Formulation and evaluation of fast dissolving tablets of haloperidol solid dispersion

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ABSTRACT

Purpose: The aim of this study was to design fast dissolving tablets (FDT) of the anti-psychiatric drug haloperidol in solid dispersion forms as a way to enhance its dissolution profile and anti-psychiatric effect.

Methods: Solubility studies of haloperidol in various polymers solutions were investigated. The selected polymer with high drug solubility (Poly ethylene glycol 4000) was used for preparation of solid dispersion through two methods solvent evaporation method and melting method. Haloperidol solid dispersion mixed with other solid powder excipients and compressed into tablets. The resulted tablets were evaluated according to British Pharmacopoeia (B.P.) specifications. Pre- and post -compression studies were performed to determine the flow properties and evaluate the solid dispersion systems, followed by in vivo studies through forced swimming test (FST)

Results: Pre-compression studies showed adequate flowability and compatibility of polymer and solid excipients with haloperidol. The selected solid dispersion tablet (SD2) demonstrated the best disintegration and water absorption ratio in addition to satisfactory friability and hardness. Attempts of in vitro dissolution results and thermodynamic stability studies showed acceptable results for (SD2) formulation containing PEG 4000 polymer prepared by melting method. The in vivo study of (SD2) formulation revealed the highest immobility time to rats compared to control rats and others treated with commercial haloperidol product.

Conclusion: Fast dissolving tablets prepared from solid dispersion of haloperidol with PEG4000 expressed rapid onset of action with enhanced anti-psychiatric effect of haloperidol.

1. Introduction

Oral route is the preferred and foremost utilized route of drug administration due to several reasons namely: convenience and cost-effective. Tablet is well known among all oral dosage forms existing now a days since of its comfort of self-administration, compactness and simple manufacturing (Almukainzi et al., 2019). Fast dissolving tablets can be disintegrated, dissolved, or suspended by saliva in the mouth without the need of water (Gupta et al., 2018). FDA developed the orally disintegrating tablets (ODT) definition as a new dosage form in1998. It stated that “The ODT is a solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds when placed up on the tongue”(Vikas et al., 2007).

Drug with poor solubility had a greater limitation for the formulation. Solubility enhancement is the prime concern for a dosage form to get ideal bioavailability. Salt formation, solubilization, particle size reduction have been used to increase dissolution rate, and thereby oral absorption and bioavailability of low water soluble drugs. Solid dispersion technique had been utilized as effective strategy to improve the dissolution and bioavailability of poorly water soluble drugs (Aggarwal et al., 2015). Fast dissolving tablets are valuable for patients with difficulties swallowing normal tablets and capsules, for example pediatric patients, patients of chemotherapy treatment and mentally ill patient to permit quick dissolving of dosage forms within the mouth. These type of tablets comprise either very porous and soft-molded matrices or tablet with very low compression force (Masih et al., 2017).
Haloperidol is a phenyl butyl piperidine derivative with antipsychotic, neuroleptic, and antiemetic activities, marketed under the trade name Haloperidol, Haldol, Halonace, among others. It is a typical antipsychotic medication (Joint Formulary Committee, 2013). Haloperidol competitively blocks postsynaptic dopamine (D2) receptors in the mesolimbic system of the brain by eliminating dopamine neurotransmission and leading to anti delusionary and anti-hallucinogenic effects (Nasrallah et al., 2017). As per BCS, haloperidol is class II drug with poor solubility and high permeability. Haloperidol bioavailability is about (60–70 %). It is extensively metabolized in the liver with only about 1 % of the administered dose excreted unchanged in urine. (Joshir et al., 2018). It is available as tablets, oral drops and IM/IV ampules dosage forms (Hughley et al., 2015).

In the present work an attempt had been made to improve the solubility of haloperidol by solid dispersions using melting method and solvent evaporation method along with the using polymers and further developed into fast disintegrating tablets. The produced tablets had subjected to physicochemical, in vitro release and stability studies. This had been followed by behavioral evaluation of anti-psychotic action on healthy rats using forced swim test. The results had compared to those of commercial haloperidol product.

2. Materials and methods

2.1. Materials

Haloperidol obtained from (EL. Kahira pharmaceutical chemicals, Cairo, Egypt); Avicel pH 102, Sodium starch glycrolate, Magnesium stearate and Talc obtained from (Cid company, Giza, Egypt); Polyethylene glycol (PEG4000), Poly vinyl pyrrolidine (PVP Ek) and carboxy methyl cellulose (CMC) obtained from (EL. Nasr pharmaceutical chemicals Co. Egypt); potassium dihydrogen orthophosphate, disodium hydrogen orthophosphate and absolute ethanol obtained from (EL. Gomhoria company, Egypt); Commercial haloperidol product purchased from local community pharmacy. All reagents & solvents used were of analytical grade.

2.2. Preparation of physical mixture

Physical mixture of haloperidol with polymer PEG 4000, PVP and CMC at different ratio (1:2, 1:4, 1:6 and 1:8) were prepared by mixing the accurately weighed quantity of drug and polymer in a glass mortar with the help of pestle. This mixture was then subsequently passed through sieve number 60 and stored in a desiccator for 24 h.

