Controlled release study on certain central nervous system acting drug

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The aim of this thesis was to improve the oral bioavailability of antipsychotic drug Amisulpride.

The factors affecting particle size (PS), and entrapment efficiency (EE%) of the prepared Amisulpride nanostructured lipid carriers were studied. Statistical assessment showed that all factors had significant impact on both EE% and PS. Results showed EE% ranging from 29.01% to 69.06 %, PS ranging from 184.9 nm to 708.75 nm, polydispersity index (PDI) for most formulae ranged from 0.21 to 0.59 and zeta potential (ZP) ranged from -21mV to -33.55 mV. Based on the desirability criterion as calculated by Design-Expert® software, formulae (G12-G10-G7) had the highest desirability value (0.915-0.845-0.768) respectively, and thus they were selected as optimal formulae. Determination of reconstitution time, PS and EE% after lyophilization of the selected formulae (G12-G10-G7) with the addition of either 5% trehalose or 5% mannitol, lead to the selection of (MG10 - TG7) with the shortest reconstitution time (1.13 min-1.16 min) and with EE% (61.34 ± 1.4% - 62.7 ± 0.89%), and PS in the nano-range (652.5 ± 53.53 nm - 636.70 ± 46.32 nm). They were both filled in hard gelatin capsules size (0), their weight uniformity and content uniformity complied with the pharmacopoeial limits. In the *in-vitro* release it was noticed that capsules containing (TG7) showed more controlled release with 96.56% released after 8 hours, while capsules containing (MG10) completely released its AMS content after about 5 hours. So TG7 Capsule was selected for further in-vivo investigations. Amisulpride was formulated also into matrix tablets characterized with pH independent release using direct compression technique. Full factorial design ($2^1.4^1$) was used to investigate the influence of (type of polymer and polymer concentration) on the Amisulpride Labrasol Penetration Enhanced (ALPE) matrix tablets release patterns. The statistical assessment of the factorial design output showed that both independent formulation variables had significant impact on the percent of AMS released after both 2 and 8 hours ($p < 0.05$ for both factors), formula H30, composed of HPMC with concentration 30% w/w with desirability value (0.657) was selected for further optimization with acidic modifiers. Another full factorial design (2^2) was used to investigate the influence of (type of acidic pH modifiers and acidic pH modifier concentration) on the acid modified ALPE matrix tablets release patterns. According to similarity factor analysis, all formulae with acidic pH modifier (FH15, FH30, TH15 & TH30) have $f_2 \geq 50$ that implies the achievement of pH independent release of AMS. The statistical assessment of the factorial design output showed that both independent formulation variables had significant impact on the percent of AMS released after both 2 and 8 hours ($p < 0.05$ for both factors). Formula TH30, composed of 30% HPMC and 30% Tartaric acid, with desirability value (0.703) was selected as the optimum pH independent ALPE matrix tablet, and was selected for further *in-vivo* investigations. According to the results of the *in-vivo* study, the relative bioavailability was found to be 252.78% based on the mean $AUC_{0-\infty}$ of the TG7 Capsule compared to that of the Amipride® tablet and was found to be 132.27% based on the mean $AUC_{0-\infty}$ of the TH30 Tablet compared to that of the Amipride® tablet. This means that both formulae prepared in the two previous chapters were successful in increasing the extent of oral absorption of AMS.

Keywords: Amisulpride, Nanostructured Lipid Carriers, pH independent, Matrix Tablets and *in-vivo* pharmacokinetics.