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Development and Evaluation of Fast Dissolving Liquisolid Haloperidol Tablets

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Aim: The aim of this study was to design fast dissolving tablets (FDT) of the anti -psychiatric drug, Haloperidol in liquisolid forms as a way to enhance its dissolution profile and anti-psychiatric effect.
Methodology: Solubility studies of Haloperidol in various solvents and surfactants were conducted. The solvent with high solubilizing ability was tween 20 (80%), selected and absorbed into the carrier and then coating material added with other solid powder excipients, finally all powder compressed into tablets. The resulting liquisolid 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 liquisolid systems, followed by *in vivo* studies through forced swimming test (FST).
Results: Pre-compression studies showed adequate flowability and compatibility of liquid and solid excipients with haloperidol. The selected liquisolid tablet (LS4) demonstrated the best disintegration and water absorption ratio in addition to satisfactory friability and hardness. Attempts of in vivo dissolution results and thermodynamic stability studies showed acceptable results for the F4 formulation containing 80% Tween 20,Avicel and aerosel (0.22:81.6:10.2%), respectively. The in vivo study of (LS4) formulation revealed the highest immobility time to rats compared to control rats and others treated with purchased halonace®.
Conclusion: Fast dissolving liquisolid tablets expressed rapid onset of action with enhanced anti-psychiatric effect of haloperidol.

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Keywords: Haloperidol; liquisolid; fast dissolving tablets; tween 20.

1. INTRODUCTION

The concept of Fast Dissolving System emerged from the desire to provide patient with conventional means of taking their medication. Because of physiological changes associated with, especially, elderly and pediatrics are quite unable to swallow (Dysphagia); rather, this is a common problem of all age groups patients [1]. Food and drug administration (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"[2] . Fast dissolving tablets comprise either very porous and soft-molded matrices or tablet with very low compression force [3]. Drug with poor solubility has 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. Liquisolid technique has been utilized as effective strategy to improve the dissolution and bioavailability of poorly water-soluble drugs [4]. Haloperidol belongs to a class of drugs called Antipsychotics, 1st generation CYP3A4 inhibitor, prescribed to treat the symptoms of schizophrenia and psychosis. 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 [5]. As per Bio pharmaceutics Classification System (BCS) ,Haloperidol is class Ⅱ drug with poor solubility and high permeability .Oral bioavailability of haloperidol ranged between 60%and 70% ,it under goes extensive metabolism in liver ,with only around 1% of the drug originally administered being excreted in the urine unchanged [6]. It is available as tablets, oral drops ,Intramuscular (IM/) Intravenous (IV) ampules dosage forms .Haloperidol is a phenyl butyl piperadine derivative with antipsychotic, neuroleptic, and antiemetic activities, marketed under the trade name Haloperidol, Haldol, Serenace, among others.

Our aim of this research was to develop fast dissolving tablets of haloperidol using tween 20(80%) as non-volatile solvent, Avicel PH102 and aerosel PH200 as carrier using direct compression method.

2. MATERIALS AND METHODS

2.1 Materials

Haloperidol obtained from (El.Kahira pharmaceutical chemicals. Cairo. Egypt); Avicel PH 102(AV1), Aerosel PH200, Sodium starch glycolate (SSG), Magnesium stearate and Talc obtained from (Cid company, Giza, Egypt); polyethylene glycol (PEG 400), Poly viniyl pyrolidine (pvp Ek) and Carboxy methyl cellulose (CMC) obtained from (EL. Nasr pharmaceutical chemicals Co .Egypt); Tween 20, Tween 80, polyethylene glycol(PEG400), propylen glycol(PG), potassium dihydrogen orthoph-osphate, disodium hydrogen orthophosphate and Absolute ethanol obtained from (EL Gomhoria company, Zagazig, Egypt). All reagents &solvents used were of analytical grade.

2.2 Methods

2.2.1 Solubility studies and selection of non-volatile solvent

High boiling point, inert and water miscible organic solvents such as propylene glycol, tween 20, tween 80, polyethylene glycol 400 were selected and solutions were prepared. To each of these solvents, excess quantity of drug (10mg) was added and saturated solutions were prepared by shaking on a mechanical shaker water bath at 25°C for 72hrs. The saturated solutions were kept aside overnight, filtered and appropriate dilutions were made, the absorbance was measured at 243 nm using UV visible spectrophotometer (Geneysis-UV1201,USA).

2.2.2 Selection of carrier and coat material ratio and calculation of liquid load factor

From the solubility studies tween 20 (80%) solution in water was selected as nonvolatile liquid for the preparation of liqui-solid compacts. For the present study microcrystalline cellulose (AV1 pH 102) and aerosol PH 200 were used as carrier materials. Calcium carbonate and aerosol were tested as coating material. Mixtures of carrier and coating materials in different ratios 5:1, 6:1, 7:1 and 8:1 were prepared and a load

factor was determined by adding a quantity of tween 20 (80%) in small increments to obtain free flowing powder using a mortar and pestle. Loading factor is calculated by Lf = W/Q, Where W = Amount of liquid medication Q = Amount of the carrier material [7].

2.2.3 Preparation of liqui-solid tablets

Weighed amount of haloperidol (5mg), and (0.43 ml) of nonvolatile liquids Tween20 (80%) were taken in a glass beaker and mixed well with a glass rod in order to dissolve the drug in liquid. This liquid medication solution was added slowly to the mortar containing carrier (AV1 PH102) and coat (Aerosel PH200) material blend and triturated to distribute the liquid medication uniformly throughout the powder mixture. This entire powder blend was left aside for 5 min to absorb the liquid by carrier and coat material mixture, then SSG and magnesium stearate were added and compressed by direct compression technique via single bunch tablet machine (Korsh Frogerais; type AO, Berlin, Western Germany).

2.2.4 Pre Composition evaluation parameters

2.2.4.1 Bulk Density (BD)

The bulk density is calculated according to [8]. It is expressed in g/ml. (BD = M/ Vb) Where, M: is the mass of powder and Vb: is the bulk volume of the powder.

2.2.4.2 Tapped Density (TD)

The tapped density is calculated according to [8]. It is expressed in g/ml. (TD = M / Vt), Where, M: is the mass of powder and Vt: is the tapped volume of the powder.

2.2.4.3 Angle of Ρεποσε (θ)

The angle of repose is calculated according to [9], (tan (θ) = h / r), (θ = tan-1 (h / r)) Where, θ : is the angle of repose, h: is the height in cms and r: Is the radius in cms.

2.2.4.4 Carr's index (I) or compressibility%

It is calculated according to [10], I =$\frac{BD-TD}{TD} \times 100$.

2.2.4.5 Hausner ratio

It is calculated according to [10], Hausner ratio = $\frac{TD}{BD}$.

2.2.4.6 Void volume (Vo)

It is calculated according to [11]. (Vo =Vb – Vt) Where, Vo: is the void volume, Vb: is the bulk volume and Vt: is the volume after tapping.

