Olanzapine, improvement of biopharmaceutical performance in solid dosage form

Thesis

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Olanzapine, improvement of biopharmaceutical performance in solid dosage form

Abstract

Olanzapine is an effective antipsychotic drug used for the treatment of positive and negative symptoms of schizophrenia. It suffers from poor water solubility in addition to extensive first-pass metabolism in the liver to inactive metabolites, resulting in a poor oral bioavailability of nearly 60%. The intestinal lymph vessels drain directly into the thoracic duct, after that to the systemic circulation, consequently avoiding being subjected to the portal circulation.

Lipid-based formulations had been introduced in order to improve the bioavailability of orally administered drugs by targeting the lymphatic transport. Self-nanoemulsifying drug delivery system (SNEDDS) as lipid-based formulations has recently received increasing attention in the development of oral dosage forms with the aim of improving the solubility and bioavailability of lipophilic drugs. While SNEDDS usually use high amounts of low molecular weight liquid surfactant that may cause degradation, instability of the drugs and being moreover toxic for the gastrointestinal tract. Therefore, Pickering emulsions constitute an interesting alternative, where by the emulsion droplets are stabilised by solid particles alone or in combination with the low-molecular-weight liquid surfactants. These solid stabilised emulsions showed improved stability, especially at high internal phase ratio, when compared to the classical surfactant-based emulsions. The solid emulsifier, selected was the Cyclodextrins type which enhances the drug solubility, the drug stability and the drug loading.

To achieve these goals, the work in this thesis is divided into three chapters:

❖ **Chapter I: Formulation and evaluation of liquid self-nano emulsifying drug delivery systems and Pickering nanoemulsion systems.**

This chapter deals with the preparation, characterization and evaluation of olanzapine loaded self-nanoemulsifying drug delivery systems and Pickering nanoemulsion systems.

The work in this chapter complies the following:

Solubility study of olanzapine in different oil types either single oil or combination at different ratios.

Solubility study of olanzapine in different surfactants and different co-surfactants. Olanzapine showed highest solubility in 5 single oils at the following ascending order: Capmul® MCM, Labrafil® M 2125, Maisine™ 35-1, Labrafac™ CC and Miglyol® 812 N. Olanzapine showed highest solubility in Cremophor® EL (as surfactant) and Transcutol® HP (as co-surfactant).

Three ternary phase diagrams were prepared with oil and surfactant/co-surfactant ratios from 1:9 to 9:1. The phase diagrams were constructed and evaluated for the largest nanoemulsion area under the phase diagram. Results showed that the ternary phase diagram composed of Capmul® MCM: Labrafil® M 2125 (2:1)/Cremophor® EL/Transcutol® HP, showed a wider nanoemulsion region among all the tested phase diagrams.

Successful systems (transparent or translucent) obtained from the 3 phase diagrams were evaluated for maximum drug loading at 10 mg, 12.5 mg, 15 mg or 20 mg on 100 mg system. Results revealed that all systems at 10 mg and 12.5 mg drug loading showed drug content approach 100% and 75% respectively. Except for systems based on Capmul® MCM/ Labrafil® M 2125 mixtures oils at 20% showed 85% drug content at 12.5 mg drug loading. Further increase in drug loading resulted in precipitation

All systems pass the previous test at 10 mg drug loading were tested for thermodynamic stability study, through heating-cooling cycles, centrifugation and freeze-thaw cycles. Results showed that only systems based on Capmul® MCM/ Labrafil® M 2125 mixtures oils at 20% succeeded to pass the test. Therefore, these systems were further evaluated for the effect of pH of the dispersion media on their globule size and PDI measurements. Selected systems loaded with the drug showing

no globule size change or precipitation in phosphate buffer pH 7.4 were further evaluated for stability on dilution using water, pH 1.2 and phosphate buffer pH 7.4. All the tested systems remained clear with no phase separation. The successful SNEDDS systems (at high surfactant content about 60% and at 10 mg drug loading) were further subjected to *in-vitro* dissolution studies and compared to the plain drug and the brand product (Zeprexa® 10 mg). Results showed that the prepared SNEDDS succeeded to release more than 95% of the drug after 15 min in pH 1.2 and phosphate buffer pH 7.4. On the other hand, brand product (Zeprexa®) showed only 70% and 10% drug released after 15 minutes in buffer pH 1.2 and 7.4 respectively. The plain drug showed only 25% and 6% drug released after 15 minutes in buffer pH 1.2 and 7.4 respectively. The surface morphology of the selected SNEDDS was evaluated using transmission electron microscope which revealed the formation of spherical and homogenous droplets.

