

Recent developments in the technology have prompted scientists to develop fast disintegrating dosage forms with improved patient compliance and convenience. Fast release tablets and fast dissolving films are the most exciting recent developments in the category of intraoral dosage forms.

Risperidone is a well known antipsychotic drug belonging to the chemical class of benzisoxazole. This drug has bitter taste, low solubility in aqueous medium. Risperidone has a small daily dose and moderate molecular weight so it may be considered a good candidate for fast release tablets or fast dissolving films.

Therefore the work in this thesis aimed to formulate and evaluate masked taste Risperidone fast release tablets and fast dissolving films, that could enhance its *in-vitro* dissolution and *in-vivo* absorption. Consequently, the bioavailability of the drug can be improved by pregastric absorption as the drug suffers from first-pass metabolism.

Thus the work in this thesis is divided into four chapters:

Chapter I: Formulation and Evaluation of Masked Taste Risperidone Fast Release Tablets.

Chapter II: Formulation and Evaluation of Masked Taste Risperidone Fast Dissolving Films.

Chapter III: Stability Studies of Selected Formulae of Risperidone Fast Release Tablets and Fast Dissolving Films.

Chapter IV: Bioavailability Studies for Selected Formulae of Risperidone Fast Release Tablets and Fast Dissolving Films.

Chapter I 25

Formulation and Evaluation of Masked Taste Risperidone Fast Release Tablets

The aim of work in this chapter was to mask the bitter taste of Risperidone then formulate it as fast release tablets. Comptability studies were carried out for Risperidone using a number of excipients namely, Ac-Di Sol®, Explotab®, camphor, lactose monohydrate, aspartame, Crospovidone®, mannitol, spray dried lactose, Pharmaburst®, vanillin, magnesium stearate, Avicel® PH102, PVP K25, PVP K90, PEG 4000, PEG 6000, glycine and gelatin in 1:1 ratio. These samples were subjected to visual examination, Differential Scanning Calorimetry (DSC) and Infrared Spectroscopy (IR).

Based on visual examination, DSC and IR results, all the used additives were found to be compatible with the drug except vanillin.

According to the phase solubility results for Risperidone with 2-HP β -cyclodextrin, stability constant ($K_{1:1}$) value was $39.13M^{-1}$ and complexation efficiency (CE) was 0.2015.

To mask the bitter taste of Risperidone; complexes of the drug with Indion® 234 at 1:1, 1:2 and 1:3 ratio and a complex of Risperidone with 2-HP β -cyclodextrin at 1:1 molar ratio were prepared by solvent evaporation method. The prepared complexes evaluated using taste evaluation, DSC, FTIR, PXRD, SEM, flowability studies and drug content.

The results of *in-vitro* and *in-vivo* taste masking evaluation tests revealed that the inclusion complex of drug with 2-HP β -cyclodextrin exhibited excellent taste masking.

In the DSC studies, the endothermic peak of Risperidone could be easily noticed in Risperidone/Indion® 234 complexes while it completely 26

disappeared in Risperidone/2-HP β -cyclodextrin complex. This could be clearly attributed to the inclusion of the drug in the cyclodextrin cavities. According to PXRD studies, the diffractograms of the drug/Indion® 234 complexes showed decreasing both the intensity and sharpness of the characteristic peaks of crystalline Risperidone. Moreover, the diffractogram of the drug/cyclodextrin complex showed more reduction in the intensity and sharpness of the characteristic peaks of the drug. The IR spectra of Risperidone/2HP β -CD complex corresponding to C-N and C-F were strongly stretching, this was explained by the dissociation of the intermolecular hydrogen bonds associated with crystalline drug molecules. The broadening and decrease in the intensity of the drug aromatic stretching band observable in these systems, might be due to its restriction within the cyclodextrin cavity.

The spectrum of the physical mixture was the superposition of pure components spectra, indicated the absence of interaction between Risperidone and 2HP β -CD, and in particular the characteristic carbonyl stretching band of Risperidone was unchanged.

The spectra of Risperidone/Indion® 234 complexes exhibited the absence of the characteristic drug peak at 1350.71 cm^{-1} , confirmed the complexation of C-N in the drug with resin.