2.2.4.7 Porosity (ϵ)

Total porosity ϵ is the ratio of void volume to bulk volume, It was calculated according to [11]

(ε = 1- (vt /vb)) and expressed in percentage ε = 1- (vt /vb) ×100
Vb: bulk volume and Vt: the true volume of the powder blend

2.2.5 Post compression evaluation parameters

Haloperidol liquisolid tablets were evaluated. Weight variation were measured with electric balance (Metter Toledo,Ag, CH8606, 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 25rpm speed and calculate the percent of weight loss. Disintegration testing was applied with disintegrating test machine (Pharma test type PTZ3).Ten tablets were used for each test [12].

2.2.6 Determination of drug content

Randomly selected 10 tablets were powdered in a mortar. From this powder, a quantity equivalent to 5mg of haloperidol was dissolved in 5 ml ethanol by shaken for 15 min in volumetric flask. Then the volume was made up to 10 ml by ethanol, the solution was filtered, analyzed at λmax 243 using ((Geneysis-UV1201), spectrophotometer USA).

2.2.7 The wetting time

Ten tablets were selected randomly and each tablet was placed carefully in a mortar in which drops of water soluble methylene blue dye were added. Wetting time was calculated as the time required for the top surface of tablet to take the blue color [13].

2.2.8 *In vitro* dissolution profile of prepared tablets

The *in vitro* release rate of haloperidol tablets contain pure drug, physical mixture and liquisolid

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 at 5, 10, 20, 30, 40, 50 and 60 min and replaced with fresh dissolution medium of the same quantity. The samples were filtered through whattman filter paper and assayed for haloperidol content at 243nm after making suitable dilution using UV spectrophotometer (Geneysis-UV1201), USA. Each run was done in triplicate [14].

2.2.9 Fourier Transform Infrared (FTIR) spectroscopy

Drug-excipient compatibility were tested, Avicel PH 102, Aerosel, Tween20 (80%), SSG, Mg stearate, physical mixture and selected liquisolid 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}.

2.2.10 Differential scanning Calorimetry (DSC)

Analysis was made using (Shimadzu DSC-60). Samples weighing 5mg of pure haloperidol powder, excipients, physical mixture and selected liquisolid 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 (30ml/min).

2.2.11 X-Ray powder Diffraction (XRD)

X-ray powder diffraction patterns were obtained with analytical Philips diffractometer with cukα-radiation (ƛ = 1.50406 A°) at 30 mA and 40 KV in the region of 5°≤ 20°≤ 50° with an angular increment of 0.02°/sec.

2.2.12 Stability studies

To assess the stability of the selected haloperidol fast dissolving–tablets, the stability studies were implemented for 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 [13].

2.3 Statistical Analysis

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

2.3.1 Evaluation of antipsychotic properties of haloperidol fast dissolving tablets

The forced swim test (a rodent behavioral test) for evaluation of antidepressant drugs [15]. Twelve Swiss male rats, weighing 200–250g 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 for 2 min daily, 5 days prior to the beginning of the experimental procedure [16].

Table 1. Coded and composition of the batches

F	Drug (mg)	Solvent (mg)	R	Ca.co3	Avicel (mg)	Aerosel (mg)	LF	SCC (mg)	Mg. Stearate (mg)	*Total Wt (mg)*
Pure drug	5	-	-	-	150	-	-	7.75	1.627	164.38
Physical mixture	5	0.43	5	-	150	30	0.036	9.27	1.947	196.68
LS 1	5	0.43	5	-	150	30	0.036	9.27	1.947	196.65
LS 2	5	0.43	6	-	154.8	25.7	0.035	9.27	1.947	196.65
LS 3	5	0.43	7	-	157.5	22.5	0.034	9.27	1.947	196.65
LS 4	5	0.43	8	-	160	20	0.033	9.27	1.947	196.65
LS 5	5	0.43	5	250	-	50	0.022	15.27	3.207	323.91

LS: prepared liquisolid fast dissolving tablet R: Avicel /Aerosel LF: Loading factor

Rats were divided into three different groups (n=4 per group).Group1: Control group (No drug given), Group 2: Rats were treated with orally liquisolid fast dissolving tablets (1.125mg)(F4) and Group 3: Rats were treated orally with purchased halonace® tablet (1.125 mg).Rats are placed in an inescapable transparent tank that is filled with water and their escape related mobility behavior is measured [17].

Rats in this study were treated according to the guideline of institutional animal care 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 is 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 fore limbs are 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 [18].

3. RESULTS AND DISCUSSION

3.1 Solubility Studies and Selection of Nonvolatile Solvent

The solubility of Haloperidol in presence of different solvents at 25˚C are shown in Table (2). Drug solubility was higher in all solvents used than that of water Table (2). In case in (tween 20/dist. water 80:20) it is solubility was 27 fold increase. For this, Tween 20 (80%) solvent was selected to prepare liquisolid system of haloperidol.

Table 2. Solubility Studies of haloperidol at different solvents

Non-volatile solvent	Solubility (mg/ml) ±SD n=3
Distilled .water	0.044±0.12
PEG 400	3.278 ±0.32
PEG400 (75%)	1.445±0.19
PEG 400 (50%)	0.6387±0.22
PEG 400 (25%)	0.208±0.17
PG	1.78 ±0.20
PG (75%)	0.813±0.11
PG (50%)	0.309±0.20
PG (25%)	0.21±0.23
PEG400+PG (1:1)	0.748±0.23
Tween20	0.958 ±0.15
80%Tween20	**12.23 ±0.21**
Tween 80	1.12 ±0.23
80%Tween 80	1.3 ±0.14
Labrfac	3.193 ±0.11

3.2 Selection of Carrier and Coat Material Ratio and Calculation of Liquid Load Factor

Table 3. Selection of carrier and coating material and calculation of LF

Formula	Concentration of drug% w/w in liquid vehicle (12.2mg/ml)	Calcium carbonate (mg)	Avicel PH 102 (Q) (mg)	Aerosil 200 (q) (mg)	R =Q/q	Lf
LS1	12	-	150	30	5	0.036
LS2	12	-	154.8	25.7	6	0.035
LS3	12	-	157.5	22.5	7	0.034
LS4	12	-	160	20	8	0.033
LS5	12	250	-	50	5	0.0216