In an attempt to improve the drug loading ability of the selected system, higher oil load and solid emulsifier HP-β-CD were introduced, resulting in the formation of Pickering nanoemulsion. The prepared Pickering nanoemulsion were subjected to several studies including thermodynamic stability studies, effect of pH of dispersion media and were further evaluated for stability upon dilution using water, pH 1.2 and phosphate buffer pH 7.4. Results showed that all the prepared Pickering nanoemulsion formulae had no signs of precipitation or phase separation and maintained their globule size after dilution with different dispersion media at different pH. The surface morphology of the selected prepared Pickering nanoemulsion formulae were evaluated using transmission electron microscope which revealed the formation of spherical and homogenous droplets. The *in-vitro* dissolution studies showed faster drug release from the Pickering nanoemulsion formulae in comparison to the corresponding SNEDDS where about 95% of the drug was released after 10 min from all tested systems in pH 1.2 and phosphate buffer pH 7.4.

<u>Chapter II</u>: Formulation and evaluation of solid Pickering nanoemulsion Systems.

- This chapter deals with the preparation, characterization and evaluation of olanzapine loaded solid Pickering nanoemulsion formulae.

The work in this chapter complies the following:

The prepared Pickering nanoemulsion formulae from chapter I were loaded onto different types of solid carriers using spray drying and adsorption techniques. The

carriers were divided into 2 classes; two porous hydrophobic carriers (Aeroperl® 300 and Neusilin® UFL2) and the other two hydrophilic carriers (Kleptose® HP and pearlitol® 200 SD). Differentiation of the two solidification techniques using micrometric testing (angle of repose, bulk and tapped density, Hausner ratio and compressibility index) was done for the prepared formulations. Results showed superior results for the spray drying technique over the adsorption technique in all tested carriers. Therefore, the spray dried formulations were selected for further evaluation for reconstitution time, drug content, globule size analysis and *in-vitro* dissolution studies. Results showed that all the tested formulations had short reconstitution time (< 1 min). Globule size analysis results revealed that all formulations maintain nearly the same globule size of their liquid Pickering nanoemulsion formulae after reconstitution. While only spray dried solid Pickering formulae showed the same globule size of their liquid formulae were selected for further studies. Results of the *in*-vitro dissolution studies showed that the spray dried solid Pickering nanoemulsion formulae release about 95% of the drug after 15 minutes in both buffer pH tested (pH 1.2 and pH 7.4) while the two liquid Pickering nanoemulsion formulae release the drug faster about 95% after 10 minutes.

Physicochemical characterization of the selected formulae was done using DSC, and FT-IR. Differential scanning calorimetry (DSC) showed that olanzapine has a sharp single endothermic peak, indicates its high crystalline nature. While this drug peak intensity decreased or disappear in the liquid and the solid Pickering formulae respectively, which signifying the capability of the emulsion system and the spray drying technique in maintaining the drug in its dissolved state and inhibiting drug recrystallization.

FT-IR (Fourier transform infrared) results indicates that the occurrence of interactions type hydrogen bonding between the free hydroxyl or silanol group of the cyclodextrin or silica respectively and the amino group of olanzapine.

Accelerated stability study of the optimized spray dried solid Pickering nanoemulsion formulae each filled in hard gelatin capsules size (0) was tested for 6 months (at 0, 3 and 6). Results showed that the tested solid formulae remained intact under stress conditions showing no physical variations at the end of 180 days. No significant change was observed in the physical appearance, reconstitution time and globule size. Hence, it is evident that the solidification of liquid Pickering nanoemulsion formulae resulted in a stable formula.

Based on the previous results the prepared spray dried solid Pickering nanoemulsion formulae were selected for *in-vivo* studies.

<u>Chapter III</u>: *In-vivo* performance of capsules filled with two spray-dried solid Pickering nanoemulsion systems.