From the SEM micrographs, Risperidone adsorbed on the surface of Indion® 234 which was a carrier for the drug. On the other hand Risperidone/2HP β -CD complex showed the complete disappearance of drug particles due to their inclusion in the cyclodextrin cavities.

According to all the physical parameters of the blends; Risperidone /2-HP β -CD had better flowability than the other complexes. This could be attributed to the crystal shape of the inclusion complex.

The drug content percentages of all the prepared complexes were found to be more than 96%. 27

Based upon the previous results; Risperidone/2-HP β -cyclodextrin complex at 1:1 molar ratio was found to be the best and was further selected for formulation.

Four types of fillers; (mannitol, spray dried lactose, lactose monohydrate and Avicel® PH102) and four types of superdisintegrants; (Ac-Di-Sol® 2-5%, Explotab® 2-4%, Crospovidone® 2-5% and Pharmabrust® 10%) were investigated. So a mixture of mannitol and lactose monohydrate was selected as diluent and 5% Ac- Di Sol® was selected as superdisintegrant in the formulation of Risperidone fast release tablets formulae.

Five fast release tablets formulae of Risperidone (R1-R5) were prepared by sublimation method using camphor as a subliming agents; at 2.5, 5, 7.5, 10 and 15% w/w.

Ten Risperidone fast release tablets formulae (R6-R15) were prepared by freeze drying method using gelatin as a matrix former, a sugar alcohol (mannitol) and a collapse protectant (glycine).

The prepared fast release tablets formulae were subjected to the following tests: tablet weight and weight variation, uniformity of tablet diameter and thickness, drug content, tablet hardness, friability, *in-vitro* disintegration time, wetting time and *in-vitro* dissolution studies.

All the prepared masked taste Risperidone fast release tablets formulae showed acceptable weight variation, a uniformity of diameter and thickness and hardness

The mean percentage of Risperidone content in fast release tablets from all formulae was found to conform to pharmacopoeial limits (85% - 115%) of the labeled potency.

All the prepared fast release tablets formulae had acceptable friability and complied with the compendial standards except formulae R6 and R8 prepared by freeze drying method, were excluded from the study. 28

The *in-vitro* disintegration results of Risperidone fast release tablets revealed that fast release tablets formulae prepared by freeze drying method had the shorter disintegration time and higher dissolution rate than fast release tablets formulae prepared by sublimation method. Formula R15 (containing Tween 20) showed the highest dissolution where 100% of the labeled dose was dissolved within 3 minutes and the least disintegration time (2 seconds). Scanning electron micrograph of the surface of R15 formula showed the highly porous nature of the prepared lyophilized tablet which explained the rapid penetration of water, resulting in rapid wetting, disintegration and dissolution in the oral cavity. So the formula R15 was used for further stability and bioavailability studies.

Chapter II

Formulation and Evaluation of Masked Taste Risperidone Fast Dissolving Films

The work in this chapter aimed to formulate and evaluate masked taste Risperidone fast dissolving films. The compatibility studies between Risperidone and a number of excipients namely; HPMC-E5, NaCMC, PVP K25, aspartame and citric acid revealed that there was no interaction using visual examination, IR and DSC.

Various trials were taken using propylene glycol and glycerol as plasticizer for plain films using solvent-casting method. The films were evaluated for imperfections, surface roughness, appearance and *in vitro* disintegration time.

Based on film forming capacity, appearance and disintegration time, nine oral films (F1-F9) were prepared by solvent casting method using HPMC-E5, NaCMC and PVP K25 polymers. Propylene glycol was used

as a plasticizer in 30% of polymer concentration. Aspartame 1%, menthol 1% and citric acid 1% were used as sweetening agent, flavouring agent and saliva stimulating agent; respectively.

The prepared films formulae were uniform, transparent, colorless and soft with no spots found on them. The observations showed that the surface pH of the prepared films were found to be in the range of salivary pH. The folding endurance and tensile strength for all the formulations were satisfactory to reveal good film property; except formula F1 was brittle. The drug content in all the prepared films formulae was more than 97%. All the prepared films formulae showed acceptable *in-vitro* disintegration time and dissolution rate.

Formula F2 (containing 2% HPMC) showed the shortest *in-vitro* disintegration time and the highest dissolution rate so it was selected for further stability and bioavailability studies.