3.3 Evaluation of Tablets

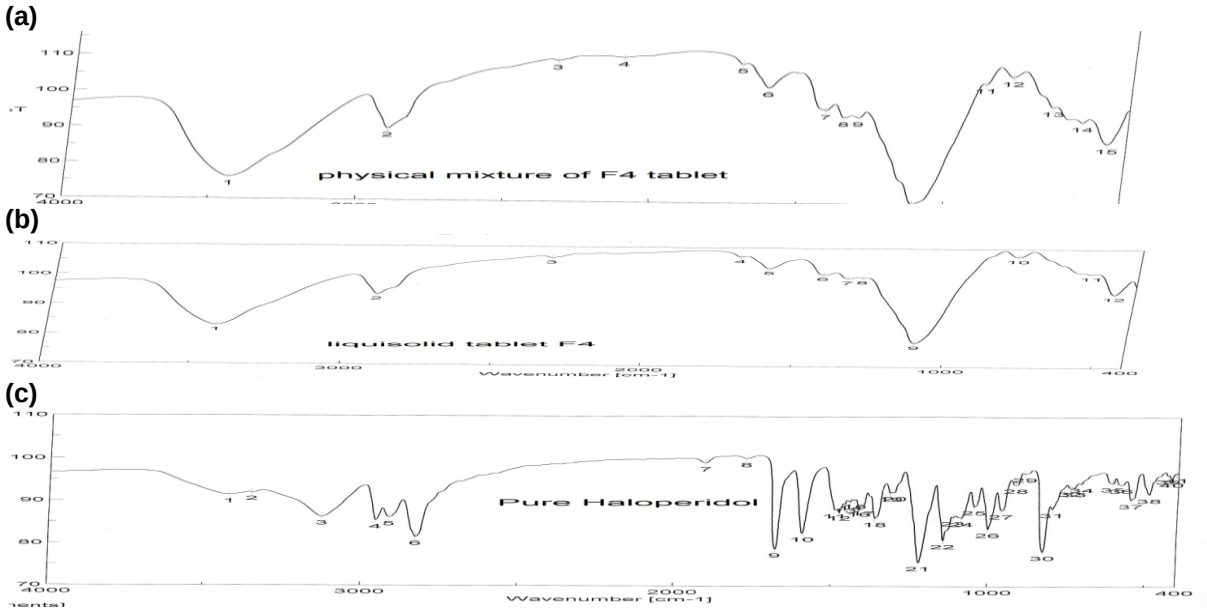
3.3.1 Pre compression tests

Pre compression tests Table (4) shows that all prepared formulas have good angle of repose, Carr's index %, Hausner ratio, void volume and porosity compared to pure drug, so all prepared formulas were then compressed and tested for post compression test.

Table 4. Pre- compression evaluation of tablets

F	Bulk Density ±SD	Tapped Density ±SD	Angle of repose ±SD	Carr's Index %±SD	Hausner Ratio ±SD	Void Vol. ±SD	Porosity % ±SD
Pure drug	0.31 ±0.11	0.38 ±0.32	24.20 ±0.09 Good	19.2 ±0.14 Fair	1.20 ±0.23 Fair	0.5±0.07	19.23±0.20
Physical Mixture	0.17 ±0.20	0.21 ±0.05	21.80 ±0.22 Good	14.5 ±0.17 Good	1.60± 0.28 Good	0.8±0.10	14.50±0.21
LS 1	0.23 ±0.01	0.27 ±0.41	26.65 ±0.32 Good	12.5 ±0.16 Good	1.14 ±0.41 Good	0.8±0.25	8.30±0.11
LS 2	0.25 ±0.21	0.28 ±0.11	20.10 ±0.20 Good	10.54 ±0.25 Good	1.11 ±0.22 Good	1±0.22	10.70±0.31
LS 3	0.28 ±0.32	0.32 ±0.21	26.57 ±0.41 Good	12.69 ±0.22 Good	1.14 ±0.32 Good	0.8±0.21	12.70±0.33
LS 4	0.25 ±0.24	0.29 ±0.11	20.14 ±0.33 Good	14.28 ±0.41 Good	1.16 ±0.11 Good	1.2±0.30	14.30±0.42
LS 5	0.21 ±0.31	0.22 ±0.11	26.30 ±0.24 Good	15.1 ±0.32 Good	1.18 ±0.22 Good	1.3±0.11	13.20±0.22

3.3.2 Fourier Transform Infrared (FTIR) spectroscop



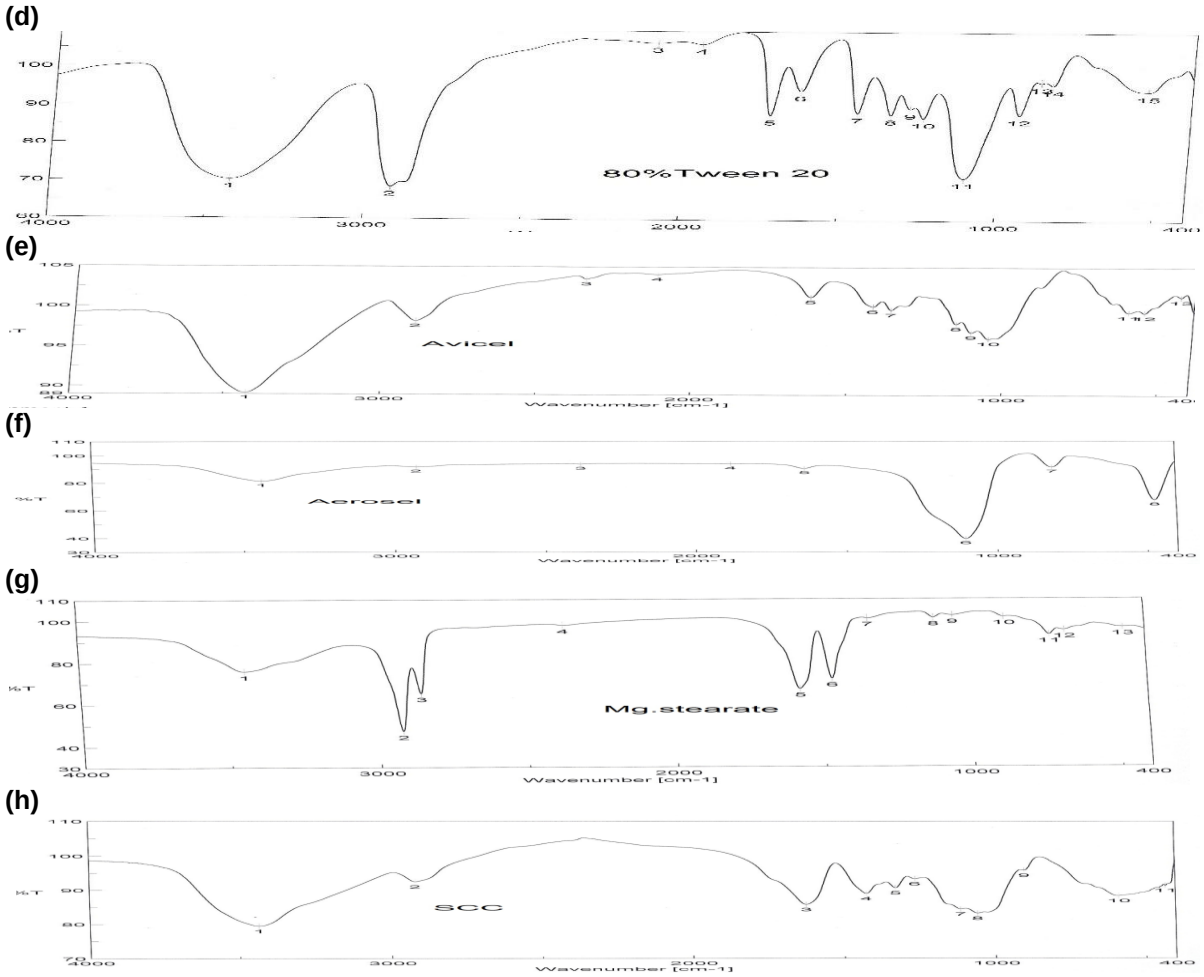


Fig. 1. IR spectra of (a) physical mixture of liquisolid formula (b) liquisolid formula F4 tablet (c) Pure haloperidol (d) Tween 20 [80%] (e) Avicel (f) Aerosel (g) Mg stearate (h)SCC

From FTIR data, it is shown in Fig. 1 (c) 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 tween 20 (80%) showed in Fig. 1 (d) an intense band at 1100 cm-¹corresponding to C-O-C group, at 3500 cm-¹ corresponding to O-H group and at 2880 cm-¹corresponding to CH3.