Bioavailability studies were carried out to monitor the efficacy of the prepared formulae to target the lymphatic system. The study was performed on three treatments, Zyprexa® tablets, capsules filled with the two optimized spray dried solid Pickering nanoemulsion formulae. The bioavailability study was performed on six adult male albino rabbits, weighing 2.5±0.2 Kg on three phases, with two weeks' washout periods between them. A cross over design was applied so that each group received a single oral dose (10 mg/Kg of the body weight) of each of the tested treatments. Plasma samples were collected for 48 hr after oral administration. Sensitive HPLC assay was used to determine the concentration of olanzapine in the plasma and the relative bioavailability of the two spray dried Pickering nanoemulsion formulae and the market product Zyprexa ® tablets. In order to assess olanzapine bioavailability, the mean plasma concentrations were plotted versus time, from which the different pharmacokinetic parameters and the relative bioavailabilities of the prepared formulae with reference to Zyprexa® tablets were determined.

Results showed that olanzapine in the spray dried solid Pickering nanoemulsion filled capsules resulted in great enhancement in oral bioavailability, in comparison to the market product. The mean values for the Cp_{max} were, 80.896±9.635, 209.309±51.984 and 375.976±66.150 ng/mL after the oral administration of Zyprexa® tablets, capsules filled with spray dried solid Pickering nanoemulsion formula based on Kleptose® HP carrier and spray dried solid Pickering nanoemulsion formula based on Neusilin UFL2 carrier, respectively. The mean values for the t_{max} were 5.500±0.547, 5.000±0.516 and 3.000±0.408 hr, for the previously mentioned formulae, respectively. The mean values for the AUC $_{(0-\infty)}$ were 994.845±115.318, 1372.668±65.911 and 2819.591±341.012 ng.hr/mL, for the aforesaid formulae, in a respective order. Additionally, capsules filled with Neusilin UFL2 based formula showed higher relative bioavailability of 283.4% with respect to the market product.

Statistical testing using two-way ANOVA using SPSS® software, revealed significant difference between the tested formulae regarding Cp_{max}, t_{max}, AUC $_{(0-\infty)}$. Multiple comparisons between the mean pharmacokinetic parameters (to determine the source of difference between the three treatments at 95% confidence level) was carried

out using LSD (in case of Cp_{max} and $AUC_{(0-\infty)}$) and Mann-Whitney (in case of t_{max}) tests. Results showed that the values of t_{max} of the spray dried solid Pickering nanoemulsion formula based on Neusilin UFL2 carrier differed significantly from the other two treatments (spray dried solid Pickering nanoemulsion formula based on Kleptose® HP carrier and Zyprexa® tablets). With respect to Cp_{max} and $AUC_{(0-\infty)}$, a significant difference was observed between the three treatments.

Finally, it can be concluded that capsules filled with spray dried solid Pickering nanoemulsion formula based on Neusilin UFL2 carrier showed superiority over those filled with spray dried solid Pickering nanoemulsion formula based on Kleptose® HP carrier regarding the achievement of our goal concerning the enhanced oral bioavailability of olanzapine.

Introduction

Oral route is one of the most commonly used for drug administration. This route remains most popular since ancient time due to easy administration. To by-pass the first-pass effect of the orally administered drugs. The lymphatic transport increases drug's bioavailability because the intestinal lymph vessels travel directly into the thoracic duct, then to the systemic circulation, hence avoiding being subjected to the portal circulation. Enhancing the bioavailability by lymphatic transport is achieved by the use of lipid-based formulation. Among the lipid based formulations, there has been a growing interest in developing self-emulsifying systems as they are efficient in hydrophobic drug delivery. Olanzapine is an antipsychotic drug that belongs to the thienobenzodiazepine class. It is effective in treating positive and negative symptoms of schizophrenia. It belongs to class II drug in the Bio-classification system (BCS) which suffer from poor water solubility and high lipophilicity resulting in a highly variable oral bioavailability. The drug suffers the first-pass effect nearly 40% of the absorbed drug is metabolized to inactive metabolites.

The effectiveness of LBDDS to improve the gastrointestinal absorption of poorly water-soluble drugs is predominantly due to their higher solubilisation capacity, being a prerequisite for absorption from the GIT. The lipid droplets formed upon dispersion of self-emulsifying LBDDS may directly facilitate drug absorption.