2.3. Solubility study

The solubility of pure haloperidol and in presence of polymer was determined in distilled water. An excess quantity of the drug and weighted amount of physical mixture (175.28 mg) were added to 10 ml of water in screw-capped bottles. All the bottles were shaken in a shaker water bath at 25°±0.5 °C for 72 h. After attainment of equilibrium, the solutions were filtered, and concentration of drug was determined by spectrophotometer at λ max 243 nm (Huang and Dai, 2014).

Solubility enhancement ratio was calculated using the following equation.

\[
\text{Solubility enhancement ratio (SER) } = \frac{\text{Solubility of drug in presence of polymer}}{\text{Solubility of drug in water}}
\]

2.4. Preparation of solid dispersion of haloperidol

Solid dispersions containing haloperidol and polymer (PEG4000, PVP and CMC) in the proportion of 1:2, 1:4, 1:6 and 1:8 had been prepared by melting method, and solvent evaporation method.

2.4.1. Melting method

Solid dispersions were prepared by melting each of haloperidol alone and polymer in porcelain dish. The fusion temperature was controlled between 60 and 70 °C. The molten mixture was immediately cooled and solidified in an ice bath with vigorous stirring. The solid obtained was scrapped, crushed, pulverized and passed through sieve number 60. The obtained product was stored in a desiccator until used for further studies (Dhote et al., 2014).

2.4.2. Solvent method

In this method, haloperidol and polymer was dissolved in 0.38 ml ethanol. The solvent was evaporated until a clear, solvent free film is left. The film was further dried to constant weight. The co-precipitiate was crushed and the dried powder passed through sieve number 60. The final product was stored in a desiccator until further use (Adeli, 2016).

2.5. Dissolution studies

The in vitro dissolution study of haloperidol alone or from solid dispersions and physical mixtures was determined using Dissolution Pharma Tester type II (pharma test sp6-400, Gmpf, Germany). The dissolution test was performed using 900 ml of phosphate buffer (pH = 6.8), at 37 °C ± 0.5 °C and 50 rpm. Weight amount equivalent to 5 mg of haloperidol were added to dissolution medium. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at 5, 10, 20, 30, 40, 50 and 60 min. The sample was replaced with fresh dissolution medium of the same quantity. The removed samples were filtered through whatman filter paper and assayed for haloperidol content at λ max 243 nm after dilution. Each run was performed in triplicate. The amount of drug dissolved was calculated using the standard curve (Yasir and Sara, 2014).

2.6. Evaluation of powder (Determination of flowability and compressibility)

2.6.1. Bulk density (BD)

The bulk density was calculated according to (Rania and Kassem, 2008). It is expressed in g/ml and is given by the following formula: (BD = M/Vb).

Where, M: is the mass of powder and Vb: is the bulk volume of the powder.

2.6.2. Tapped density (TD)

The tapped density was calculated according to (Rania and Kassem, 2008). It is expressed in g/ml and is given by the following formula: (TD = M/Vt).

Where, M: is the mass of powder and Vt: is the tapped volume of the powder.

2.6.3. Void volume (Vo)

It was calculated according to (Irfan et al., 2016), by the following formula: (Vo = Vb – Vt). Where, Vb: is the void volume, Vb: is the bulk volume and Vt: is the volume after tapping.

2.6.4. Porosity (ε)

Total porosity (ε) = (1 – (vt /vb))

Where, vt: is the volume after tapping and Vb: is the bulk volume, Vt: is the tapped volume of the powder.
and expressed in percentage e = 1 - (vt /vb) × 100, Vb: bulk volume and Vt: the true volume of the powder blend.

2.6.5. Carr's index (I) or compressibility%

It was calculated according to (Mukesh Kumar et al., 2009), by the following formula: I = \( \frac{h}{r} \) × 100 Where, I: the Carr's index, TD: the tapped density of the powder and BD: the bulk density of the powder.

2.6.6. Hausner ratio

It was calculated according to (Mukesh Kumar et al., 2009), by the following formula: Hausner ratio = \( \frac{TD}{BD} \) Where: TD is the tapped density and BD: is the bulk density.

2.6.7. Angle of repose (θ)

The angle of repose was calculated according to (Mishra et al., 2006), by the following formula: \( \tan(\theta) = \frac{h}{r} \) \( \theta = \tan^{-1} \left( \frac{h}{r} \right) \) Where, θ is the angle of repose, h: is the height in Cm and r: is the radius in Cm.

2.7. Fourier transform infrared (FTIR) spectroscopy

Drug-excipients compatibility were tested, comparisons were made between the spectra of pure haloperidol powder, Avicel pH 102, polymer, SSG, Mg stearate, physical mixture and selected solid dispersion formula by (Perkin-Elmer 1600 FTIR spectrophotometer) using potassium bromide disk method. The wave number scanning range was 4000–400 cm⁻¹ and the resolutions was 1 cm⁻¹.