FTIR results of the selected formulation of liquisolid tablet Fig. 1 (b) approved the formulation of hydrogen bond between Haloperidol drug and tween20 (80%) resulted to the disappearance of the intensed O-H peak of pure Haloperidol in the FTIR spectra of liquisolid tablet, but this intensed peak appear at FTIR spectra of physical mixture Fig. 1 (a).

3.3.3 Differential Scanning Calorimetry (DSC)

DSC studies were performed in liquisolid formula, physical mixture and their component in Fig. (2) and pure haloperidol (g) show 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 amorphalization of haloperidol.

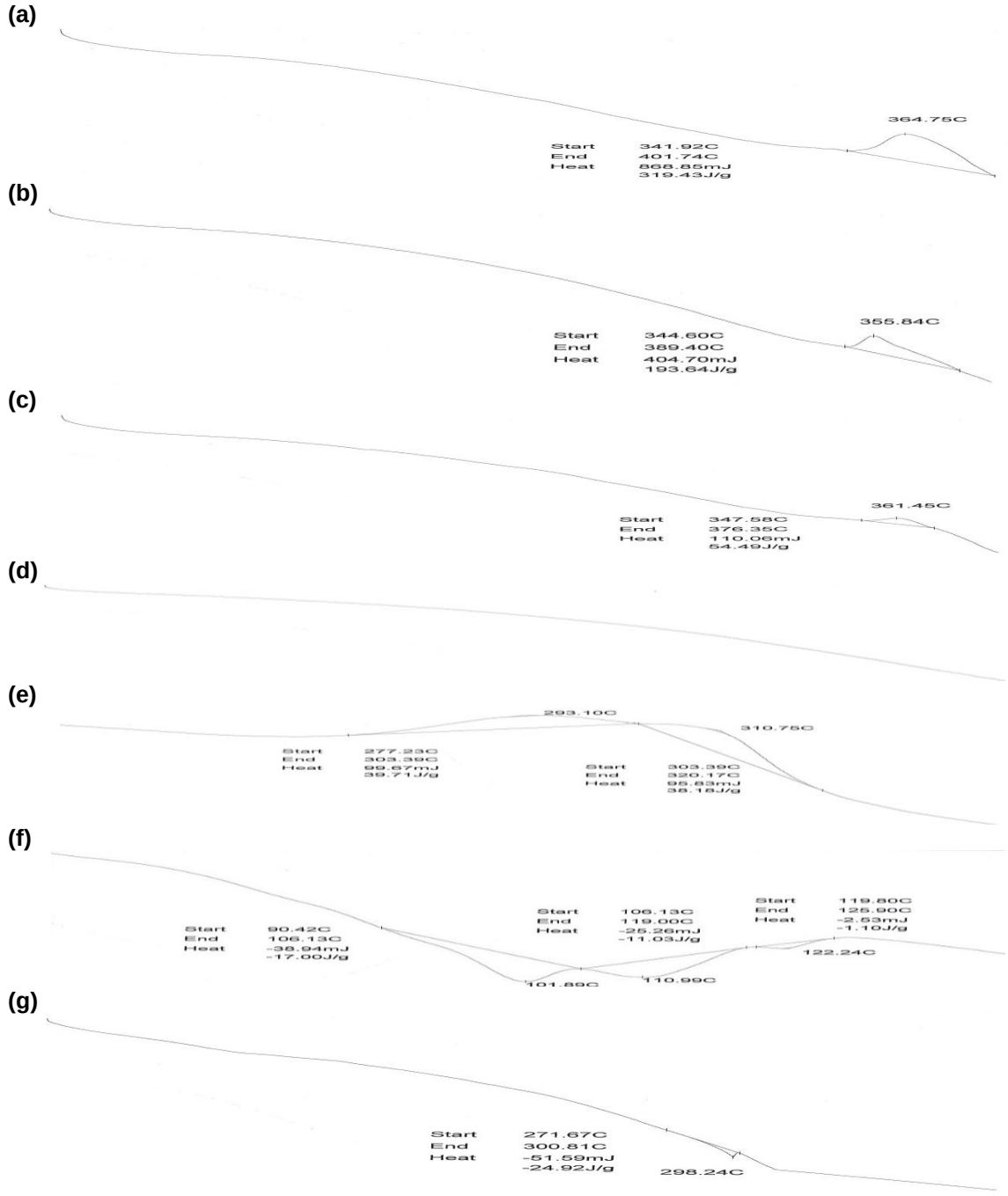
3.3.4 X-Ray powder Diffraction (XRD)

As shown in Fig. (3) Haloperidol displayed sharp peaks at different diffraction angles indicating its crystalline shape. The major characteristic peaks of haloperidol drug and tween 20 (80%) solvent were observed in physical mixture with lower intensity, where the x-ray diffractiogram of

liquisolid FDT (F4) showed no obvious peaks of haloperidol powder.

3.3.5 Evaluation of tablets (post compression tests)

All tablets show friability <0.5 indicating good mechanical strength and ability to tolerate physical handling conditions [11], Table (5). Hardness values for the prepared formulation ranged from 2.4±0.31 kg to7.4±0.41 kg, None of the prepared tablets showed hardness below 2kg table (5). These value is within the range of preferable range of 2-8 kg for mouth dissolve tablet, where it provides sufficient mechanical strength porosity for disintegration and wetting time. Thickness values for the prepared formulation ranged from 1.52 ±0.71 to 2.39±0.02.The mean percentage of haloperidol content is 97.8. Weight uniformity range from 164±0.22 to 323±0.81. Disintegration time range from 15±0.41 sec to 38±0.5 sec [19].



