Formulation and Evaluation of Paliperidone controlled release dosage form using new technique

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Introduction

Paliperidone (PAL) is a new antipsychotic molecule used in the treatment of schizophrenia marketed under the trade name of *Invega*® marketed by Janssen pharmaceutical company that shows less extrapyramidal side effects due to slow release of PAL. Major drawbacks of antipsychotics are sedation, weight gain and extrapyramidal side effects. This side effect profile is mainly affected by drug release pattern from the dosage form. Moreover, many of the marketed products are immediate release products with high side effect profile. This work aims at sustaining the release of PAL by a new technique in which the drug was mixed with a non-volatile vehicle, carrier and coating materials to change drug solution into powder admixtures that were compressed into tablets.

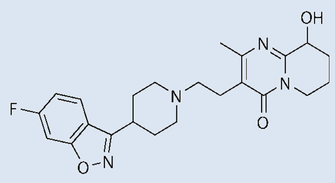

Figure: Paliperidone Chemical Structure

Materials and Methods

Preparation of Paliperidone sustained release formulation

Dosage form was prepared by mixing Paliperidone with vehicle to dissolve the drug then calculated amounts of carrier and coating materials were added to the drug solution to convert it to non-adherent free flowing powder that is compressed into tablets.

Characterization of Paliperidone sustained release formulation

A- Pre-compression studies

Angle of repose, % Carr's index and Hausner ratio measurement

Powdered sample of sustained PAL formulation were tested for its flowability through measuring its angle of repose, % Carr's index and Hausner ratio.

B- Post-compression studies

1. DSC & FT-IR

Samples of PAL sustained release formula were tested for transformation of PAL nature through DSC testing and also tested for ingredients compatibility by performing FT-IR spectroscopy.

2. *In-vitro* release study

In-vitro release studies were carried out using a USP dissolution apparatus type II (Paddle type) at body temperature in acidic medium to test release of PAL from the formulation.

3. *In-vivo* evaluation of PAL formulations

Pharmacokinetic parameters were measured upon administration of formulated PAL dosage form, such as Tmax, Cmax and AUC.

Results

Pre-compression studies

Formula	Angle of repose (θ)	Compressibility Index (%)	Hausner Ratio
F1 (Control Formula)	38.6 ± 0.49	19.65 ± 0.101	1.24 ± 0.01
F2 (10% PAL)	33.28 ± 0.77	14.79 ± 0.2	1.17 ± 0.102
F3 (20% PAL)	35.01 ± 0.38	15.15 ± 0.071	1.18 ± 0.01
F4 (40% PAL)	41.39 ± 1.27	21.08 ± 0.993	1.27 ± 0.101
F5 (50% PAL)	48.64 ± 0.53	27.875 ± 1.52	1.38 ± 0.308

Table. Flowability parameters of different PAL sustained release formulas

In-vitro release studies

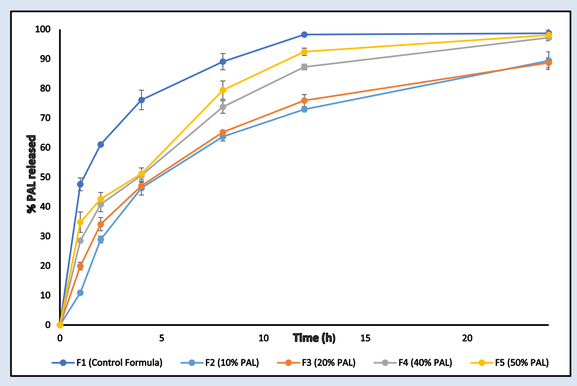

Figure. Percentage paliperidone released from different liquisolid formulas into USP dissolution apparatus type II at 37 ± 0.5℃ in 900 ml 0.1 N HCl with a stirring rate of 50 rpm

PAL formula with 20% drug concentration showed very close in-vitro release profile to Invega®.

Post-compression studies

QC tests	Weight uniformity (mg)	Content uniformity (%)	Thickness (cm)	Diameter (cm)	Hardness (mN)	Disintegration time (Min)	Friability (% - weight loss)
Formula	Results expressed in Mean ± SD						
F1 (Control)	350.89 ± 0.756	93.92 ± 6.408	0.31 ± 0.008	1.01 ± 0.010	0.49 ± 0.081	0.61 ± 0.270	0.82 ± 0.512
F2 (10% PAL)	935.75 ± 0.246	88.61 ± 9.657	0.78 ± 0.009	1.21 ± 0.007	0.39 ± 0.312	0.28 ± 0.182	1.5 ± 0.87
F3 (20% PAL)	467.58 ± 0.671	95.15 ± 4.123	0.42 ± 0.004	1.012 ± 0.007	0.60 ± 1.952	118.2 ± 6.196	0.90 ± 0. 712
F4 (40% PAL)	233.60 ± 0.509	92.72 ± 5.164	0.35 ± 0.006	0.81 ± 0.010	0.43 ± 2.712	0.33 ± 0.139	0.7 ± 1.256
F5 (50% PAL)	187.13 ± 0.394	87.32 ± 27.908	0.27 ± 0.004	0.814 ± 0.009	0.56 ± 1.004	8.2 ± 0.82	0.85 ± 2.704

Formula with 20% PAL showed acceptable results in respect to flowbility parameters and quality control testing

In-vivo evaluation

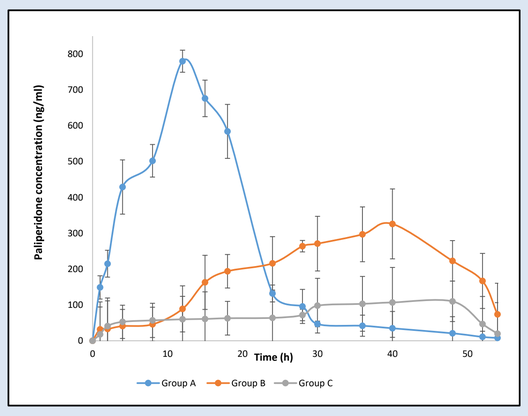

Figure. Paliperidone concentration in plasma of three rabbit groups; (Group A) receiving PAL control formula, (Group B) receiving F3 and (Group C) receiving Invega®

DSC and FT-IR

Formula with 20% PAL showed conversion of PAL from crystalline to amorphous (DSC findings) and showed no compatibility issues between PAL and other ingredients (FT-IR findings)

PK parameters	Group A	Group B	Group C
C_{max} (ng/ml)	780.66 ± 15.04	326.16 ± 17.38	110.33 ± 6.97
T_{max} (h)	13.5 ± 1.64	40 ± 4.32	48 ± 6.19
AUC (ng.h/ml)	12875.5 ± 1.43	10372 ± 5.24	4049 ±3.47

Table. Mean pharmacokinetic parameters of; (Group A) receiving control Paliperidone formula, (Group B) receiving F3 and (Group C) receiving Invega® in three rabbit groups (n=6 in each group)

Selected PAL formula achieved a significantly longer duration of action compared to the control PAL formula

Conclusions

Formulation of Paliperidone with Liquisolid technique successfully achieved acceptable pre-compression results in the form of acceptable flowability parameters. Also, after compression, the produced tablets showed acceptable quality control results together with sustained release profile for Paliperidone and no compatibility issues were observed. In-vivo tests yielded acceptable comparison between selected PAL formula and the selected comparator product.

References

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