Chapter III

Stability Studies of Selected Formulae of Risperidone Fast Release Tablets and Fast Dissolving Films

The stability studies included accelerated testing at different temperatures (40°C, 50°C and 60°C) for a period of 12 weeks. Periodically, samples were withdrawn at different predetermined time intervals and examined physically for any changes in color or physical 30

appearance as well as chemically for their Risperidone content using HPLC method.

The mobile phase consisted of filtered and degassed mixture of 0.025 M phosphate solution of pH 6.8 and acetonitrile (62:38 v/v) with a flow rate 1.2 mL per minute and the injection volume was 20 μ L. The samples were analysed using HPLC equipped with a 235 nm U.V. detector. A calibration curve of peak area ratios of (Risperidone/Dapoxetine) in the mobile phase versus the concentration of Risperidone was done.

The formulations were crushed into powder and an amount of the powder equivalent to the drug dose was accurately weighed then mixed with 100 ml mobile phase.

It was found that the percentage of Risperidone determined by stability indicating HPLC assay was within the range permitted by the USP (90-120%) up to the end of the storage period indicating good chemical stability.

Kinetic analysis of the stability data revealed that the degradation of Risperidone from the prepared formulae followed first-order kinetics and the predictive shelf life of formulae R15 and F2 was 1.68 and 2.19 years; respectively.

Chapter IV

Bioavailability Studies for Selected Formulae of Risperidone Fast Release Tablets and Fast Dissolving Films

A three-period crossover design was followed in this study. The study was performed on three phases for the four healthy volunteers, using Risperidal® (4mg) oral tablets as a reference. 31

The blood samples (5 ml) were collected after 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hours then centrifuged at 3000 rpm for 10 min. The collected plasma samples were analyzed using a sensitive, reproducible and accurate LC-MS/MS method.

The isocratic mobile phase consisted of acetonitrile and 2mM ammonium acetate pH 4.3 (95:5 v/v), with a flow rate of 0.5 mL/min into the mass spectrometer's electrospray ionization chamber.

The calibration curve was obtained by plotting the chromatographic peak area ratios (Risperidone/Dapoxetine) against the corresponding nominal Risperidone concentration added. Concentrations of Risperidone in unknown samples were calculated with reference to the prepared calibration curve.

The mean peak plasma concentration (C_{max}) of Risperidal® tablets was 198.26 ± 14.72 ng/ml with mean t_{max} of 2.375 ± 0.65 hr. Additionally, the mean $AUC_{(0-12)}$ was found to be 955.486 ± 153.02 ng hr/ml. The $AUC_{(0-\infty)}$ was 1056.12 ± 189.73 ng hr/ml. The mean elimination half-life ($t_{1/2}$) and elimination rate constant (K) were 3.289 ± 0.4 hr and 0.2215 ± 0.03 hr⁻¹, respectively.

The prepared formula R15 showed mean peak plasma concentration (C_{max}) of 235.765 ± 31.00 ng/ml, and the mean time of peak plasma concentration (t_{max}) was 1.25 ± 0.22 hr. The mean $AUC_{(0-12)}$ was found to be 1194.664 ± 177.95 ng hr/ml and $AUC_{(0-\infty)}$ was found to be 1499.401 ± 288.29 ng hr/ml. The mean elimination half-life ($t_{1/2}$) and elimination rate constant (K) were 5.052 ± 0.56 hr and 0.1394 ± 0.01 hr⁻¹, respectively.

Concerning the formula F2, it was apparent that the mean peak plasma concentration (C_{max}) was 293.46 ± 16.62 ng/ml. The mean time of peak plasma concentration (t_{max}) was 0.625 ± 0.25 hr. The mean $AUC_{(0-12)}$ was found to be 1550.938 ± 190.34 ng hr/ml. In addition, $AUC_{(0-\infty)}$ was found to be 2078.135 ± 256.89 ng hr/ml. The mean elimination half-life ($t_{1/2}$) and

elimination rate constant (K) were 5.9459 ± 0.65 hr and 0.1175 ± 0.017 hr⁻¹, respectively.

The relative bioavailability of F2 was 162.31% compared to 125.31% for R15 when Risperidal® tablets which were taken as reference standard.