2.8. Differential scanning calorimetry (DSC)

Analysis was made using (Shimadzu DSC-60). Samples weighing 5 mg of pure haloperidol powder, excipients, physical mixture and selected solid dispersion formula were heated in hermetically sealed aluminum pans over the temperature range (0–200 °C) at a constant rate of 10 °C/min under a nitrogen purge (30 ml/min).

2.9. X-ray powder diffraction (XRD)

X-ray powder diffraction patterns were obtained with analytical Philips diffractometer with cuKα-radiation (1.50406 Å) at 30 mA and 40 KV in the region of 5°≤ 2θ≤ 50° with an angular increment of 0.02°/sec.

2.10. Formulation and preparation of tablets

Tablets of pure haloperidol, physical mixture and solid dispersion were prepared by direct compression method. The physical mixtures and solid dispersions equivalent to 5 mg of haloperidol were weight and uniformly mixed with diluents (Avicel), lubricant (Magnesium stearate) and super disintegrants (Sodium starch glocolate) according to Table 1. All the ingredients were passed through sieve number 60 prior to mixing and then directly compressed using compression machine (Single punch tablet machine fitted with 10 mm flat faced punches and dies (Korsh Frogerais; type AO, Berlin, Western Germany) (Yasir and Sara, 2014).

2.11. Evaluation of tablets

Haloperidol solid dispersion tablets had been evaluated. Weight variation were measured with electric balance (METTER Toledo, Ag, CH8806, Greifensee, Switzerland). Dimension was measured with (Pharma test, PTP311). The tablet hardness was measured with hardness tester (PTP-311, western Germany). Friability testing was conducted using friabelator tester (PTFR-A, western Germany) at 25 rpm speed and the percent of weight loss was calculated. Disintegration test was performed with disintegrating test machine (Pharma test type PTZ3). Ten tablets had been used for each test.

2.12. Determination of drug content

Ten tablets were randomly selected and powdered in a mortar. From this powder, a quantity equivalent to 10 mg of haloperidol was transferred into a 10 ml volumetric flask containing 5 ml of ethanol and shaken for 15 min. Then the volume was made up to 10 ml with ethanol, the solution was filtered, and 1 ml of the filtrate was diluted and analyzed at \( \lambda \) max 243 using (Genesys-UV1201, spectrophotometer USA). Haloperidol content was calculated from the prepared calibration curve.

2.13. The wetting time

Ten millimeters of water-containing methylene blue, a water-soluble dye, was added to the petridish containing tissue paper. The dye solution was used to identify complete wetting of the tablet surface. Ten tablets were selected randomly and each tablet is carefully placed on the surface of the wetted tissue paper in the petri dish at 25±0.5 °C. The time required for water to reach upper surface of the tablet was noted as a wetting time (Bush et al., 2008).

2.14. In vitro dissolution profile of prepared tablets

The in vitro release rate of haloperidol tablets contain pure drug, physical mixture and solid dispersion was determined using Dissolution Pharma tester (pharma test sp6-400, Gmph, Germany). The dissolution test was performed using 900 ml of phosphate buffer (pH = 6.8), at 37 °C ± 0.5 °C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at 5, 10, 20, 30, 40, 50 and 60 min. The samples were replaced with fresh dissolution medium of the same quantity. The removed samples were filtered through whatman filter paper and assayed for haloperidol content at 243 nm after making suitable dilution using UV spectrophotometer (Genesys-UV1201, USA). Each run was done in triplicate.

2.15. Stability studies:

To assess the stability of the selected haloperidol fast dissolving tablets, the stability studies were implemented for one, three and six months under different temperature and humidity conditions. Tablets were packed in glass container and stored at 25 °C / 75 % RH and 40 °C / 75 % RH. The tablets were evaluated for dimensions, hardness, friability, disintegration and drug release (Aftab et al., 2006).

2.16. Statistical analysis

All studies were performed in triplicate and the values were expressed as mean ± S.D. The data were analyzed by one way ANOVA test.

2.17. Evaluation of antipsychotic properties of haloperidol fast dissolving tablet

The forced swim test, was applied in this study. It is a rodent behavioral test used for evaluation of antidepressant drugs (Kurtuncu et al., 2005). Twelve Swiss male rats, weighing 200–250 g were employed in the study. Rats were purchased from unit.
of laboratory animal, faculty of veterinary medicine, Zagazig University. Rats were housed in poly acrylic cage in environmentally controlled rooms temperature (24–27 °C) and humidity 60–65 % with 12hr light: dark cycle. During the days of the experimental procedure the rats were given free access food and water, except for the specific time spent in the procedure room. The rats were handled 2 min daily, days prior to the beginning of the experimental procedure. Rats in this study were treated according to the guideline of institutional animal care and use committee (IACUC) of faculty of pharmacy, Zagazig University. (Approval number, ZU-IACUC/3/ F/17/2021).

Rats were divided into three different groups (Table 2), each group consisted of four rats (Deitzel et al., 2001). Tablets with a dose of 5 mg/kg body weight of rats (Dose = 1.125 mg) were administered by dispersing in distilled water through oral feeding pipe. Rats were placed in an inescapable transparent tank that was filled with water and their escape related mobility behavior had been measured (Hascoét, and Bourin, 2009).

