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Original Article

FORMULATION AND *IN VITRO* EVALUATION OF BROMOCRIPTINE MESYLATE AS FAST DISSOLVING ORAL FILM

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ABSTRACT

Objective: The aim of this study was to formulate and *in vitro* evaluate fast dissolving oral film of practically insoluble bromocriptine mesylate to enhance its solubility and to improve its oral bioavailability by avoiding first pass effect as well as to produce an immediate release action of the drug from the film for an efficient management of diabetes mellitus type II in addition to an improvement of the patient compliance to this patient-friendly dosage form.

Methods: The films were prepared by the solvent casting method using hydroxypropyl methylcellulose of grades (E3, E5, E15), polyvinyl alcohol (PVA), pectin and gelatin as film-forming polymers in addition to polyethene glycol 400 (PEG400), propylene glycol (PG) and glycerin were used as a plasticizer. Poloxamer 407 was used as a surfactant, sodium saccharin as a sweetening agent, citric acid as a saliva stimulating agent, vanilla as a flavouring agent and crospovidone as a super disintegrant. The prepared films then tested for physical characterization, thickness, weight uniformity, mechanical characteristics (folding endurance, tensile strength, percent elongation and Young's modulus), surface pH, *in vitro* disintegration time, drug content and an *in vitro* drug release.

Results: Films were found to be satisfactory when evaluated for physical characterization, thickness, weight uniformity, mechanical tests, *in vitro* disintegration time, folding endurance, drug content and an *in vitro* drug release. The surface pH of all the films was found to be neutral or minor change. Films *in vitro* drug release studies were also done using USP dissolution apparatus type II (paddle type). The *in vitro* drug release profile in the optimized formulation F14 was gave 86.8 % of drug released at 2 min. The optimized formulation F14 was also showed satisfactory pH (6.2±0.2), drug content (99.2±0.5%), the disintegration time of 9.2±0.1 seconds and the time needed for 80% of medication to be released (T80 %) was 1.35 minute.

Conclusion: The bromocriptine mesylate fast dissolving oral film was formulated. The given film disintegrates within nine seconds which release the drug rapidly and gives an action.

Keywords: Bromocriptine mesylate, Fast dissolving oral film, Solvent casting method

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INTRODUCTION

Among all routes of drug administration, the oral route is one of the most favored routes, as it is more convenient, cost-effective, and ease of administration lead to high level of patient compliance, but the problem associated with this route is the swallowing difficulty for pediatric and geriatric patients who have a fear of choking. In addition to that, patient convenience and compliance-oriented research have resulted in present safer and newer drug delivery systems [1].

Buccal drug delivery recently becomes an important route of drug administration in which problems like high first-pass metabolism and drug degradation in the gastrointestinal environment can be avoided by administering the drug through buccal route [2].

Drug delivery via the oral mucosa is a promising route when one wishes to achieve a rapid onset of action or an improved bioavailability for drugs which have a high first-pass metabolism. Thus, fast dissolving films allow the films to dissolve in the mouth, so the drug gets directly absorbed into the systemic circulation through the oral mucosa [3].

Oral fast dissolving films (OFDFs) are the most advanced form of an oral solid dosage form. These are solid dosage forms, which disintegrate or dissolve within a minute when placed in the mouth without drinking water or chewing. The oral films are formulated using polymers, plasticizer, flavors, colors, and sweeteners. OFDFs are prepared using hydrophilic polymers that rapidly dissolves in the oral cavity delivering the drug to the systemic circulation. Water-soluble polymers are used in OFDFs as they achieve rapid disintegration. Plasticizer helps to enhance the flexibility of the strip and reduces the brittleness of the strip [4].

The films are intended to place in the buccal cavity, and fewer doses are required which improves the patient compliance. Stability of the dosage form can also be enhanced when formulated as a film. Also, the ODF is a solid unit dosage form provides an accurate dosing and a great precision [5].

Bromocriptine is a semisynthetic ergot alkaloid that interacts with D2 dopamine receptors to inhibit spontaneous and TRH-induced release of prolactin. It is used in neuroleptic malignant syndrome, acromegaly, infertility, hyperprolactinemia, prolactinoma, Parkinson's disease, and type 2 diabetes mellitus. It was approved by the Food and Drug Administration (FDA) in May 2009, for the treatment of type 2 diabetes [6].

Bromocriptine mesylate is rapidly absorbed, after oral administration, the bioavailability of the drug is 28% of the oral dose consumed, and the plasma protein binding amounts to 96%. It is highly distributed in the liver, stomach, and intestine. The drug is extensively metabolized in the liver. The fate of bromocriptine mesylate primarily involves with renal excretion of two major metabolites accounting for 6% of the total dose. The elimination of the parent drug from the plasma is biphasic with a terminal half-life of 15 h. Bromocriptine mesylate stimulates dopamine type-II receptors and antagonizes type-I receptors in the hypothalamus and neostriatum of the CNS [7].

Bromocriptine mesylate acts centrally as an antidiabetic agent by a novel mechanism and reduces plasma glucose, triglycerides, free Fatty Acid (FFA) levels, and possibly cardiovascular events [8].

The aim of this study was to formulate and *in vitro* evaluate a fast dissolving oral film of practically insoluble bromocriptine mesylate to enhance its solubility of drug and to improve its oral

bioavailability of drugs by avoiding first pass effect as well as to produce an immediate release action of drug from the film for an efficient management of diabetes mellitus type II in addition to an improvement of the patient compliance to this patient-friendly dosage form.

MATERIALS AND METHODS

Material

Bromocriptine mesylate was purchased from Avril Chemical Limited, China. HPMC E3, E5, E15, PVA, pectin and gelatin was purchased from Hangzhou Hyper Chemical Limited, China. Poloxamer 407 was purchased from Hangzhou Hyper Chemical Limited, China. PEG400, glycerin was purchased from Fluka Chemical AG, Switzerland. Propylene glycol was purchased from Evans Medical Ltd, Liverpool, England. All other chemicals and solvents were of analytical reagent grade, and deionized water also was used in this study.

