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Solid state characterization of Olmesartan medoximil solid dispersion and in-silico formulation design using Quality by design techniques engendered by definitive screening design

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Introduction:

Olmesartan medoxomil (OM) is employed for treating patients who are intolerant of ACE inhibitors. The challenge to the researchers is because of its poor oral bioavailability and poor solubility. The approach for this problem is to use a hydrophilic carrier in formulation of oro-dispersible tablet (ODT) which presents a suitable way to improve the bioavailability by using quality by design (QbD) techniques with design of experiments (DoE) which produce a robust and rugged formulation.

The focus of the research was to formulate OM/PVP solid dispersion (SD) and formulation of an Oro dispersible tablet (ODT) by QbD techniques. The main focus of this research is to provide a rugged and robust formulation using QbD concept with the application of Definitive screening design for optimization.

The dissolution studies of OM/PVP K30 1:1% w/w showed full release within 30 min which may be attributed due to the hydrogen bond formation between OM and PVP K30 in the FTIR spectra which enhanced the solubility. The present research highlights a thorough understanding of the dosage form development with the knowledge of the critical risks involved in formulation to have an impact on Critical Quality Attributes (CQAs). The Critical material attributes (CMAs) were refined by DoE using definitive screening design (DSD) to develop design space. Olmesartan medoxomil (OM) used an antagonist of angiotensin II receptor for the treating high blood pressure. OM administered as a prodrug, has few drawbacks that it is completely de-esterified to Olmesartan as an active metabolite. It acts by inhibiting the vasoconstrictor effects. The usual recommended initial dose is 20 mg per day. Several preparations containing Olmesartan medoxomil and other antihypertensives are available in the market . To overcome the drawbacks of low oral bioavailability the researcher aims to improve the dissolution of least water-soluble drugs by solubilization using some vehicle, reduction of particle size, solid dispersion and salt formation. The drugs polymorphism can be changed from crystalline to an amorphous state in solid dispersion system thus improving the solubility and also particle size reduction done for improved wettability. The drug solubility is also improved by the presence of the carrier which creates a microenvironment. Polyvinylpyrrolidone (PVP) is a synthetic high molecular weight polymer having linear groups of monomers of 1-vinyl-2-pyrrolidone exhibiting least toxicity with more hydrophilic property, physiological tolerance and enhances drug release and bioavailability [8] as it is having universal solubility in hydrophilic and hydrophobic solvents.

Taking all the above into account, the. The aim of this research work is to prepare solid dispersions of OM in PVP K30 using solvent evaporation technique and formulate it into an Oro Dispersible Tablet with QbD technology by using the design of experiments.

Objectives:

Olmesartan medoxomil, an active pharmaceutical ingredient, was procured from MSN organics Pvt. Ltd, Hyderabad, India. PVP K30, Crosspovidone and starch purchased from Ascot Pharmachem Pvt. Ltd, Vadodara, India, Mannitol, Aspartame and methanol purchased from Sigma Aldrich, Mumbai, India, Magnesium stearate S. D. Fine Chemicals.

Preparation of Olmesartan medoxomil solid dispersion:

Solid dispersions with mass ratio of OM to PVP K30 ranging from 1:0.5 to 1:1.5 were formulated by solvent evaporation method[9]. In brief, PVP K30 was dissolved in ethanol, followed by addition of OM. Ultra-sonication at room temperature was done for about an hour to dissolve the drug completely and the remaining solvent was subjected to reduced pressure for evaporation. The resulting product was dried for 24 h at room temperature over anhydrous CaCl2 desiccators in vacuum. The dried product was then pulverized and subjected through BSS 60# and stored in a desiccators and further evaluation done using Fourier transform infrared spectroscopy (FTIR Systronics, Ahmedabad, India).

Formulation of tablets with SD technology:

Listed ingredients were weighed in required quantity and passed through suitable mesh. Binder solution was prepared by dissolving in starch in required amount of hot water and it is added to the drug-ingredient mixture to get uniform mass and passed through the suitable sieve and dried for 4hrs in hot air oven at 450C. Lubricants were added to the dried granules and micrometric properties were analysed and compressed 5.2 mm concave punch. Formulated product was evaluated for physicochemical parameters.

Optimization of ODT parameters as per enhanced QBD:

Optimization of the formulation using design of experiments with QbD approach, QRM and knowledge management gives a robust formulation throughout the life cycle of the product.

Identification of CMA and CQA with justification:

CQAs are linked with the drug substance, drug product and excipients. Relevant CQAs were identified based on the experience and prioritized through QRM and experimentation was done to assess the extent of variation of CMA's impact on the CQA.

Risk assessment of material attributes by QRM is a scientific approach that help in identifying CMA and CPP which show effect on product CQAs (Table 1) along with justification Experimentation was done using Design of Experiments (DoE)

software to refine the list further to evaluate the importance of individual variables and interactions to gain a higher degree of understanding .