Rats in this study were treated according to the guideline of institutional animal care and use committee (IACUC) of faculty of pharmacy, Zagazig University. (Approval number, ZU-IACUC/3/ F/17/2021).

The duration of time spent as “Immobile” if the rats was floating with the absence of any movement except for those necessary for keeping the nose above water was calculated. The duration of time spent as “Struggling /climbing” if quick movements of the forelimbs were observed such that the front paws break the surface of the water was observed. The duration of time spent as “Swimming” if movement of forelimbs or hind limbs in a paddling fashion was observed (Cryan, 2005).

3. Results and discussion

3.1. Solubility studies

The solubility of haloperidol in distilled water at 25 °C was found to be 0.044 mg/ml. The result of solubility and enhancement ratio of haloperidol in presence of different ratios of PEG4000, PVP EK and CMC at 25 °C are shown in (Table 3.).The three polymers produce solubility enhancement. The enhancement ratio ranged between 2.30 and 11.40. The solubility of haloperidol increased as the polymers concentration increased.

The polymer can be ranked according to its effects on increasing the solubility of haloperidol as PEG4000 > PVP EK > CMC. PEG 4000 polymer gives the highest enhancement ratio. The increased solubility of haloperidol in the presence of these polymers may be attributed to both complex formation and reduction of surface tension of water and hence intermolecular force and polarity existed by their presence (Abdul-Fattah and Bhargara, 2002).

3.2. Preparation of solid dispersion

Solid dispersion of haloperidol in different ratio of PEG 4000, PVP EK and CMC were prepared using two different methods solvent evaporation and melting method. Table 4 shows the composition of haloperidol solid dispersion.

3.3. Dissolution studies

The prepared solid dispersion were subjected to dissolution study and compared with physical mixture and pure drug. The solid dispersion were evaluated by in vitro dissolution rate. As
shown in (Fig. 1, 3 and 5) the percent of haloperidol dissolved was increased after 60 min from 32.7 ± 0.11 % to 100.2 ± 0.11 %, 91.25 ± 0.22 % and 97.5 ± 0.03 % using 1:8 (PEG4000, PVP EK and CMC) respectively in case of solvent evaporation method and increased to 104 ± 0.23 %, 90.1 ± 0.22 % and 97.5 ± 0.31 % using 1:8 (PEG4000, PVP EK and CMC) respectively in case of melting method (1:8) for PEG4000. (See Figs. 2-6).

It is obvious from the dissolution results that the polymer type affect the dissolution rate of haloperidol from its solid dispersion. The dissolution rate of haloperidol was enhanced as the proportion of each polymer increased. The dissolution results of haloperidol from the solid dispersion show that the melting method was more efficient to improve the dissolution of drug from solid dispersion of the three polymers in different ratio. The percent of haloperidol released in 60 min from 1:2 PEG4000 solid dispersion prepared by solvent evaporation and melting method were 53.8 ± 0.51 % and 84.3 ± 0.22 % respectively (Guo et al., 2014).

Table 4
The composition of Haloperidol dispersion.

| Code | Composition | Ratio | Method       |
|------|-------------|-------|--------------|
| SD 1 | Haloperidol / PEG 4000 | 1:2 1:4 1:6 | Solvent evaporation Method |
| SD 2 | Haloperidol /PEG 4000 | 1:2 1:4 1:6 | Melting Method |
| SD 3 | Haloperidol / PVP EK | 1:2 1:4 1:6 | Solvent evaporation Method |
| SD 4 | Haloperidol /PVP EK | 1:2 1:4 1:6 | Melting Method |
| SD 5 | Haloperidol /CMC | 1:2 1:4 1:6 | Solvent evaporation Method |
| SD 6 | Haloperidol /CMC | 1:2 1:4 1:6 | Melting Method |

3.4. Evaluation of tablets

3.4.1. Pre compression tests

Pre compression tests show that all prepared formulas have good angle of repose, Carr’s index %, Hausner ratio, Void volume and porosity. So all formulas were then compressed and tested for post compression tests (Table 5).

3.4.2. Fourier transform infrared (FTIR) spectroscopy

From FTIR data (Fig. 7), it is shown that pure haloperidol had an intense characterization absorption band at 2700 cm⁻¹ corresponding to O—H group, at 750 cm⁻¹ corresponding to C—H group aliphatic and at 3100 cm⁻¹ corresponding to C—H group aromatic. FTIR of PEG 4000 showed an intense band at 1170 cm⁻¹ corresponding to O—C—O group and at 2650 cm⁻¹ corresponding to O—H group.

FTIR results of the selected formulation of solid dispersion (F2) showed the formation of hydrogen bond between haloperidol drug and PEG4000 polymer resulted to the disappearance of the intense O—H peak of pure haloperidol in the FTIR spectra of solid dispersion (Fig. 7), but this intesned peak appear at FTIR spectra of physical mixture.