Method

Determination of λ max

10 mg of bromocriptine mesylate was dissolved in100 ml of 0.1 N HCl (pH 1.2) and phosphate buffers (pH 6.8) with (0.5% w/v Brij-35) individually to make a stock solution of concentration (0.1 mg/ml). Then From this prepared stock solution, a diluted solution (0.065 mg/ml) was established and determined the λmax of bromocriptine mesylate using UV spectrophotometric analysis at 200-400 nm.

Construction of calibration curves

Calibration curves for bromocriptine mesylate in 0.1 N HCl and phosphate buffers (pH 6.8) with (0.5% w/v Brij-35) were made by preparing consecutive dilutions of the drug from a stock solution (0.1 mg/ml), samples (65, 55, 45, 35, 25 and 15 µg/ml) were then analyzed by spectrophotometric method for bromocriptine mesylate at its λ max (305 nm) [7].

Determination of saturation solubility of bromocriptine mesylate

The solubility of Bromocriptine Mesylate was determined by dissolving the excess amount of drug in different medium 0.1N HCl, phosphate buffer(pH 6.8) and phosphate buffer (pH 6.8) containing 0.5% w/v Brij-35) at room temperature and kept for 48h with regular shaking. The solutions were centrifuged then filtered and examined by using UV-spectrophotometer at its λ max, and from this absorbance, the concentration of that saturated solution was determined which represents the solubility of bromocriptine mesylate in these solutions.

Method for preparation of fast dissolving oral film of bromocriptine mesylate

Fourteen formulas were prepared (F1-F14) as listed in (table 1) by using solvent casting technique; every film of about 4 cm2 area must contain 0.8 mg of bromocriptine mesylate. The size and number of films that formulated for every group designed as the following:

Each film with an area of 4 cm2 (2 cm ×2 cm) and contain 0.8 mg of bromocriptine mesylate.

The amount of drug in the film was calculated as follows:

The dose of the drug to be incorporated in each 4 cm^2 film = 0.8 mg of bromocriptine mesylate.

Diameter of petri dish = 11 cm, so that the radius = 5.5 cm.

Area of Petri dish = π r2 = 3.14 × $(5.5\ cm)^2$ = 94.985 cm^2 approximately =95 cm^2.

Number of 4 cm2 films obtained from main film =95 cm^2 ÷ 4 cm^2 = 23.75 films approximately = 24 films each with area 4 cm^2.

Amount of drug in the area considered = 24 film × 0.8 mg =19.2 mg

The fast-dissolving oral films of bromocriptine mesylate were prepared by solvent casting method using: hydroxypropyl methylcellulose (HPMC) with different grades like HPMC E3, E5, and E15, and another type of hydrophilic polymers as the film-forming polymers, PEG 400, propylene glycol (PG) and glycerin were used as plasticizer, poloxamer 407 as a surfactant, citric acid as a saliva stimulating agent, sodium saccharin as a sweetening agent, vanilla as a flavoring agent and crospovidone as a super disintegrant. The considered quantity of film-forming polymer was dissolved in 20 ml of solvent (distilled water) with constant stirring by using magnetic stirrer for two h to form a homogenous polymeric solution. To this polymeric solution, a suitable amount of plasticizer was added with a continuous stirring for another one h. The next step was that, the drug (bromocriptine mesylate), surfactant, saliva stimulating agent and sweetener were dissolved in 10 ml of water and ethanol as a co-solvent (5 ml water+5 ml ethanol) in another beaker to form clear solution, mix the two solutions using magnetic stirrer for one hour, the solution was kept in a sonicator for degassing. Then the bubble free solution was cast on to a petri dish with a diameter of 11 cm^2 and kept in hot air oven (60 °C) overnight. The dried film was then removed and cut into the desired shape and size (2 cm × 2 cm) for the intended application. Cuts or defectiveness were omitted from the study [9].

Table 1: Composition of bromocriptine mesylate oral films formulas

Ingredients present in each film (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14
Bromocriptine mesylate	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
HPMC E3	25													
HPMC E5		25					27.5	30	25	25	25	25	25	25
HPMC E15			25											
Polyvinyl alcohol				25										
Pectin					25									
Gelatin						25								
Polyethylene glycol 400	10	10	10	10	10	10	10	10			7.5	12.5	12.5	12.5
Propylene glycol									10					
Glycerin										10				
Poloxamer 407	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Crospovidone													0.5	1.5
Citric acid	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Vanilla	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Sodium saccharin	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5

Evaluation of fast dissolving oral film of bromocriptine mesylate

Physical characterization of the prepared films

Physical characterization can be carried out by visual inspection for characteristics such as color, thickness, brittleness, peeling ability, transparency, surface smoothness, tack property and film-forming capacity [10].

Weight variation

Weight variation test confirms the uniformity of the film formed. Ten randomly selected films from each patch (each of 2 cm × 2 cm) were cut and weighed individually and matched with the mean weight for deviation [11].

Thickness measurements

Film thicknesses were determined using the Digimatic and Vernier Caliper. Each wafer was measured at five positions (central and the four corners) the mean thickness was calculated. This test was performed on six films of each formulation and mean±S. D calculated [12].

Drug content uniformity

This test was done by using the procedure described in United States Pharmacopoeia in which a solvent solution was prepared by dissolving 1g of tartaric acid in 500 ml of water, then 500 ml of methanol was added with mixing.

A standard solution was prepared, which consists of bromocriptine mesylate, dissolved in the solvent solution at a concentration of 0.04 mg/ml.

The test solution was prepared by transferring a tablet, for which the drug content to be determined, into a volumetric flask contains the 15 ml solvent solution. It was shaken mechanically for 30 min then diluted with the solvent solution up to 25 ml with mixing, after filtration, 10 ml of the clear filtrate was diluted to 50 ml.