The daily intake of lipids for a normal adult consists of about 60-80 gm. Moreover, endogenous lipids like phospholipids, cholesterol and membrane lipids from desquamated intestinal cells and bacteria represent 40-60 gm of fat. Hence, the digestive system of an adult can digest about 100-140 gm of lipid per day.

After taking the lipid formulation orally, a coarse emulsion of high surface area will be formed due to the physical breakdown of lipid formulation. Subsequently, the chief cells in the stomach will release gastric lipase to hydrolyze triglycerides. Afterwards the digested lipid products (fatty acids and mono-glycerides) and the undigested lipids will drain into the duodenum. Being acidic in nature the drained lipids (digested and undigested), will simulate the release of secretin from the duodenal mucosa which in turn increases the blood flow to the liver. At that time the pancreas will secrete bicarbonate (along with lipase and co-lipase) into the duodenum to neutralize its environment to exploit the pancreatic lipase and co-lipase activities. Also, pancreas will release TG lipase and co-lipase necessary for the digestion of

triglycerides within the emulsified particle. Mixed micelles (produced by interaction of bile salts with fatty acids and mono-glycerides) and vesicles (formed from triglycerides and fatty acids) are the end products of the digestive phase. It had been stated that the same quantity of long chain lipids can enhance the contraction of the gall bladder and hence, raise intestinal biliary lipid accumulation without affecting gastric emptying time more efficiently than medium chain lipids.

b) Absorption phase:

The produced colloidal species from lipid digestion will be taken up by the enterocyte membrane. Then the absorbed free drug will be associated with chylomicrons inside the enterocytes. Being large in diameter and colloidal in nature, the formed chylomicrons will be taken by size-selective transport through intestinal lymphatic transport. This indicates the presence of an extra pathway by which lipids increase oral bioavailability.

c) Circulatory phase:

As known, most of the orally taken drugs are absorbed by the systemic circulation then to the portal blood. On the other side, lipophilic drugs (log P > 5) will be absorbed to the systemic circulation through the lymphatic route avoiding the first-pass effect. It had been previously published that all compounds which possessed elevated bioavailability when co-administered with long chain lipids (dietary or lipid-based formulation) are absorbed by means of the intestinal lymph. While short and medium chain lipids are taken up directly by the portal blood.

LBDDS can be known as SNEDDS and Pickering nanoemulsion formulations where both were evaluated for maximum drug and oil load and also for maximum system stability.

❖ **Self nano-emulsifying drug delivery systems (SNEDDS):**

Self nano-emulsifying drug delivery systems (SNEDDS) are isotropic mixtures of oil, surfactant, co-surfactant and drug that form fine oil-in-water nanoemulsion when introduced into aqueous phases under gentle agitation.

❖ **Pickering nanoemulsion formulations:**

Solid-stabilised nanoemulsions constitute an interesting alternative, whereby the stabilization of emulsion droplets by solid particles instead of conventional low-molecular-weight surfactants. Using Cyclodextrins as the solid emulsifier

Cyclodextrins did not change the surface tension of water alone but decreased the o/w interfacial tension with the increase of their concentration.

Traditional preparation of liquid SMEDDS involves dissolution of drugs in oils and their blending with suitable solubilizing agents. However, SMEDDS formulations are normally prepared as liquids that produce some disadvantages such as high production costs, low stability and portability, low drug loading, irreversible drugs/excipients precipitation and few choices of dosage forms.

To address these problems, solid SMEDDS (S-SMEDDS) have been investigated, as an alternative approach. These systems require the solidification of liquid SMEDDS into powders/nanoparticles which can be converted to various solid dosage forms like tablets, capsule, and pellets and so on. Choice of solid carrier is very important as it influences the performance of the S-SMEDDS. Ideal solid carrier should possess properties like; inert, high oil adsorption capacity, good flow property and compatible with the processing technology.

there are different techniques could be used to convert liquid SNEDDS to solid SNEDDS powder like adsorption to an inert solid carrier which is a simple solidification method. Also the spray drying technology in which a liquid SNEDDS stream (solution, suspension or emulsion) is constantly converted into SNEDDS powder.