3.4.3. Differential scanning calorimetry (DSC)

DSC studies were performed for pure haloperidol, solid dispersion formula, physical mixture and their component. DSC thermogram are presented in Fig. 8 and Table 6. Pure haloperidol shows distinct sharp peak at 152 °C corresponding to its melting point. The peak was disappear in physical mixture and solid dispersion indicate complete homogeneity with the tablet component and formation amorphous form of haloperidol.

3.4.4. X-ray powder diffraction (XRD)

As shown in Fig. 9, Haloperidol displayed sharp peaks at different diffraction angles indicating its crystalline shape. The major characteristic peaks of haloperidol drug and PEG4000 polymer were observed in physical mixture with lower intensity, where the X-ray diffractiogram of solid dispersion (SD2) showed no obvious peaks of haloperidol.

3.4.5. Post compression tests

The results of tablets evaluation are shown in (Table 7). All tablets show friability < 0.4 indicating good mechanical strength and ability to tolerate physical handling conditions (Irfan et al., 2016).

Hardness values for the prepared formulation ranged from 3.8 ± 0.32 kg to 6.4 ± 0.11 kg. None of the prepared tablets showed hardness below 3 kg. These value is within the range of preferable
Fig. 2. Cumulative dissolution of haloperidol solid dispersion with PEG4000 by melting method.

Fig. 3. Cumulative dissolution of haloperidol solid dispersion with PVP EK by solvent evaporation method.

Fig. 4. Cumulative dissolution of haloperidol solid dispersion with PVP EK by melting method.
Table 5
Results of pre-compression tests.

| Formula | Bulk Density ± SD<br>n=3 | Tapped Density ± SD<br>n=3 | Angle of repose ± SD<br>n=3 | Carr’s Index (%) ± SD<br>n=3 | Hausner Ratio ± SD<br>n=3 | Void Volume ± SD<br>n=3 | Porosity (%) ± SD<br>n=3 |
|---------|---------------------------|---------------------------|-----------------------------|---------------------------|---------------------------|---------------------------|---------------------------|
| F P     | 0.22 ± 0.11               | 0.31 ± 0.22               | 31.20 ± 0.09 passable       | 29.03 ± 0.11 poor         | 1.41 ± 0.23 poor          | 0.40 ± 0.17               | 19.20 ± 0.12               |
| F PM    | 0.19 ± 0.23               | 0.24 ± 0.11               | 21.80 ± 0.22 Good          | 14.6 ± 0.12 Good          | 1.60 ± 0.28 Good          | 0.70 ± 0.12               | 14.33 ± 0.10               |
| F1      | 0.39 ± 0.1                | 0.45 ± 0.08               | 17.20 ± 0.24 Good          | 13.95 ± 0.22 Good         | 1.16 ± 0.02 Good          | 0.80 ± 0.02               | 18.60 ± 0.22               |
| F2      | 0.41 ± 0.21               | 0.48 ± 0.11               | 18.40 ± 0.22 Good          | 14.60 ± 0.32 Good         | 1.17 ± 0.07 Good          | 0.60 ± 0.04               | 14.60 ± 0.21               |
| F3      | 0.42 ± 0.12               | 0.52 ± 0.09               | 26.50 ± 0.25 Good          | 15.00 ± 0.24 Good         | 1.17 ± 0.13 Good          | 0.60 ± 0.01               | 15.00 ± 0.14               |
| F4      | 0.41 ± 0.14               | 0.47 ± 0.12               | 20.56 ± 0.33 Good          | 11.10 ± 0.22 Good         | 1.17 ± 0.13 Good          | 0.40 ± 0.01               | 10.00 ± 0.03               |
| F5      | 0.44 ± 0.08               | 0.515 ± 0.22              | 26.50 ± 0.32 Good          | 15.38 ± 0.90 Good         | 1.18 ± 0.06 Good          | 0.60 ± 0.03               | 15.40 ± 0.22               |
| F6      | 0.42 ± 0.07               | 0.491 ± 0.23              | 21.80 ± 0.41 Good          | 15.00 ± 0.14 Good         | 1.17 ± 0.22 Good          | 0.60 ± 0.05               | 15.00 ± 0.12               |

FP: Formula of pure drug.
FPM: Formula of physical mixture F1: Solid dispersion PEG (1:8) solvent evaporation method
F2: Solid dispersion PEG (1:8) melting method.
F3: Solid dispersion PVP (1:8) solvent evaporation method.
F4: Solid dispersion PVP (1:8) melting method.
F5: Solid dispersion CMC (1:8) solvent evaporation method
F6: Solid dispersion CMC (1:8) melting method.
range of 2–8 kg for mouth dissolve tablet (Irfan et al., 2016), where it provides sufficient mechanical strength porosity for disintegration and wetting time. Thickness values for the prepared formulation ranged from 1.22 ± 0.06 to 1.86 ± 0.08. The mean percentage of haloperidol content is 98.38. Weight uniformity range from 166 ± 0.32 to 190 ± 0.18. Disintegration time range from 14 ± 0.22 sec to 37 ± 0.5 sec. All physical characterization tests were within limit of pharmacopeia (British Pharmacopeia, 2005). Post compression evaluation show that all prepared formula have good dimensions, hardness, friability, disintegration time, wetting time and drug content then these formula tested for dissolution.