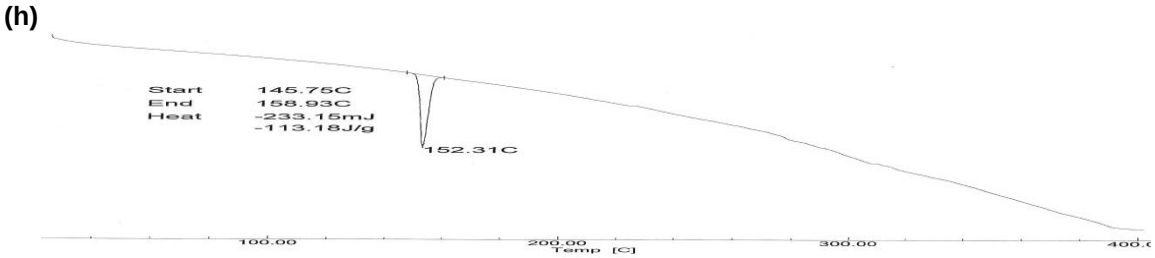
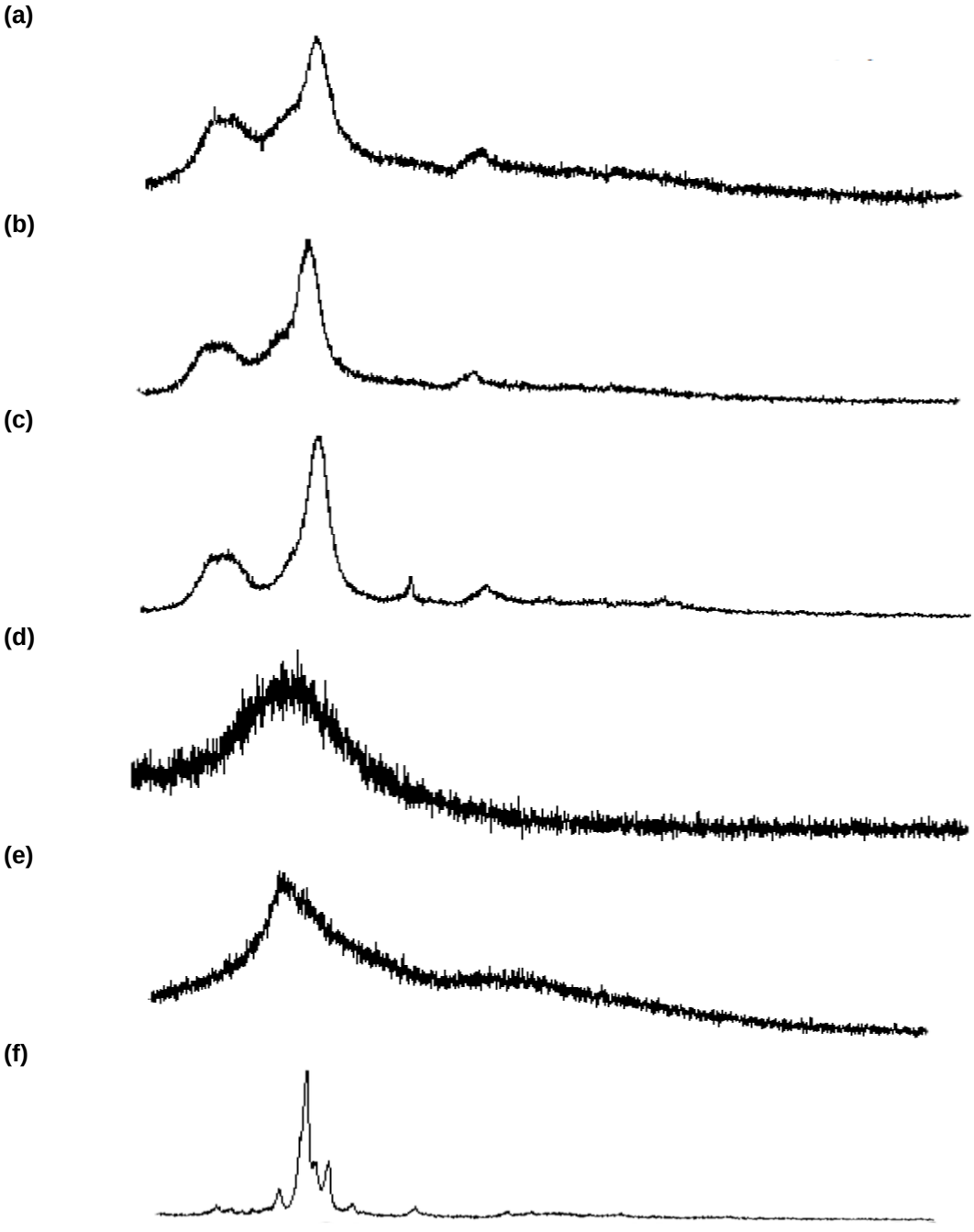


Fig. 2. DSC thermogram of (a) liquiolid tablets (b) physical mixture F4 (c) Avicel (d) Aerosel (e) SCC (f) Mg stearate (g) Tween 20[80%] (h) Pure haloperidol



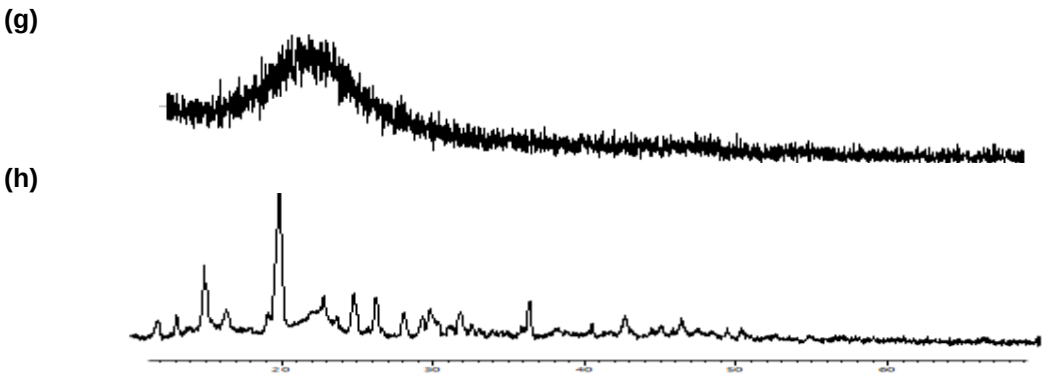


Fig. 3. XRD scanning of (a) liquiolid tablets (b) physical mixture F4 (c) Avicel (d) Aerosel (e) SCC (f) Mg stearate (g) Tween 20 [80%] (h) Pure haloperidol

All physical characterization test were within limit of pharmacopeia [20], except LS5, as weight of LS5 tablet is 323.91mg (above 200mg) so the LS5 formula was excluded and not prepared in form of tablet. 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 (Table 5).

3.3.6 *In vitro* dissolution profile of prepared Haloperidol liquisolid tablets

The cumulative percent release of haloperidol from prepared liquisolid haloperidol tablets in different formulas was higher than the release of haloperidol from physical mixture and in pure form. The prepared F4 show the highest release of haloperidol drug in comparison with other formulas as F4 gives about 48.85% after 5 min and gives about 109.1% of drug release after 60 min [14].