Then the following equation was utilized to determine the film content of bromocriptine mesylate:

Bromocriptine mesylate content in mg = (TC/D)(At/As)

In which T is the labeled quantity, in mg, of bromocriptine mesylate in the film, C is the concentration, in microgram per ml, of bromocriptine mesylate in the standard solution, D is the concentration in microgram per ml, of bromocriptine in the solution from the film, based upon the labeled quantity in the film and the extent of dilution, while At and As are the absorbance of the solution from the film and the standard solution [13].

Determination of surface pH

The determination of surface pH is important to investigate opportunity of any side effects when using the ODFs *in vivo*, because the acidic or basic pH may irritate the mucosal membrane of an oral cavity. To measure the pH value of ODF one strip was allowed to dissolve in 2 ml of distilled water and the PH of the obtained solution is determined using pH-meter.

Different pH value will be expected because of the fact of using a different film forming polymers in the formulation of ODFs along with the drug [14].

Folding endurance

Folding endurance is measured by manual repeated folding of the film at the same place till it broke. The number of time the film is folded without breaking is known as the folding endurance value. A strip of 2 × 2 cm diameter (an area of 4 cm2) was subjected to folding endurance by folding the film at the same place repeatedly several times until a visible crack was observed, and the average values were calculated and reported. Folding endurance more than 300 indicating that the formulation good tough and flexible [15, 16].

Tensile strength

It is the maximum value of forces applied to the film at which its breakdowns. The tensile strength was determined by way of holding a film of 5 cm × 2 cm (which must be pure from air bubbles or any physical defectiveness and cut as dumbbell-shaped) longitudinally in the tensometer, Then the ODFs were drawn at a level of 10 mm/min. The tensile strength was measured mathematically by dividing the applied force at which the film is broken by the cross-section area of the stripe and was expressed in force per unit area: mega Pascal (MPa) as shown in the following equation [16].

Tensile Strength = Load to Break/Width × Thickness × 100

Percent of elongation

When stress is applied the film sample stretches and is referred to as strain. The strain is the deformation of the film divided by the original dimension of the film. Elongation of the film increases as the plasticizer concentration increases. Percentage elongation was calculated by measuring the increase in the length of the film after tensile strength measurement by using the following formula [17]:

Percentage Elongation = [Final length-initial length] X 100/initial length

Young's modulus (YM)

Young's modulus or elastic modulus is the measure of the stiffness of strip. It is represented as the ratio of applied stress over strain in the region of elastic deformation as follows:

Young's modulus = Slope X 100/Strip thickness X Cross-head speed

Hard and brittle strips demonstrate a high tensile strength and Young's modulus with small elongation [18].

Percent moisture loss (PML)

The films were weighed accurately and kept in a desiccator containing anhydrous calcium chloride. After three days the films were taken out and weighed. The moisture loss was calculated using the formula [19]:

$$\% \text{ Moisture content} = \frac{\text{Initial weight -final weight}}{\text{Initial weight}} \text{X } 100$$

Percent moisture absorb (PMA)

This test was carried out to check the physical stability of films at high humid conditions. In the present study, the moisture absorption capacity of the bromocriptine mesylate fast dissolving films were determined by keeping the pre-weighed films in the desiccator containing a saturated solution of potassium chloride, which maintains 79.5% relative humidity at room temperature for 72 h. Average percentage moisture absorption of three films can be calculated by the following equation [20]:

$$\% \text{ Moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \text{ X } 100$$

***In vitro* disintegration time (DT)**

DT is the time at which the fast dissolving oral films start to break down or disintegrate (in second). The *in vitro* DT is measured by using petri dish method. The test is done by taking three films of each patch in a petri dish, and after adding 2 ml of distilled water for each film, the petri-dish was shaken continuously, then measure the time at which the ODFs start to break down or disintegrate. The determination of DT was done in triplicate for all the formulations [21].

***In vitro* dissolution study**

The dissolution study was carried out using USP type II (paddle apparatus) with 300 ml of Phosphate buffer pH 6.8 with (0.5% w/v Brij-35) as a dissolution medium maintained at 37±0.5 °C. The medium was stirred at 50 rpm for 30 min. Samples were withdrawn by using a syringe at regular intervals (1, 2, 3, 4, 5, 10, 15 and 20 min) replaced with fresh medium in order to maintain sink conditions; before analyzing the withdrawn samples using UV-spectrophotometry at λmax 305 nm they must be filtered by using filter syringe (0.45µm).

Samples were suitably diluted with the dissolution media and analyzed for the drug content at 305 nm. Cumulative percent drug release of bromocriptine mesylate was calculated and plotted against time [22].

Drug-polymer compatibility study

Fourier transform infrared spectroscopy (FTIR)

The compatibility of the drug and the formulation was confirmed by IR spectra of pure drug and formulations that were determined by KBr disc method.

Drug-polymer interactions were studied by FT-IR spectroscopy. The spectrum was recorded for the drug, blank polymer, the physical mixture of polymer and the drug in a ratio (1:1) and the selected formula. Samples were mixed with potassium bromide and pressed in the form of a disc. The disc was analyzed by FTIR spectroscopy from 4000-400 cm^{-1} [23].

X-ray powder diffraction (XRPD)

Powder X-ray diffraction can be used to confirm the crystalline nature of materials. So, this information is used to verify whether the substances are crystalline or amorphous. The diffractograms of bromocriptine mesylate as a pure drug and the selected formula were obtained. The study was confirmed by using Shimadzu XRD-6000 powder X-ray diffractometer at continuous scan range of 5 °-80 ° of 2Θ The operating voltage was 40 (kV) and current 30mA [24].

Statistical analysis

The results of the experiments are given as a mean of triplicate samples±standard deviation and were analyzed according to the one way analysis of variance (ANOVA) at the level of ($P<0.05$) to determine if the changes in the applied factors are statistically significant at level of ($P \leq 0.05$) and non-significant at level of ($p>0.05$).