3.4.6. In vitro dissolution profile of tablets

Table 8 and Fig. 10 show that the release of haloperidol from tablets (1:8 PEG 4000, PVP EK and CMC polymer prepared by solvent evaporation and melting method) were higher than the release of haloperidol from tablet containing pure drug (See Figs. 11-14).

The enhancement in release rate of solid dispersion tablets as compare to that of tablets containing pure drug can be attributed to both increase in the surface area and solubilization effect (Joshir et al., 2018). Owing to formation of amorphous structure haloperidol, a greater solubility would result in faster dissolution rates.
Complex formation between drug and inert soluble polymer may be a factor in release enhancement (Hughey et al., 2015).

3.4.7. Stability test

Tablets contain pure haloperidol, physical mixture and prepared solid dispersion were subjected to stability study by storing for 1, 3 and 6 months at 25°C/75RH & at 40°C/75RH. Tablets were analyzed for dimensions, friability, hardness, disintegration and drug release. Tables 9, 10, 11 and 12 show non–significant change in dimensions, friability, hardness, disintegration and drug release.

**Table 6**

| Component          | Endothermic peak |
|--------------------|------------------|
| Pure Haloperidol   | 152.31 °C        |
| Solid dispersion   | 372.23 °C        |
| Physical mixture   | 60.59 °C         |
| PEG 4000           | 63.15 °C         |
| Avicel pH 102      | 355.84 °C        |
| SCC                | 310.75 °C        |
| Mg stearate        | 122.24 °C        |

Fig. 8. DSC thermogram of (a) solid dispersion tablets (b) physical mixture (c) Avicel (d) SCC (e) Mg stearate (f) PEG-4000 (g) Pure haloperidol.
Fig. 9. (XRD) scanning of (a) solid dispersion tablets (b) physical mixture (c) Avicel (d) SCC (e) Mg stearate (f) PEG4000 (g) Pure haloperidol.

Table 7
Results of post compression test.

| Formula | Thickness (mm) ± SD n=3 | Diameter (mm) ± SD n=3 | Weight uniformity (mg) ± SD n=3 | Hardness (kg) ± SD n=3 | Friability (%) ± SD n=3 | Disintegration time (sec) ± SD n=3 | Wetting time (sec) ± SD n=3 | Drug content (%) ± SD n=3 |
|---------|-------------------------|------------------------|-------------------------------|-----------------------|------------------------|-------------------------------|----------------------------|--------------------------|
| FP      | 1.22 ± 0.06             | 10.00 ± 0.06           | 166 ± 0.32                    | 6.4 ± 0.11            | 0.41 ± 0.12            | 14 ± 0.22                     | 96.2 ± 0.11                | 96.00 ± 0.18             |
| FPM     | 2.3 ± 0.11              | 10.30 ± 0.11           | 190 ± 0.18                    | 4.0 ± 0.22            | 0.19 ± 0.22            | 37 ± 0.5                      | 98.3 ± 0.31                | 98.00 ± 0.13             |
| F1      | 1.85 ± 0.04             | 10.02 ± 0.02           | 173 ± 0.81                    | 4.0 ± 0.10            | 0.17 ± 0.23            | 35 ± 0.33                     | 33.00 ± 0.22               | 99.21 ± 0.14             |
| F2      | 1.86 ± 0.08             | 10.13 ± 0.03           | 174 ± 0.20                    | 3.8 ± 0.32            | 0.19 ± 0.20            | 30 ± 0.21                     | 35.00 ± 0.23               | 101.50 ± 0.22            |
| F3      | 1.63 ± 0.01             | 9.98 ± 0.05            | 174 ± 0.25                    | 4.5 ± 0.13            | 0.18 ± 0.31            | 24 ± 0.16                     | 36.00 ± 0.2                | 98.60 ± 0.13             |
| F4      | 1.68 ± 0.05             | 10.01 ± 0.01           | 175 ± 0.17                    | 4.6 ± 0.10            | 0.13 ± 0.12            | 28 ± 0.33                     | 34.00 ± 0.12               | 98.90 ± 0.25             |
| F5      | 1.71 ± 0.03             | 10.03 ± 0.04           | 174 ± 0.12                    | 4.3 ± 0.22            | 0.12 ± 0.08            | 37 ± 0.24                     | 35.00 ± 0.06               | 100.10 ± 0.31            |
| F6      | 1.70 ± 0.02             | 10.01 ± 0.02           | 174 ± 0.34                    | 4.5 ± 0.14            | 0.16 ± 0.21            | 26 ± 0.31                     | 37.00 ± 0.31               | 97.88 ± 0.26             |
3.4.8. In vivo evaluation of fast dissolving tablets

The anti-psychotic activity of Haloperidol was postulated to measure the enhanced absorption of haloperidol as well as its onset of action, compared to commercially haloperidol product. The model for anti-psychotic used in this study is the "Forced Swim test". This method evaluates haloperidol efficacy and the effects of various behavioral and neurobiological manipulations. The FST (Forced Swimming Test) is used to monitor depressive-like behavior and is based on the assumption that immobility reflects a measure of behavioral despair.