Optimization of material attributes and development of design space:

Based on Initial risk matrix analysis (IRMA), formulation understanding experiments viz DoE were implemented for the formulation. The effect of every independent CMAs on dependent CQAs (e.g. disintegration and dissolution) were analysed for establishment of Design space (DS) through timely evaluation of CQA which were modelled out with the target of achieving quality product. Definitive screening design (DSD) was used for optimization procedure for establishment of DS, because the design offers three levels and provides main effects estimation which were unbiased through any second order effects and requires only one trial greater than twice as many trials as there are factors and eliminates confounding effects on any pair of second order models thus favouring optimization of material attributes to achieve desired CQA. DSD was done using Design-Expert® software (Version 12, Stat-Ease Inc., Minneapolis, MN)[17]. Depending on IRMA, DoE were implemented for formulation having higher risk priorities.

Results:

The present work was aimed to prepare ODT for Olmesartan medoxomil solid dispersion to increase bioavailability. Among the various approaches involved ODT approach was selected as they are easy to fabricate and thereby enhancing the absorption of the drug. For this purpose, wet granulation technique was used with different excipients.

Drug-carrier interaction studies:

FT-IR spectra helps in interpreting the interaction between the drug and other materials as shown in (fig. 2 and 3). The spectra of pure OM showed bands at 3398.91 cm-1 owing to N-H stretch, at 1706.98 cm-1 owing to C=O stretching, The spectra also showed bands at 1225.39 cm-1 owing to C-N bending. In the region, the 3398.91 cm-1 NH stretching vibration peak of OM disappeared in the SD. It seems that there is a formation of intermolecular hydrogen bond between -NH of OM and -C=O of PVP. Thus, the appearance of characteristic absorption bands of OM and the solid dispersion containing OM showed no interaction between the OM and excipients.

Formulation Development Study:

A Definitive Screening Design (DSD) with four factors and three levels were chosen to optimize varied response variables. Disintegration and Dissolution (Q15, Q30 i.e. % drug release at 15 and 30 minutes) were taken as response variables (CQAs) and the corresponding results were shown . The experimental results for disintegration and dissolution at 15 min & 30 min when compressed at hardness 8 kpa and thickness 2.5 mm indicate that all weight variation, thickness, friability and hardness were within the permissible limits of USP.

Summary ANOVA results of the model and influencing parameters:

This indicates the ANOVA for Response Surface Quadratic for disintegration was found to be significant indicating fitness of the choosen and Contour plot for disintegration indicates an interaction between the critical factors and response variables respectively. The 2D graph for disintegration indicates the effect of carrier and disintegrant on disintegration time. At high levels of disintegrant, the disintegration time decreases and carrier does not have much influence on disintegration time.

This indicates the ANOVA for Response Surface Quadratic for % drug release profile at 15 mins(Q15) was found to be significant indicating fitness of the choosen and Contour plot for % drug release profile at 15 mins(Q15) indicates an interaction between the critical factors and response variables respectively. The 2D graph for Q15 indicates that effect carrier and disintegrant on %drug release at 15minutes. As the carrier level increases from 10mg to 20mg dissolution increases and remains constant whne the carrier level further increases.

This indicates the ANOVA for Response Surface Quadratic for % drug release profile at 30 mins(Q30) was found to be significant indicating fitness of the choosen and Contour plot for % drug release profile at 30 mins(Q30) indicates an interaction between the critical factors and response variables respectively. The 2D graph for Q30 indicates that effect carrier and disintegrant on %drug release at 30minutes. As the carrier level increases from 10mg to 20mg dissolution increases and remains constant when the carrier level further increases. The dissolution % slowly increases as the amount of disintegrant increases from 15mg to 20mg.

After analysing the data obtained through ANOVA using the final equation, the desired goal for each CMA and CQA were chosen using numerical optimization option in Design Expert software. The goal selection starts at initial point and goes to a maximum where it was required to select a region where requirements meet the CQA. Graphical optimization showed the area of feasible response values in yellow colour. The gray shaded region indicates that the optimization criteria did not met as represented. The yellow region constituted a possible design space for robust and rugged Formulation. From the results obtained through design space, the risk assessment of the material attributes were updated as given.

Thus, a composition having desired level of excipients is mentioned. The optimized formulation has bulk density 0.295g/ml, angle of Repose 25°.56, Tapped Density 0.335 g/ml, Hausner’s ratio 1.15 and Carr’s index 11.94 %. The optimized formulation blend is compressed in to the tablets and quality control tests were done. The disintegration and dissolution results were found to be satisfactory and meeting the desired quality target product profile (QTPP).

Conclusion:

The possible enhancement of dissolution rate was due to solid dispersion containing 1:1 mass ratio of OM:PVP K30. The appearance of hydrogen bonding between the >NH of OM and –C=O of PVP K30 in SD characterised by FTIR leads to decrease in crystallinity and the primary reason for the marked increase of dissolution rate. The results showed that OM–PVP K30 SD formulated using solvent evaporation served as a means of increasing OM dissolution rates. The results of QRM study of ODT formulation proved that statistical tools of QbD helped in achieving the quality product throughout the lifecycle".