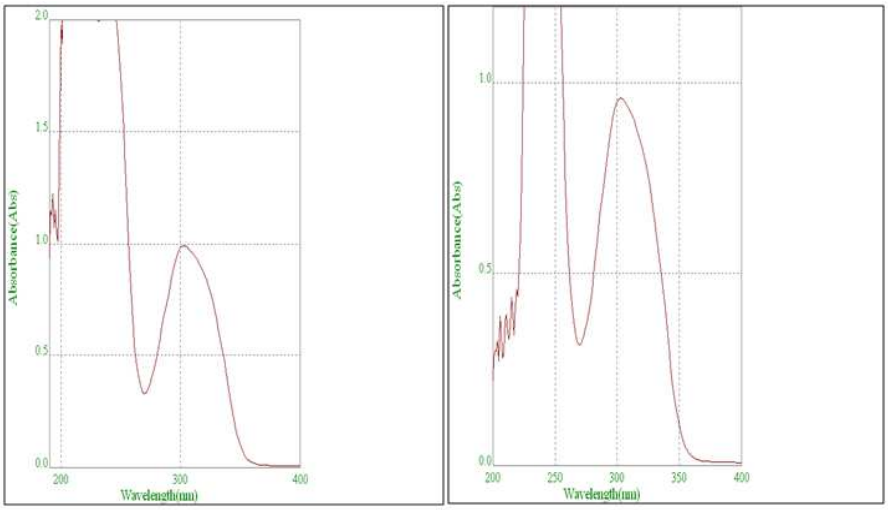
RESULTS AND DISCUSSION

Determination of λ max

Scanning the diluted solutions of bromocriptine mesylate in 0.1N HCl and in pH 6.8 phosphate buffers with (0.5% w/v Brij-35) by using UV spectrophotometer at range of 200-400 nm provided the spectra revealed in (fig. 1-A and 1-B) respectively with the same peak for λmax at 305 nm as reported in reference [7].

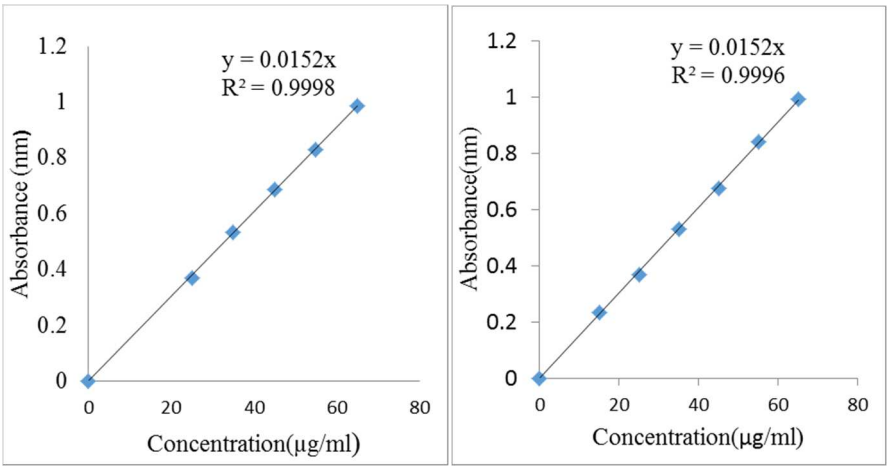
Calibration curves of bromocriptine mesylate

The constructed calibration curves of bromocriptine mesylate in 0.1 N HCl (pH 1.2) and phosphate buffers (pH 6.8) With (0.5% w/v Brij-35) are shown in (fig. 2-A and 2-B) respectively. A straight line was obtained by plotting the absorbance versus concentration with a high coefficient of determination. This indicates that the calibration curve obeys Beer's law within the range of concentration used.



A B

Fig. 1: UV Spectrum of bromocriptine mesylate in A-0.1 N HCl (pH 1.2) B-phosphate buffers (pH 6.8) with (0.5% w/v Brij-35)



A B

Fig. 2: Calibration curve of bromocriptine mesylate in A-0.1 N HCl (pH 1.2) B-phosphate buffers (pH 6.8) with 0.5% w/v Brij-35. (Results are expressed as mean, n=3)

Saturation solubility of bromocriptine mesylate

The solubility of the drug at acidic pH was significantly higher than in that of buffer (pH 6.8), as shown in the table (2), this can reflect the alkaline nature of the drug.

Bromocriptine mesylate is practically insoluble in water, so the addition of surfactant (Brij-35) can increase the solubility of bromocriptine mesylate by acting as an excellent solubilizing agent for the drug. It was found that 0.5 % of the Brij-35 act to increase the solubility of bromocriptine mesylate in buffer (pH 6.8) up to approximately six-fold.

Table 2: Saturation solubility of bromocriptine mesylate in different media

Solvent	PH 1.2	PH 6.8	PH6.8+0.5%brij
Solubility(µg/ml) mean±SD*	160±0.11	24.7±0.5	158.88±0.3

*SD standard deviation from mean, n=3

Visual inspection

All the prepared fast dissolving films showed homogenous and smooth surface properties which they contain (HPMC of grades E3, E5, E15), PVA, pectin, and Gelatin.

Whereas HPMC and PVA films were transparent, colourless, thin and soft, those prepared from gelatin were thin, soft and semi-transparent with yellowish color whereas pectin films turned to be opaque with brown color.

Weight variation

The outcomes reveal that: the average weights for all the prepared formulations were uniform and fit to the referred values as shown in the table (3), demonstrating that the strategy utilized for the preparation of films is reproducible and give films of uniform weight. The weight of the patches was determined using digital balance. All patches show consistency.

Thickness

The average thickness values of films for all formulas were shown in the table (3). The thickness was found to vary between 0.08±0.01 to 0.12±0.02 mm. A very low standard deviation value is indicating that the method used for the formulation of films is reproducible and give films of uniform thickness and hence dosage accuracy in each film can be ensured.

Drug content

The formulated bromocriptine mesylate films showed an acceptable quantity of medicament ranged from 96.9±1.2 %-101.6±0.6 % as shown in the table (3). The accepted range of content uniformity labeled in BP is ranged from 85 % to 115 %, so the result of content uniformity is obeying this range this indicating that the solvent casting method used in preparing bromocriptine mesylate fast dissolving oral films is very efficient. On this basis, it was found that the drug was spread uniformly throughout the four cm^2 constant area of the films.