3.3.7 Stability studies

Tablets contain pure haloperidol, physical mixture and prepared liquisolid were subjected to stability study by storing for1, 3 and 6 months at 25°C/ 75RH & at 40°C/ 75RH. Tablets were analyzed for dimensions, friability, hardness, disintegration and drug release. Tables (6,7&8)) show non- significant change in dimensions, friability, hardness, disintegration and drug release.

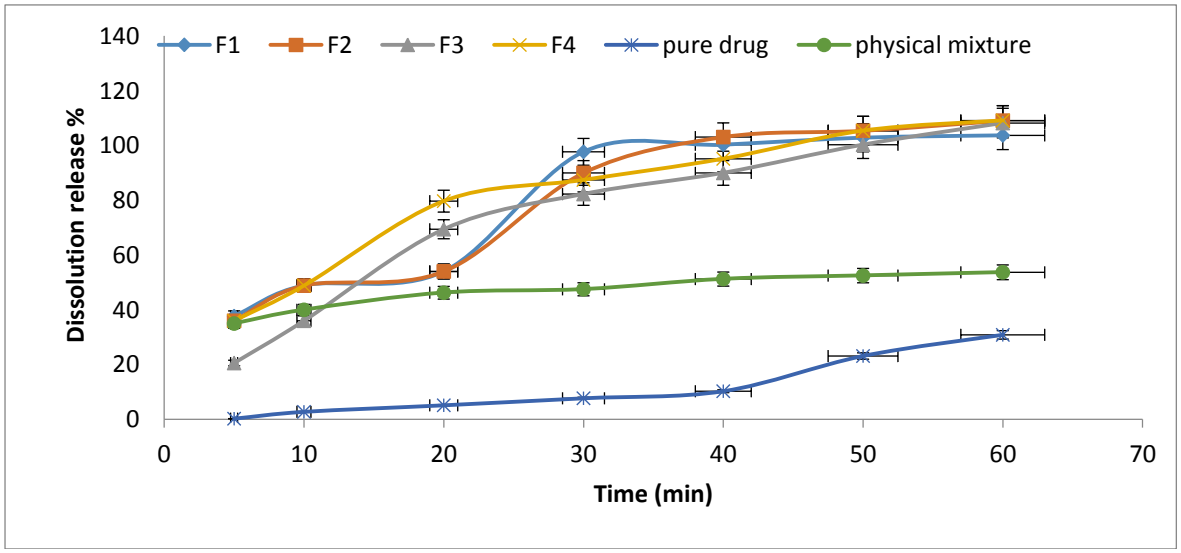


Fig. 4. Results of Cumulative percent released of Haloperidol liquisolid tablets and pure drug ±SD n=3

Table 5. Tablets evaluation (post compression) (n=3)

Formula	Thickness ±SD	Diameter ±SD	Weight uniformity ±SD	Hardness ±SD	Friability ±SD (%)	Disentegra time ±SD (sec)	Wetting time ±SD (sec)	Drug content% ±SD
Pure drug	1.63±0.07	10±0.09	164±0.22	7.4± 0.41	0.31±0.122	15±0.41	22±0.28	97.2± 0.15
Physical mixture	2.21±0.1	10.04±0.21	196±0.38	4.0± 0.24	0.18±0.32	38±0.5	29±0.33	99.3± 0.24
LS1	2.38±0.03	10±0.03	197±0.91	2.7± 0.31	0.52±0.09	30± 0.15	30±0.10	103.1± 0.17
LS2	2.30±0.08	10.04±0.02	198± 0.32	2.8± 0.22	0.28±0.10	38± 0.23	28± 0.05	98.0± 0.23
LS3	2.35±0.06	10.10±0.06	195± 0.75	2.8± 0.23	0.45± 0.21	37±0.34	27± 0.22	98 .8±0.21
LS4	2.39±0.02	10.06±0.01	196± 0.31	2.9± 0.14	0.26±0.31	33± 0.25	30±0.31	100.1± 0.15
LS5	1.52±0.71	09.30±0.05	323±0.81	2.4± 0.31	0.50±0.20	16±0.11	20±0.42	87.2±0.22

Table 6. Stability studies after 1 month at 25°C&40°C

Item		Pure drug ±SD n=3	Physical mixture ±SD n=3	LS 1 ±SD n=3	LS 2 ±SD n=3	LS 3 ±SD n=3	LS 4 ±SD n=3
Thickness	**25°C**	1.62±0.21	2.22±0.08	2.02±0.03	2.09±0.22	2.02±0.22	2.10±0.08
	40°C	1.58±0.22	2.3±0.31	2.04±0.09	2.09±0.11	2.02±0.22	2.10±0.61
Diameter	**25°C**	10.01±0.11	10.03±0.07	10.06±0.22	10.12±0.31	10.02±0.10	10.13±0.13
	40°C	10.02±0.14	10.01±0.22	10.02±0.05	10.04±0.21	10.02±0.13	10.01±0.24
Hardness	**25°C**	7.3±0.32	4.1±0.32	4.4±0.08	3.2±0.11	4.1±0.08	4.3±0.22
	40°C	7.2±0.23	4.3±0.13	4.9±0.16	5.2±0.31	3.8±0.21	4.7±0.06
Friability (%)	**25°C**	0.33±0.02	0.16±0.71	0.21±0.05	0.15±0.05	0.8±0.02	0.4±0.07
	40°C	0.22±0.11	0.21±0.25	0.17±0.02	0.02±0.22	0.09±0.01	0.71±0.31
Disintegration (sec)	**25°C**	16±0.61	39±0.36	32 ±0.16	38±0.61	35±0.31	43±0.22
	40°C	15 ±0.04	38±0.03	32±0.31	47±0.07	48±0.02	42±0.01
Cumulative percent released (%)							
5min	**25°C**	0.3±0.22	33±0.51	35±0.22	35±0.03	35±0.61	40±0.11
	40°C	0.25±0.12	31.8±0.11	35±0.02	35±0.22	33.2±0.14	43.8±0.12
10 min	**25°C**	2.8±0.33	36±0.22	41.30.31	38.7±0.16	46.3±0.72	42.5±0.03
	40°C	2.6±0.31	35.2±0.12	42.5±0.31	40.1±0.23	40±0.12	47.5±0.31
20 min	**25°C**	5.1±0.15	40.2±0.36	48.8±0.15	48.8±0.08	50±0.22	52.5±0.14
	40°C	4.6±0.15	40.5±0.31	51.2±0.08	47.5±0.31	48.8±0.61	52.5±0.22
30 min	**25°C**	7.6±0.17	45.3±0.71	51.3±0.06	52.5±0.02	58.8±0.31	60±0.11
	40°C	7.7±0.07	44.3±0.05	57.5±0.17	57.5±0.07	56.3±0.33	54±0.41
40 min	**25°C**	10.22±0.08	51.1±0.11	60±0.23	65.3±0.11	64.5±0.22	63.5±0.33
	40°C	11.12±0.08	51.3±0.12	61.2±0.05	60±0.71	67.8±0.51	65±0.18
50 min	**25°C**	22.11±0.13	52.1±0.06	72.5±0.16	72.4±0.15	70±0.41	70±0.08
	40°C	21.10±0.03	52.2±0.11	74.3±0.14	72.5±0.23	71.3±0.42	85.2±0.23
60 min	**25°C**	30.8±0.22	53.3±0.33	88±0.51	83.8±0.41	85±0.21	85.2±0.22
	40°C	31.7±0.12	53.1±0.42	85±0.33	85±0.11	82.4±0.23	91.8±0.51