Carrier types used throughout the study:

❖ **Hydrophobic Carriers:**

1- NEUSILIN® UFL2

is a synthetic, white amorphous powder form of magnesium aluminometasilicate (mixture of aluminum oxide 32% + magnesium oxide 12.4% + silicon oxide 31.9%)

2- AEROPERL® 300 Pharma

is a granulated form of colloidal silicon dioxid. The spherical granules have a diameter of approximately 30 μm

- **Hydrophilic carriers:**

1- PERLITOL®200 SD

Obtained industrially by hydrogenation of fructose, spray dried mannitol.

2- KLEPTOSE® HP

Hyroxypropyl-beta-cyclodextrins (HP-β-CD) are purified polydisperse white crystalline powder resulting from controlled reaction of propylene oxide and native betacyclodextrin under base catalysis.

Aim of work

The aim of the present thesis is the preparation, characterization and evaluation of the liquid SNEDDS and the liquid Pickering nanoemulsion formulae followed by preparation, characterization and evaluation of the solid Pickering nanoemulsion formulae through adsorption or spray drying technique based on the 4 carrier types, Kleptose® HP, pearlitol® 200 SD, Neusilin® UFL2 and Aeroperl® 300 at three different liquid/carrier ratios 1:2, 1:1 and 2:1. Followed by the bioavailability study and pharmacokinetic parameters calculation of olanzapine from the capsules filled with two spray dried solid Pickering nanoemulsion formulae in comparison to the commercially available (Zyprexa®) tablets in rabbits.

Summery

Olanzapine is an effective antipsychotic drug used for the treatment of positive and negative symptoms of schizophrenia. It suffers from poor water solubility in addition to extensive first-pass metabolism. Lipid-based formulations had been introduced in order to improve its bioavailability by targeting the lymphatic transport. The aim of the present thesis is the preparation and evaluation of self-nanoemulsifying drug delivery systems followed by the preparation and evaluation of the Pickering-Nano-emulsion systems. Solubility study of olanzapine in different oil types either single oil or combination at different ratios, surfactants and co-surfactants. Based on the solubility results three ternary phase diagrams were prepared. Fourteen Successful self-nanoemulsifying systems were collected and evaluated after drug loading at 10 mg on 100 mg system for thermodynamic stability study, the effect of pH of the dispersion media on their globule size and PDI measurements, further evaluated for stability on dilution and finally *in-vitro* dissolution studies and compared to the plain drug and the brand product (Zeprexa® 10 mg). The surface morphology of the selected SNEDDS formula was evaluated using transmission electron microscope which revealed the formation of spherical and homogenous droplets. These selected formula was further evaluated for Pickering-Nano-emulsion technique after drug and oil increment to about its double content per system. Therefore, four Pickering-Nano-emulsion formulae were prepared and evaluated for the previously mentioned tests. Results showed that all the prepared Pickering-Nano-emulsion formulae had no signs of precipitation or phase separation and maintained their globule size after dilution with different dispersion media of different pH. The surface morphology of the selected prepared Pickering-Nano-emulsion formulae were evaluated using transmission electron microscope which revealed the

formation of spherical and homogenous droplets. The *in-vitro* dissolution studies showed faster drug release from the Pickering-Nano-emulsion formulae in comparison to the corresponding SNEDDS where about 95% of the drug was released after 10 min from all tested systems in both buffer pH tested (pH 1.2 and pH 7.4). The four successful liquid Pickering-Nano-emulsion formulae were transferred to the solid form through spray drying and adsorption technique methods using four carriers were divided into 2 classes; two porous hydrophobic carriers (Aeroperl® 300 and Neusilin® UFL2) and the other two hydrophilic carriers (Kleptose® HP and pearlitol® 200 SD). Differentiation of the two solidification techniques using micrometric testing (angle of repose, bulk and tapped density, Hausner ratio and compressibility index) was done for the prepared formulations. Results showed superior results for the spray drying technique over the adsorption technique in all tested carriers. Therefore, the spray dried formulations were selected for further evaluation for reconstitution time, drug content, globule size analysis and *in-vitro* dissolution studies. Results showed that all the tested formulations pass all the tests and not significantly changed from the liquid form. The selected two formulae were further evaluated for Physicochemical characterization of the selected formulae was done using DSC, and FT-IR. Differential scanning calorimetry (DSC) and accelerated stability study for 6 months. Results showed that the two formulae drug peak intensity were disappeared in the DSC analysis and the occurrence of interactions type hydrogen bonding in the FT-IR analysis. Also the two formulae remain stable. Hence, it is evident that the solidification of liquid Pickering-Nano-emulsion formulae resulted in a stable formula.The two formulae were evaluated in-vivo in male Albino rabbits to study bioavailability in comparison to the orally administered Zyprexa® tablets .The results demonstrated that the in-vivo pharmacokinetic study showed that the selected spray dried formula based