Surface pH measurement

All the prepared films showed an acceptable surface pH value (5.8±0.08-6.3±0.26) as viewed in the table (3) when compared to that pH of oral mucosa indicating that it does not irritate the oral mucosa.

Percent moisture loss (PML)

The moisture loss study gives an idea about nature, stability, and ability of films to retain its physicochemical properties under normal storage conditions. It also indicates hydrophilicity of films. All the obtained values are reported in the table (3). The obtained values were almost uniform and ranged from 0.7±0.5 % to 2.03±0.4 % indicating little moisture loss and stable formulations.

Percent moisture absorb (PMA)

Moisture uptake study is an essential factor to be determined, as the presence of moisture bearings a critical investigation on drug stability. All the reported values of moisture uptake are listed in the table (3). It was detected that all the polymers were hydrophilic and the moisture absorbed values ranged from 1.35±0.6 % to 5.5±0.2%. Moisture uptake had an inverse relation to disintegration time, in another word as the moisture uptake increase the disintegration time decrease.

Table 3: Physical evaluation parameters of bromocriptine mesylate fast dissolving films formulas

Formula code	Weight variation (mg)*** mean±SD	Thickness mm)** mean±SD	Drug content* mean±SD	Surface pH* mean±SD	*In vitro* DT(s)* mean±SD	PML* mean±SD	PMA* mean±SD
F1	47.3±0.2	0.08±0.05	96.9±0.2	5.9±0.3	13.2±0.6	1.5±0.6	4.7±0.3
F2	49.5±0.1	0.09±0.02	98.2±0.8	6.0±0.2	18.6±0.1	1.7±0.55	4.2±0.55
F3	50.5±0.4	0.11±0.01	98.7±0.5	6.1±0.6	29±0.5	1.4±0.26	3.2±0.28
F4	49.6±0.2	0.1±0.05	100.3±0.5	5.9±0.15	61±0.3	2.03±0.4	3.35±0.6
F5	48.9±0.5	0.09±0.03	97.82±0.3	5.8±0.08	49.3±0.2	1.67±0.3	1.83±0.2
F6	49.2±0.1	0.11±0.04	99.26±1.1	5.9±0.26	20.3±0.2	1.4±0.56	4.8±0.66
F7	50.2±0.3	0.11±0.01	101.6±0.6	6.1±0.7	28.5±0.5	1.6±0.5	3.26±0.3
F8	51.5±0.2	0.12±0.02	100.2±0.4	6.2±0.5	37.6±0.1	1.2±0.17	2.25±0.2
F9	47.4±0.2	0.08±0.01	99.5±0.55	5.8±0.2	20±0. 2	1.7±0.37	2.6±0.6
F10	48.9±0.1	0.08±0.02	98.8±0.62	6.0±0.45	19.5±0.6	1.2±0.25	2.9±0.45
F11	49.7±0.05	0.09±0.05	98.66±0.5	6.3±0.26	24.2±0.1	1.8±0.16	3.5±0.32
F12	50.8±0.1	0.1±0.03	99.98±1.2	6.2±0.5	14.5±0.6	0.7±0.5	5.4±0.25
F13	49.5±0.09	0.1±0.02	99.2±0.5	6.2±0.5	11.5±0.2	1.6±0.3	5.3±0.32
F14	49.5±0.1	0.09±0.02	99.2±0.5	6.2±0.2	9.2±0.8	1.25±0.1	5.5±0.32

*n=3, **n=6, ***n=10, SD-standard deviation, DT-Disintegration time, PML-Percent moisture loss, PMA-Percent moisture absorb.

Effect of different types of polymers

Formulas (F1-F6) table (1) were utilized to study the effect of polymer type (HPMC E3, E5, E15, PVA, pectin, and gelatin) on the physical and mechanical properties of the prepared bromocriptine mesylate fast dissolving oral films and also their effect on the drug release profile.

The mechanical properties of ODFs are essential since it related to their stability during storage, shipping, and packaging.

Tensile strength has been utilized as a marker of the general mechanical prevalence of the film. A high % elongation value shows that the film is tough and flexible. Folding endurance test results indicated that the films would maintain the integrity with buccal mucosa when applied and has good plasticity. This makes the system acceptable for movement of the mouth, indicating good strength and elasticity. The selected FDOFs must have reasonable tensile strength, a high percentage of elongation, low Young's modulus, short *in vitro* disintegration time and a high percent of drug release.

The results in the table (3) showed that the lowest disintegration time of the film-forming polymer was HPMC E3 which represent (F1) with disintegration time of 13.2 sec.

Different film forming-polymers gave different disintegration time value as shown in the fig. (3):

Table 4: Mechanical properties of bromocriptine mesylate fast dissolving films formulas

Formula code	Folding endurance mean±SD	Tensile strength mean±SD	Percent of elongation mean±SD	Young's modulus mean±SD
F1	36±0.5	14.368±0.2	5.87±0.5	391.8±0.5
F2	322±2.5	6.44±0.16	20.86±0.8	105±0.2
F3	335±3.5	8.25±0.1	21.7±0.3	112.8±1.2
F4	652±5.5	2.78±0.24	29.33±0.18	51.5±0.6
F5	20±1.0	13.61±0. 5	4.275±0.2	474.5±0.15
F6	297±1.5	7.5±0.55	11.5±0.25	212.8±0.2
F7	345±2.5	15.2±0.27	27.13±0.5	110.7±0.3
F8	362±3.5	18.2±0.15	29.14±0.66	115±0.65
F9	270±2.5	7.8±0.3	18.62±0.25	112.5±0.5
F10	254±1.5	8.1±0.8	17.35±0.45	115.4±0.26
F11	258±3.65	5.2±0.5	14.4±0.5	110±0.4
F12	355±2.55	4.39±0.2	25.5±0.3	88±1.1
F13	358±2.2	4.8±0.8	19.6±0.6	87.3±0.5
F14	362±1.2	4.9±0.4	18.6±0. 5	86.4±0.25

SD-Standard Deviation; n=3.