Table 13 and Fig. 11 show that group 2 (Rats treated with prepared solid dispersed tablet F2) and group 3 (Rats treated with commercial haloperidol product) produced a significant increase in immobility time at \( p < 0.05 \) compared to group 1 (control) revealing the presence of antidepressant actions in this groups.

![Graph 1](graph1.png)

**Fig. 10.** Results of % of dissolution release of Haloperidol physical mixture (1:8) and pure drug.

![Graph 2](graph2.png)

**Fig. 11.** Representative results of the effects of haloperidol treatment on swimming time, climbing time and immobility time in the FST.

### Table 8

Results of cumulative percent released of Haloperidol solid dispersion tablets (1:8) and pure drug.

| Formula | Time (min) | 5 | 10 | 20 | 30 | 40 | 50 | 60 |
|---------|------------|---|----|----|----|----|----|----|
| FP      | Cumulative drug release % | 00.25 ± 0.12 % | 03.75 ± 0.21 % | 06.32 ± 0.02 % | 09.60 ± 0.12 % | 11.30 ± 0.32 % | 23.40 ± 0.14 % | 28.30 ± 0.21 % |
| F1      | 38.75 ± 0.11 % | 50.00 ± 0.31 % | 55.50 ± 0.27 % | 62.50 ± 0.11 % | 62.50 ± 0.06 % | 67.50 ± 0.32 % | 72.50 ± 0.17 % |
| F2      | 35.00 ± 0.22 % | 46.25 ± 0.24 % | 55.00 ± 0.31 % | 61.25 ± 0.25 % | 67.50 ± 0.23 % | 76.25 ± 0.21 % | 85.00 ± 0.08 % |
| F3      | 41.25 ± 0.32 % | 47.50 ± 0.25 % | 51.25 ± 0.22 % | 57.50 ± 0.13 % | 58.75 ± 0.12 % | 63.75 ± 0.14 % | 65.00 ± 0.31 % |
| F4      | 46.25 ± 0.22 % | 47.50 ± 0.31 % | 48.75 ± 0.22 % | 49.50 ± 0.15 % | 56.25 ± 0.11 % | 60.00 ± 0.09 % | 65.00 ± 0.34 % |
| F5      | 41.25 ± 0.12 % | 43.75 ± 0.33 % | 53.75 ± 0.41 % | 60.00 ± 0.02 % | 62.50 ± 0.13 % | 65.00 ± 0.07 % | 67.50 ± 0.32 % |
| F6      | 41.25 ± 0.41 % | 42.50 ± 0.03 % | 48.75 ± 0.11 % | 53.75 ± 0.17 % | 60.00 ± 0.22 % | 62.50 ± 0.31 % | 67.50 ± 0.04 % |
The one way ANOVA test showed that there is a statistically significant difference in the immobility time between group 2 (Rats treated with prepared solid dispersed tablet) and group 1 (control). While, no statistically significant difference was observed between group 2 (Rats treated with prepared solid dispersed tablet and group 3 (Rats treated with commercial haloperidol tablets), revealing that the selected prepared solid dispersion formula succeeded to give anti depressive action of haloperidol.

Fig. 12. Results of the effects of haloperidol treatment on swimming time in the FST.

Fig. 13. Results of the effects of haloperidol treatment on climbing time in the FST.
Fig. 14. Results of the effects of haloperidol treatment on immobility time in the FST.

Table 9
Stability studies after 6 month at 25°C (Post compression tests).

| Test                  | Pure drug ± SD | Physical mixture ± SD | SD 1 ± SD | SD 2 ± SD | SD 3 ± SD | SD 4 ± SD | SD 5 ± SD | SD 6 ± SD |
|-----------------------|----------------|-----------------------|-----------|-----------|-----------|-----------|-----------|-----------|
| Thickness (mm)        | 1.31 ± 0.24    | 1.9 ± 0.13            | 1.79 ± 0.02 | 1.79 ± 0.13 | 1.86 ± 0.14 | 1.92 ± 0.18 | 1.93 ± 0.42 | 1.76 ± 0.3  |
| Diameter (mm)         | 10.02 ± 0.22   | 10.01 ± 0.14          | 10.01 ± 0.21 | 10.01 ± 0.3  | 10.09 ± 0.24 | 10.01 ± 0.18 | 9.99 ± 0.17 | 10.01 ± 0.34 |
| Hardness (kg)         | 4.3 ± 0.12     | 4.1 ± 0.11            | 5.8 ± 0.12  | 5.2 ± 0.13  | 5.2 ± 0.42 | 4.9 ± 0.23  | 5.1 ± 0.17  | 5.6 ± 0.12  |
| Friability (%)        | 0.19 ± 0.04    | 0.34 ± 0.33           | 0.1 ± 0.02  | 0.07 ± 0.13 | 0.31 ± 0.24 | 0.08 ± 0.33 | 0.07 ± 0.22 | 0.21 ± 0.33 |
| Disintegration (sec)  | 18 ± 0.21      | 36 ± 0.12             | 33 ± 0.11  | 37 ± 0.23  | 36 ± 0.14  | 28 ± 0.33  | 33 ± 0.02  | 29 ± 0.14  |