Table 7. Stability studies after 3 month 25°C&40°C

		Pure drug ±SD n=3	Physical mixture ±SD n=3	LS 1 ±SD n=3	LS 2 ±SD n=3	LS 3 ±SD n=3	LS 4 ±SD n=3
Thickness	**25°C**	1.56±0.12	2.3±0.31	2.23±0.21	1.89±0.11	2.15±0.22	2.15±0.03
	40°C	1.52±0.11	2.3±0.11	2.27±0.22	2.04±0.11	2.08±0.21	2.14±0.22
Diameter	**25°C**	10.01±0.11	10.01±0.22	10.23±0.11	10.35±0.35	9.94±0.13	10.32±0.07
	40°C	10.01±0.2	10.01±0.25	10.2±0.13	10.04±0.35	10.13±0.31	10.11±0.32
Hardness	**25°C**	6.8±0.13	4.3±0.13	5.1±0.08	2.9±0.41	5.2±0.08	3.7±0.25
	40°C	7.4±0.22	4.3±0.11	2.4±0.08	5.3±0.41	3.7±0.22	3.8±0.41
Friability (%)	**25°C**	0.32±0.21	0.21±0.25	0.8±0.22	0.72±0.22	0.53±0.06	0.09±0.11
	40°C	0.32±0.11	0.18±0.21	0.08±0.12	0.52±0.27	0.62±0.51	0.37±0.31
Disintegration (sec)	**25°C**	17±0.08	38±0.03	35±0.02	41±0.31	39 ±0.07	43 ±0.03
	40°C	17±0.01	37±0.06	32±0.07	40±0.06	38±0.08	44 ±0.05
Cumulative percent released (%)							
5min	**25°C**	0.27±0.11	31.6±0.21	32.5±0.11	36.3±0.23	35.8±0.19	35±0.33
	40°C	0.4±0.12	32.8±0.11	34.5±0.21	35±0.11	48.8±0.22	35±0.11
10 min	**25°C**	2.8±0.11	35.1±0.02	47.5±0.2	48.8±0.41	47.5±0.04	42.1±0.08
	40°C	2.6±0.22	35.8±0.11	47.5±0.32	42.5±0.07	50±0.31	42.8±0.41
20 min	**25°C**	4.8±0.51	39.9.±0.31	63.8±0.33	53.7±0.22	60.5±0.24	57.3±0.21
	40°C	5±0.05	40.1±0.06	57.5±0.22	55±0.17	63.7±0.07	55±0.22
30 min	**25°C**	7.3±0.12	44.1±0.15	72.5±0.17	65±0.31	77.5±0.22	66.5±0.33
	40°C	7.5±0.11	45.1±0.71	60±0.17	66.3±0.22	74.3±0.03	61.3±0.31
40 min	**25°C**	11.11±0.07	51±0..31	80±0.11	77.5±0.25	86.3±0.31	75±0.24
	40°C	10.1±0.18	50±0.43	72.5±0.28	71.3±0.13	82.8±0.11	75.1±0.12
50 min	**25°C**	20.2±0.43	52.5±0.31	86.2±0.22	85±0.18	88.7±0.07	88.1±0.27
	40°C	21.50±0.22	51.8±0.22	84.5±0.25	83.8±0.04	91.2±0.31	86.5±0.17
60 min	**25°C**	30.8±0.22	52.9±0.22	90±0.16	91.5±32	92.5±0.52	93.5±0.31
	40°C	31.1±0.15	52.9±0.31	90.1±0.33	93.8±0.19	93.5±0.17	92.1±0.22

Table 8. Stability studies after 6 month 25°C&40°C

		Pure drug ±SD n=3	Physical mixture ±SD n=3	LS 1 ±SD n=3	LS 2 ±SD n=3	LS 3 ±SD n=3	LS 4 ±SD n=3
Thickness	**25**°C	1.59±0.31	2.22±0.08	2.06±0.01	2.07±0.11	2.01±0.08	2.22±0.17
	40°C	1.52±0.03	2.3±0.08	2.05±0.12	2.05±0.21	1.92±0.11	2.08±0.32
Diameter	**25**°C	10.03±0.21	10.03±0.07	10.10±0.32	10.12±0.05	10.06±0.22	10.09±0.31
	40°C	10.03±0.01	10±0.12	10.06±0.03	10.07±0.13	10.10±	10.12±0.21
Hardness	**25**°C	6.8±0.22	4.1±0.32	5.2±0.17	3.6±0.23	4.7±0.12	4.5±0.08
	40°C	6.9±0.21	3.9±0.41	5.1±0.14	3.3±0.51	5.1±0.17	3.1±0.61
Friability (%)	**25**°C	0.31±0.12	0.16±0.71	0.61±0.22	0.42±0.17	0.1±0.07	0.23±0.11
	40°C	0.23±0.11	0.18±0.11	0.28±0.23	0.24±0.33	0.43±0.22	0.51±0.22
Disintegration (sec)	**25**°C	17± 0.02	39± 0.36	36±0.31	40 ±0.33	35±0.07	39±0.09
	40°C	15±0.03	35±0.06	38±0.11	41 ±0.32	33±0.08	37 ±0.13
Cumulative percent released (%)							
5min	**25**°C	0.28±0.37	32.5±0.11	27.3±0.11	30.2±0.33	31.2±0.22	33.5±0.22
	40°C	0.29±0.16	32.5±0.11	27.5±0.08	29.8±0.11	32.8±0.11	34±0.14
10 min	**25**°C	2.±0.13	35.8±0.12	36.5±0.7	43.9±0.15	43.3±0.13	45.2±0.32
	40°C	2.6±0.03	35.3±0.11	38.1±0.17	38±0.22	40.1±0.32	41.3±0.22
20 min	**25**°C	4.9±0.05	40.5±0.11	48.8±0.31	51.7±0.22	50.9±0.08	52.4±0.17
	40°C	5.3±0.21	41±0.23	49.2±0.23	49±0.33	52±0.03	57±0.13
30 min	**25**°C	7.2±0.03	44.8±0.71	59.3±0.08	65±0.17	67.4±0.23	66.2±0.24
	40°C	7.5±0.22	45.1±0.11	55.3±0.22	59.3±0.18	60.2±0.02	62.3±0.22
40 min	**25**°C	10.1±0.22	50.8±0.25	70.1±0.11	74.5±0.08	73.2±0.11	74±0.01
	40°C	11.12±0.8	50.7±0.51	67.4±0.18	70.2±0.11	72.8±0.18	75±0.13
50 min	**25**°C	21.9±0.22	51.3±0.12	81.2±0.32	82±0.13	81.7±0.31	83.1±0.11
	40°C	22.3±0.05	52±0.23	77.5±0.31	79.8±0.32	82.4±0.13	83.4±0.08
60 min	**25**°C	30.3±0.13	53.5±0.33	88.5±0.22	89.5±0.17	90.5±0.22	91.2±0.13
	40°C	31.8±0.12	53.1±0.41	86±0.22	88±0.09	89.8±0.11	90.2±0.03

3.3.8 *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 available halonace® tablets. The model for anti-psychotic used in this study is the "Forced Swim test" (FST), this method evaluate haloperidol efficacy and the effects of various behavioral and neurobiological manipulations. The FST is used to monitor depressive-like behavior and is based on the assumption that immobility reflects a measure of behavioral despair.