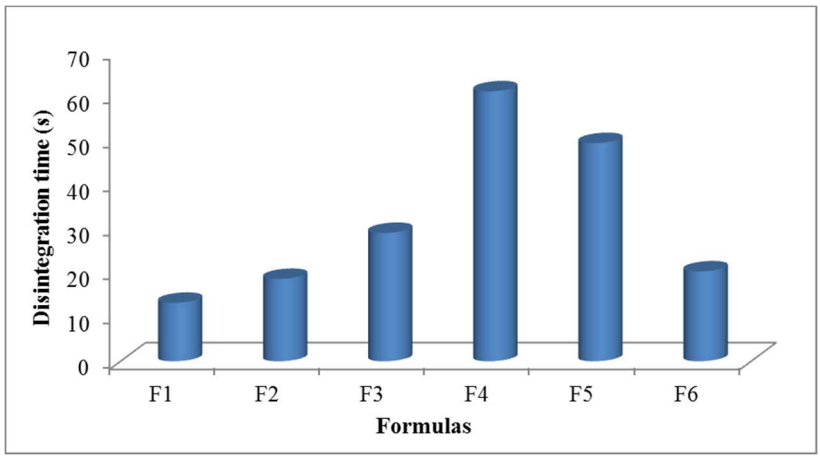


Fig. 3: *In vitro* disintegration time of different film-forming polymers, (All the values were calculated as mean±standard deviation; n=3)

The formula (F1) gave satisfactory % elongation (5.87±0.5%), but it gives low folding endurance values (36±0.5), these results were recorded by Bhikshapathi DVRN *et al.* [10]. Also, HPMC E3 film (F1) was difficult to handling that is recorded by Kumar SK *et al.* [25].

In the other hand, the films of gelatin (F6) also give low disintegration time (20.3±0.2) and with good mechanical properties (folding endurance 297) and satisfactory % elongation (11.5±0.25%). The problem seen by using this polymer was the hard peeling of the film from the petri dish (its peeled as apices) this result also reported by T. Hassanien *et al.* [26]

While films of PVA (F4) have good mechanical properties with good peeling off and good appearance but with long disintegration time (61±0.3 sec.) due to the swelling property of this polymer which makes a gel-like layer on the surface of the film upon contact with aqueous media lead to prevent penetration of water to the film, this swelling property increased with increasing of the polymer concentration [27].

The films that prepared with pectin as film-forming polymer gave as shown in the table (3) a relatively long disintegration time (49.3±0.2 sec.) with low folding endurance value (20±1) and bad mechanical properties (high (percentage of elongation, young's modulus and low percentage of elongation) as shown in table (3) this indicates that the films were brittle and weak. The reason for the brittle film formation was the insufficient concentration of polymer in the formulation [28].

While (F2) (HPMC E5) gave satisfactory % elongation (20.86±0.8) and good folding endurance values (337±2.5), these outcomes were in concurrence with those that reported by Chauhan SS *et al.* [29].

On the other hand, the film made from HPMC E15 has acceptable mechanical properties, young's modulus (112.8±1.2) and folding endurance (335±3.5), but the formulated HPMC E5 film has faster disintegration time than HPMC E15 formula (18.6±0.1 and 29±0.5) respectively.

The *in vitro* dissolution profile of bromocriptine mesylate fast dissolving oral films of the formulas (F2 and F3) as shown in fig. (4).

The values of T80% for the films prepared with HPMC E5 and HPMC E15 (F2 and F3) was 2.6 and 4.99 min respectively. The difference in the dissolution parameters caused by the variances in viscosity grade of HPMC film-forming polymer. These results agree with the

result obtained by Pradhan R *et al.* by using different grades of HPMC and studying its effect on the release profile of indomethacin and report that drug release decreased with increase in the viscosity of polymer used [30]. From results, the disintegration time in mouth increased with increasing the viscosity of HPMC polymer and with increasing the polymer level in the formulation.

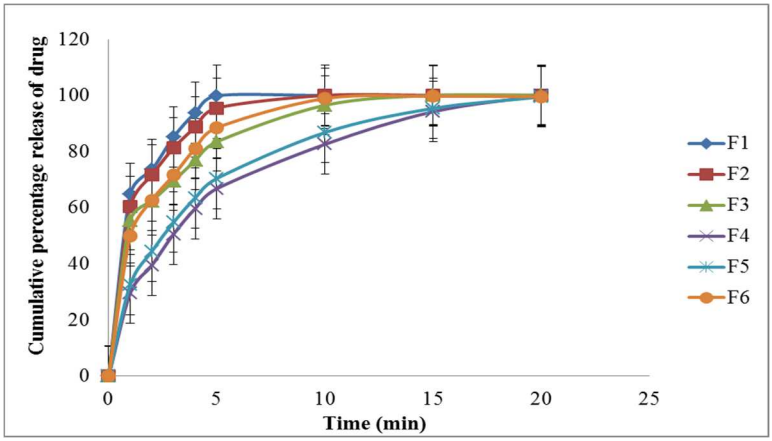


Fig. 4: Effect of polymer type on the dissolution profile of bromocriptine mesylate in phosphate buffer (pH 6.8) at 37 °C, (All the values were calculated as mean±standard deviation; n=3)

The time needed for 80 % of medication to be released (T80%) and percent medication dissolved in 2 min (% D2 min) from the formulated films (F2 and F3) are listed in the table (5). From all these results we found that the HPMC E5 had the best physical, mechanical properties and drug release profile than the other film forming polymers.

Table 5: *In vitro* dissolution considerations of (F2 and F3)

Formula	T80% (min) mean±SD	%D2 min mean±SD
F2	2.6±0.5	71.6±0.2
F3	4.99±0.15	61.4±0.25

SD-Standard deviation; n=3; T80%-time required for 80% of drug to be released; %D2 min-cumulative percentage release of drug at 2 min.