Table 10
Stability studies after 6 month at 25°C (Cumulative percent released).

| Time (min) | Cumulative drug release(%) ± SD (n = 3) |
|------------|-----------------------------------------|
| 5          | 0.35 ± 0.22 %                           |
| 10         | 3.2 ± 0.04 %                            |
| 20         | 5.9 ± 0.13 %                            |
| 30         | 8.1 ± 0.32 %                            |
| 40         | 13.9 ± 0.41 %                           |
| 50         | 22.2 ± 0.03 %                           |
| 60         | 31.7 ± 0.42 %                           |

Table 11
Stability studies after 6 month at 40°C (post compression tests).

| Test                  | Pure drug ± SD | Physical mixture ± SD | SD 1 ± SD | SD 2 ± SD | SD 3 ± SD | SD 4 ± SD | SD 5 ± SD | SD 6 ± SD |
|-----------------------|----------------|-----------------------|-----------|-----------|-----------|-----------|-----------|-----------|
| Thickness (mm)        | 1.32 ± 0.11    | 1.82 ± 0.03           | 1.79 ± 0.22 | 1.77 ± 0.14 | 1.93 ± 0.05 | 1.94 ± 0.14 | 1.76 ± 0.17 | 1.76 ± 0.02 |
| Diameter (mm)         | 10.00 ± 0.12   | 10.01 ± 0.22          | 10.00 ± 0.03 | 9.99 ± 0.09 | 10.01 ± 0.07 | 10.02 ± 0.14 | 10.00 ± 0.28 | 10.01 ± 0.31 |
| Hardness (kg)         | 4.1 ± 0.32     | 4.2 ± 0.08            | 5.1 ± 0.21  | 5.2 ± 0.51  | 5.2 ± 0.13  | 5.4 ± 0.12  | 6.1 ± 0.13  | 6.3 ± 0.22  |
| Friability (%)        | 0.2 ± 0.04     | 0.23 ± 0.14           | 0.08 ± 0.14 | 0.06 ± 0.24 | 0.3 ± 0.08  | 0.08 ± 0.17 | 0.04 ± 0.15 | 0.08 ± 0.22 |
| Disintegration (sec)  | 17 ± 0.05      | 38 ± 0.23             | 39 ± 0.14  | 33 ± 0.11  | 30 ± 0.13  | 32 ± 0.22  | 37 ± 0.14  | 38 ± 0.25  |

Table 12
Stability studies after 6 month at 40°C (Cumulative percent released).

| Time (min) | Cumulative drug release(%) ± SD (n = 3) |
|------------|-----------------------------------------|
| 5          | 0.36 ± 0.41 %                           |
| 10         | 3.8 ± 0.22 %                            |
| 20         | 5.7 ± 0.23 %                            |
| 30         | 7.81 ± 0.44 %                           |
| 40         | 13.2 ± 0.12 %                           |
| 50         | 21.9 ± 0.23 %                           |
| 60         | 31.3 ± 0.22 %                           |

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(7) prepared solid dispersion FDT
(8) Purchased tablet
Table 13 Representative results of the effects of haloperidol treatment on swimming time, climbing time and immobility time in the FST.

| Animal group | Swimming time ± SD (sec) | Climbing time ± SD (sec) | Immobility time ± SD (sec) |
|--------------|--------------------------|--------------------------|---------------------------|
| Group 1      | 140 ± 0.12               | 100 ± 0.02               | 0                         |
| Group 2      | 100 ± 0.14               | 40 ± 0.13                | 100 ± 0.21                |
| Group 3      | 95 ± 0.11                | 35 ± 0.08                | 110 ± 0.32                |

Group 1: Control rats.
Group 2: Rats treated with prepared solid dispersed tablet.
Group 3: Rats treated with commercial haloperidol tablets.

4. Conclusion

Haloperidol can be prepared in solid dispersion fast dissolving tablet using PEG 4000, PVP EK and CMC polymers by solvent evaporation method and melting method. Solid dispersion (SD) technique improve solubility of a poorly water-soluble drug in a pharmaceutical, rapid disintegration oral tablets. The best prepared formula (F2) in which the PEG4000 was used as a polymer in a ratio 1:8 using melting method produced the highest drug release. The in vitro drug release of prepared solid dispersed fast dissolving tablets were evaluated and the results show improvement of drug release using PEG 4000 polymer in ratio 1:8 by melting method in comparison to tablets containing pure drug. The prepared tablets also tested for thickness, hardness friability, disintegration and drug content. Forced swim test (FST) was used for in vivo evaluation of antipsychotic activity of haloperidol fast dissolving tablet. The in vivo results of FST show the significant antipsychotic activity of haloperidol in prepared solid dispersed fast dissolving tablet and commercial haloperidol tablets in comparison to control and no significant difference between prepared solid dispersed fast dissolving tablet and commercial haloperidol tablet.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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