on the hydrophobic carrier, Neusilin® UFL2 had significantly higher blood pharmacokinetic parameters (Cp_{max} and $AUC_{(0-\infty)}$,) in comparison to the both the spray dried formula based on the hydrophilic carrier, Kleptose® HP and the marketed product (Zyprexa®) at the same dose. In conclusion, the formulated spray dried powder improves the oral bioavailability.

(**Keywords:** Olanzapine, Nano-emulsion, Pickering- Nano-emulsion, spray-drying, lymphatic transport).

Review

Olanzapine suffers the first-pass effect nearly 40% of the absorbed drug is metabolized to inactive metabolites. Lymphatic targeting is our goal through drug formulation into SNEDDS using mixture of long chain oils and mono-glycerides, diglycerides type oil which enhance oral lymphatic targeting. Also enhance more drug and oil loading per systems and retain their globule size in the nano-range < 20 nm through Pickering nanoemulsion is our goal. Then solidification of the liquid Pickering nanoemulsion systems is finally a goal to ensure maximum system stability and avoid liquid nanoemulsion drawbacks. Therefore, olanzapine solubility was evaluated in 11 oils and oil mixtures, 5 surfactants types and two co-surfactants. Also the preliminary screening of surfactants and co-surfactants was assessed to choose the most suitable systems for maximum drug solubilisation and loading which mainly depend on tha maximum ability of systems for maximum emulsification efficiency. After word the system selected based on the emulsification efficiency were selected for further evaluations to ensure maximum system stability without precipitation. Finally, system showed highest drug load and maximum stability were chosen for further modification to attain higher drug and lipid load for highest lymphatic passage. These systems were selected for solid emulsifier addition followed by further evaluation for system stability through Pickering nanoemulsion formulation technique. Afterword these systems were converted to the solid Pickering nanoemulsion form through two solidification techniques which is the adsorption and the spray drying. Then the two selected solidified systems that showed maximum stability upon more drug and oil loading were further evaluated for bioavailability evaluation against the marketed product Zyprexa®). Results revealed that the two formulae showed higher area under the curves and higher plasma concentration. In conclusion, the formulated solid spray dried Pickering nanoemulsion powder improves the oral bioavailability.

Conclusion

The prepared formulation reveals the potentiality of incorporating olanzapine in a SNEDDS formulation to improve the biological performance of the drug. In this study, liquid SNEDDS was formulated and further developed into solid SNEDDS by a spray-drying technique using Aeroperl® 300, Neusilin® UFL2 Kleptose® HP and pearlitol as the solid carriers. From this study, it was concluded that the prepared liquid SNEDDS was thermodynamically stable with good self-emulsification efficiency and having globule size in the nanometric range which may be physiologically stable. It was also concluded that S-SNEDDS preserved the self-emulsification performance of the liquid SNEDDS and gave a faster in vitro dissolution rate than the crude powder and marketed product. Furthermore, our results suggest that S-SNEDDS could be considered and further evaluated for the oral delivery of lipophilic poor soluble drugs for which an oral route of administration is desirable. In conclusion, self-emulsifying drug delivery systems represented a promising approach for the formulation of olanzapine. S-SNEDDS appeared to be an interesting approach to improving problems associated with oral delivery of olanzapine. Thus, S-SNEDDS can be considered as a new and commercially feasible alternative to current marketed olanzapine. Finally, the oral delivery of hydrophobic drugs can be made possible by S-SNEDDS, which have been shown to substantially improve the oral bioavailability

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البيانات الشخصية :

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