Effect of concentrations of selected polymer (HPMC E5)

According to the physical and mechanical properties and the drug release profile, HPMC E5 was selected as an optimized suitable polymer for prepare fast dissolving bromocriptine mesylate oral film.

So formulas (F2, F7, and F8) of different polymer concentrations (50%, 55% and 60% w/w) respectively were further evaluated to get an optimum suitable polymer concentration by study their dissolution profile parameters.

Table (3) revealed that there is a significantly ($p \leq 0.05$) decrease in the invitro DT of the formulated strips with the decrease in concentration of HPMC E5 from (60% w/w) in formula (F8) to (50% w/w) in formula (F2).

It appears that films containing a high concentration of polymer resulted in a thicker gel upon contact with the medium, resulting in longer disintegration time as shown in fig. (3). the same result was obtained with metoprolol tartrate strips and lamotrigine fast dissolving films [31, 32].

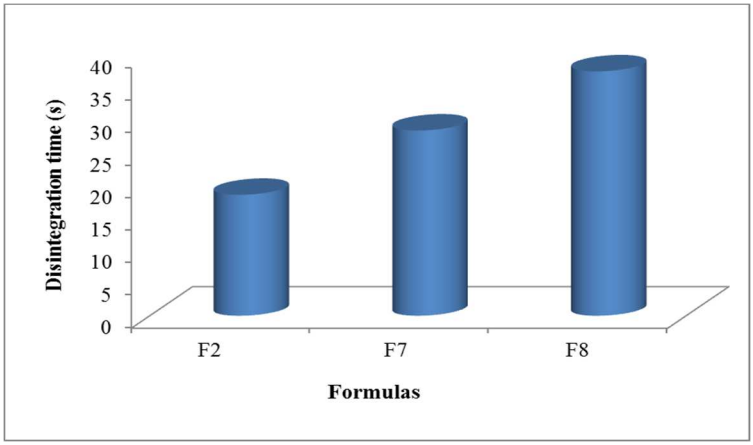


Fig. 5: *In vitro* disintegration time of different concentration of the selected film-forming polymer (HPMC E5), (All the values were calculated as mean±standard deviation; n=3)

The results of tensile testing listed in the table (4) that indicate high tensile strength film result from increasing the polymer concentration, this is due to the fact that densely packed chains of HPMC produced from increasing polymer concentration, make the film need more force to breaks [33]. Same findings were found with valsartan film [34].

Also, the results revealed that the percentage elongation and folding endurance of the films were increased with an increase in the concentration of polymer as in table (4), due to increase in the elasticity nature of the polymer [28]. Similar observations were found by Trivedi J *et al.* [35].

Table (6) shows that the formula (F2) has the highest D2 min (%) and the lowest T80% (min) (2.6 min) indicate that F2 which contain the lowest percent of polymer (50 % HPMC E5) gave fastest dissolution rate compared with the other formulas (F7and F8) as shown in fig. (6).

From the dissolution parameters that showed in table (6) for the formulas prepared with a different concentration of the selected polymer HPMC E5 (F2, F7 and F8) which contain (50%, 55% and 60% w/w respectively), it was seeing that the dissolution rate of bromocriptine mesylate reduces significantly ($p<0.05$) as the concentration of HPMC E5was increase from 50 % (w/w) in formula (F2) to 60 % (w/w) in formula (F8) as shown in fig. (6), this results may be due to that higher concentration of polymer, results in the production of high consistency gel layer created by the close interaction between the particles of HPMC E5 results in a diminished movement of medication particles in swollen lattices, which prompts a decline in dissolution rate [33].

Therefore, HPMC E5 (50 % w/w) was considered as the best polymer concentration and was chosen for the design of the subsequent formulas through the study.

Table 6: *In vitro* dissolution parameters from the prepared oral films (F2, F7, and F8)

Formula code	T80%(min) mean±SD	D2 min(%) mean±SD
F2	2.6±0.5	71.6±0.2
F7	4.7±0.25	60.5±0.55
F8	5.29±0.3	53.7±1.25

SD-Standard deviation; n=3; T80%-time required for 80% of drug to be released; %D2 min-cumulative percentage release of drug at 2 min.

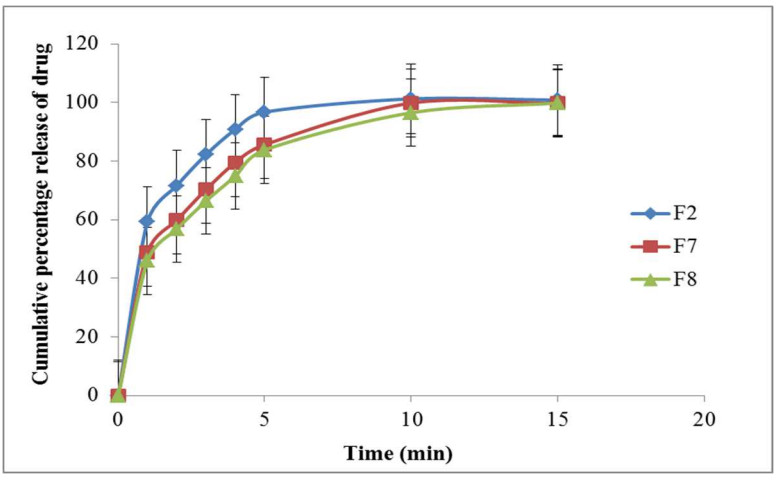


Fig. 6: Cumulative percent of bromocriptine mesylate release of different concentration of HPMC E5 in phosphates buffer (pH 6.8) at 37 °C, (All the values were calculated as mean±standard deviation; n=3)

Effect of the type and concentration of plasticizers

Formulas (F2, F9 and F10) were employed to study the effect of different plasticizer types in concentration 20% w/w (glycerin, PEG 400 and PG) and different concentration of PEG 400 (20, 20 and 25 % w/w) in formulas (F2, F11 and F12) on the mechanical, physical properties and on the dissolution profile of the bromocriptine mesylate FDOFs.