Table (9) shows that group 2and group3 produced a significant increase in immobility time at *(p =0.05)* compared to group 1 revealing the presence of antidepressant actions in this groups.

The one way ANOVA test showed that there is a statistically significant difference in the immobility time between group 2 and group 1 [17].

While, no statistically significant difference was observed between group 2 and between group 3, revealing that the selected prepared liquisolid formula succeeded to give anti depressive action of haloperidol [18].

Swimming

(1) control **(2) prepared liquisolid FDT** **(3) purchased tablet**

Climbing

(4)control **(5) prepared liquisolid FDT** **(6)Purchased tablet**

Fig. 5. Results of the effects of haloperidol treatment on swimming and climbing time in the FST

Immobility

(7) Prepared liquisolid FDT

(8) Purchased tablet

Fig. 6. Results of the effects of haloperidol treatment on immobility time in the FST.

Table 9. Representative results of the effects of haloperidol treatment on swimming time, climbing time and immobility time in the FST

Animal group	Swimming time sec ±SD	Climbing time sec ±SD	Immobility time sec ±SD
Group 1	140 ±0.12	100 ±0.02	0
Group 2	110±0.15	35±0.11	95±0.2
Group 3	95 ±0.11	35 ±0.08	110 ±0.32

Group 1: Control rats
Group 2: Rats treated with prepared liquisolid tablet (F4)
Group 3: Rats treated with Purchased tablets (halonace®)

4. CONCLUSION

Haloperidol can be prepared in liquisolid fast dissolved tablet using 80% tween 20 as non-volatile solvent, avicel PH102 as carrier and aerosel PH200 as coating agent, Liquisolid technology was effective for improving the dissolution and bioavailability of poorly water-soluble drugs as haloperidol. Fast dissolving liquisolid tablet (LS4) induced a significant anti-psychotic effect compared to the marketed halonace ® tablet.

ETHICAL APPROVAL

“All authors hereby declare that "Principles of laboratory animal care", animal care committee (IACUC) of faculty of pharmacy, zagazig university. (Approval number, ZU-IACUC /3/F/17/ 2021).

CONSENT

It is not applicable.

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COMPETING INTERESTS

Authors have declared that they have no known competing financial interests or non-financial interests or personal relationships that could have appeared to influence the work reported in this paper.

REFERENCES

1. Gupta MK, Gupta R, Khunteta A, Swarnkar SK. An overview of novel techniques employed in mouth dissolving drug delivery system. International Journal of Engineering Science and Generic Research. 2018;4:09-27.
2. Vikas A, Bhavesh HK, Derek VM, Rajendra KK. Drug delivery: Fast dissolve systems. Encycl Phar Tech. 2007; 1:1104–1114.

3. Masih A, Kumar A, Singh S, Tiwari AK. “Fast dissolving tablets: A review. Int J Curr Pharm Res. 2017;9:8-18.
4. Aggarwal P, Nautiyal U, Mali RR. A review on fast dissolving tablet. International Journal of Recent Advances in Science and Technology. 2015;2:20-28.
5. Nasrallah, Henry A, Chen, Alexander T. "Multiple neurotoxic effects of haloperidol resulting in neuronal death". Annals of Clinical Psychiatry. 2017;29(3): 195–202.
6. Almukainzi M, Araujo GL, Löbenberg R. Orally disintegrating dosage forms. J Pharm Invest. 2019;49:229-243.
7. Javadzadeh Y, Jafari-Navipour B, Nokhodchi A. Liquisolid technique for dissolution rate enhancement of a high dose water - insoluble drug (carbamazepine). Int. J. Pharm. 2007; 341:26-34.
8. Rania HF, Kassem MA. Enhancement of famotidine dissolution rate through liquisolid tablets. Formulation. *In* vitro and in vivo evaluation. Eur. J. Pharm. Biopham. 2008;69:993-1003.
9. Mishra SK, Mohanty S, Mohanty A, Das BS. Management of severe and complicated malaria J Postgrad Med. 2006;52:281-287.
10. Mukesh Kumar, F Tat Kee. A Taap Manshor Managing Service Quality: An International Journal. 2009;19(2):211-228.
11. Irfan M, Rabel S, Bukhtar Q, Qadir MI, Jabeen F and Khan A. Orally disintegrating films: A modern expansion in drug delivery system, Saudi Pharmaceutical Journal. 2016;24:537-546.
12. Fakhr Eldin S. Ghazy, Hanan M. EL-Nahas, Mohamed A. Gad, Noura G. Eisa. Buccoadhesive tablets for delivery, Bull. pharm. sci. Assuit University. 2012;35, part1:17-23.
13. Al Zahraa G. Al Ashmawy, Noura G. Eissa, Hanan M. EL-Nahas, Gehan F. Balat. Fast disintegrating tablet of Doxazosin Mesylated nanosuspnsion: preparation and characterization. Journal of drug delivery science and technology. 2021;61.
14. Yasir M, SARA UVS. Solid lipid nanoparticles for noseto brain delivery of haloperidol: in vitro drug release and pharmacokinetics evaluation, Acta. Pharm. Sin. B. 2014b;4(6):454-463.
15. Kurtuncu M, Luka LJ, Dimitrijevic N, Uz T, Manev H. Reliability assessment of an automated forced swim test device using two mouse strains. Journal of Neuroscience Methods. 2005;149:26-30.
16. Deitzel JM, Kleinmeyer J, Harris D, Beck TNC. The effect of processing variables on the morphology of electrospun nanofibers and textiles. Polymer. 2001;42(2):61-72.
17. Hascoét M, Bourin M. In Mood and Anxiety Related Phenotypes in Mice, Neuro methods. 2009;1(42):85-118.
18. Cryan JF, Holmes A. The ascent of mouse: advances in modelling human depression and anxiety, Nature reviews. Drug discovery. 2005;4:775-790.
19. European pharmacopeia, 5th Edition, Main Volume 5.0, 2005 with Supplements 5.1 and 5.2, Council of Europe, Strasbourg. 2004;2308.
20. British Pharmacopeia: Incorporating the requirements of the 5th Edition of the European pharmacopeia 2004 as Amended by supplementation 5.1 and 5.2 British pharmacopeia; 2005.

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