrystallized metformin HCl. Recrystallized metformin HCl was explored for the preparation of sustained release tablet using hydroxypropylmethylcellulose K15 M as matrix forming polymer. The release profiles adopted the Weibull model.
significant increase in dilution potential of the diluent to directly compress metformin HCl. But still the ratio 70:30 (Drug: Diluent + Binder) needs to be increased to cause more than 90% of metformin HCl compress directly. So instead of physical blending an alternative method (recrystallization) was thought to co-process metformin HCl with dry binders. Among the three polymers used previously as DC binder, namely PVP, L-HPC and EC; EC is water insoluble, so it was ruled out, while PVP and L-HPC were taken for further studies. Acetone was selected as anti-solvent for further study. For the recrystallization method, various literatures were cited. Among them, the method shown by Ford et al was sought attractive\(^5\). In the present work eight formulations F1-F8, were prepared by the recrystallization method used consists of adding solvent containing drug and polymer to anti-solvent. But there are various parameters affecting this process. Stirring rate, temperature and solvent addition rate are few to mention which can affect the yield.

A \(2^3\) full factorial design was employed to study the effect of mode of addition of solvent (\(X_1\)), temperature (\(X_2\)), and stirring rate (\(X_3\)) at two different levels i.e. low (-1) and high (+1). From the eight batches F8 showed acceptable yield (64%) of all other batches. Metformin HCl recrystallized in the presence of 2\% w/v PVP K30 solution gave acceptable results of flowability and compressibility.

A \(3^2\) full factorial design was employed to study the effect of concentration of PVP (% w/v) in the solution used to dissolve metformin HCl (\(X_1\)) and recrystallization time (\(X_2\)). Contour plot and response surface plot showing the effect of % of PVP (\(X_1\)) and recrystallization time (\(X_2\)) on % yield, Carr’s index and crushing strength for the optimized batch were shown in Figure 1.

FTIR spectra revealed no chemical interaction between metformin HCl and PVP K30 by recrystallization were shown in Figure 2. DSC curves indicated a slight decrease in melting point and a notable decrease in enthalpy of fusion (\(\Delta H_f\)) of treated metformin HCl, which indicates the conversion of needle shaped untreated metformin HCl crystals to nearly spherical shape due to formation of thin layer of PVP on their surfaces were shown in Figure 3. SEM micrographs supported these findings were shown in Figure 4. Moisture studies revealed the hygroscopic nature of treated metformin HCl. Stability studies of three months showed minimal change in tablet parameters and in vitro dissolution profile.
Recrystallized metformin HCl was explored for the preparation of sustained release tablet using HPMC K15 M as matrix forming polymer. As the polymer level was increased, the polymer gel formed is more likely to be resistant to drug diffusion and gel erosion. As the release rate limiting polymer changes from a glassy state to rubbery state, a gel structure is formed around the matrix which considerably decreases the release of drug since it has to diffuse through this gel barrier into the bulk phase. The faster drug release in case of formulation containing low amount of HPMC K15M may be due to less tortuous diffusion path. The release profiles adopted the Weibull model, showed the least value of sum of square of residuals and therefore it was used for further data analysis. The slope and intercept values for the three formulations (MS3 to MS5) were 0.7933, 0.8179, 0.8506 and -1.7688, -1.8984, -1.9891 respectively. Data mining was employed as per Kirilmaz procedure\textsuperscript{7} for model validation and optimization of the formulation. The equations for slope and intercept were evolved. The values of square of correlation coefficient (R square) for the equations of slope and intercept were 0.9933 and 0.9888 respectively. The high value of ‘R square’ indicates good correlation. Comparison of experimental (observed) and theoretical (predicted) values of drug release profile obtained using derived generalized Weibull equation were given in Table I. Based on the predicted value obtained from generalized Weibull equation batch with 43% w/w of HPMC K15M was selected for the model validation. Model validation was done by comparing the values of observed and predicted drug release for a check-point batch containing 50% drug (54.4% recrystallized metformin HCl) and 43% HPMC K15 M.

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<tr>
<th>POLYMER CONCENTRATION ( % w/w)HPMC K15M</th>
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<tr>
<td>35%</td>
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<tr>
<td>Predicted</td>
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<td>10 h</td>
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TABLE I: COMPARISON OF EXPERIMENTAL AND THEORETICAL VALUES OF DRUG RELEASE PROFILE
The theoretical and experimental release profiles showed no significant difference. The results reveal that the matrix system fabricated with 43% w/w HPMC K15M was able to provide the required release in first hour and modified release profile thereafter. The drug release profile of check-point batch was shown in Figure 5. Thus, Recrystallization of metformin HCl offers tremendous advantages in lieu of compressibility and sustained release as compared to untreated metformin HCl.

IV. CONCLUSION

The results of this investigation enabled us to fabricate hydrophilic matrices containing recrystallized metformin HCl. It is also demonstrated that the release of metformin HCl from directly compressed matrix tablets can be modified by changing the type and amount of polymer in the matrix tablets. Recrystallized metformin HCl enabled us to fabricate this directly compressible matrix tablet with high drug loading (50% w/w). This 500 mg tablet containing 250 mg metformin HCl could be given to the patient twice a day, along with sulfonyl-ureas as initial treatment of diabetes. This approach can be utilized for preparing 500 mg and 850 mg sustained release tablets.

REFERENCE