The results showed that changing of plasticizer type caused no significant effect ($p>0.05$) on the *in vitro* DT of mouth dissolving strips, as show in fig. (7), this may be due to the fact that three types of plasticizer enhanced the disintegration time by facilitating the penetration of fluids into the strip, since plasticizer alter the densely packed chains of HPMC texture by forming a polymer structure possess more pores and less densely that breaks at lower force, resulting in faster disintegration of the film [36].

The folding endurance of formulation with PEG 400 as a plasticizer were higher compared to other plasticizers. The same result was obtained with diazepam oral strips [37]. On the other hand, HPMC films that plasticized with propylene glycol were patchy and sticky in appearance, while glycerin made soft and tough strips. At the same time, films plasticized with PEG 400 exhibited good physical and mechanical properties such as tensile strength and percentage of elongation as shown in the table (4). These observations are in accordance with Choudhary *et al.* [38] and Ali MS *et al.* [37]. So PEG400 was selected for further study of suitability in films formulation.

The time needed for 80% of medication to be released (T80%) and percent medication dissolved in 2 min (D2 min) from the formulated films (F2, F9, and F10) are listed in the table (7).

The release profile of bromocriptine mesylate from formulas (F2, F9 and F10) which contain 20 % w/w of (PEG 400, PG and glycerin) respectively is displayed in fig. (8). It was seen that changing the plasticizer types had no-significant change ($p>0.05$) on the dissolution profile of bromocriptine mesylate, this may be because of that the three plasticizers are water dissolvable and they will diffuse out from the films in watery media making void spots in the film through which distribution of liquid happens to enable film breaking down leading to improve release profile of drug [39].

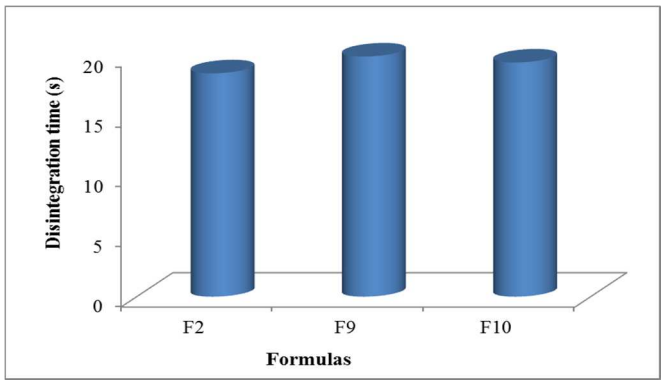


Fig. 7: *In vitro* disintegration time in seconds of formulas prepared with different types of plasticizer, (All the values were calculated as mean±standard deviation; n=3)

Table 7: *In vitro* dissolution parameters from the prepared oral films (F2, F9, and F10)

Formula code	T80% (min) mean±SD	D2 min (%) mean±SD
F2	2.6±0.5	71.6±0.2
F9	2.9±0.2	69.4±0.55
F10	3.0±0.15	68.8±0.8

SD-Standard deviation; n=3; T80%-time required for 80% of drug to be released; % D2 min-cumulative percentage release of drug at 2 min.

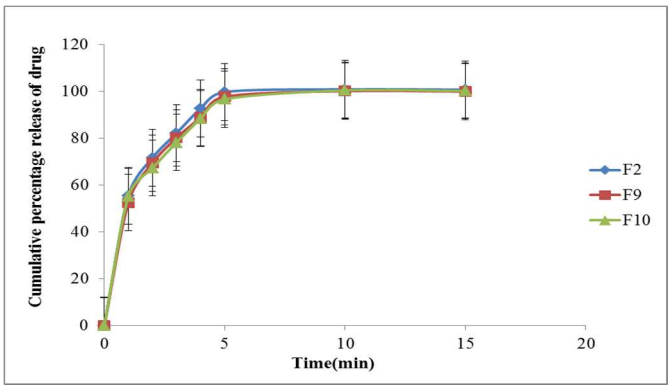


Fig. 8: Cumulative percent of bromocriptine mesylate release from formulas prepared with the different type of plasticizers in phosphates buffer (pH 6.8) at 37 °C, (All the values were calculated as mean±standard deviation; n=3)

Formulas F2, F11, and F12 were used to study the effect of different concentrations of selected plasticizer PEG400 (20, 15 and 25 %w/w of the total film weight) on the *in vitro* disintegration time, mechanical properties and the drug release profile of the oral film.

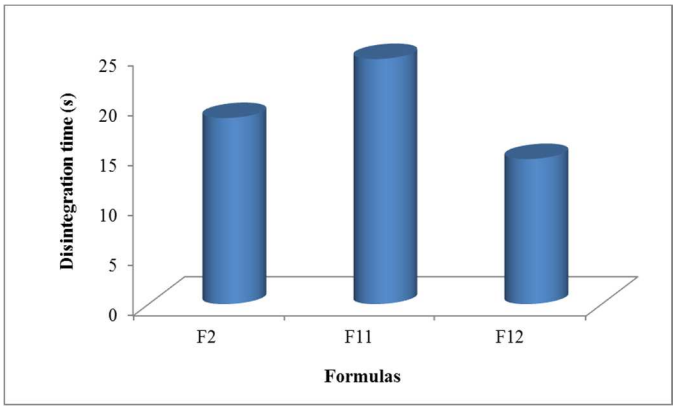


Fig. 9: *In vitro* disintegration time in seconds of formulas prepared with the different concentration of the selected plasticizer (PEG 400), (All the values were calculated as mean±standard deviation; n=3)

Different concentration of PEG400 (20, 15 and 25 %) which present in formulas (F2,F11 and F12) show a decrease in disintegration time as the plasticizer concentration increased as shown in fig. (9) this occurs because PEG 400 act as a co-solvents that reduce the ability

of water to squeeze out non-polar, hydrophobic compounds, thus increasing solubility [40].

The mechanical properties of formulas (F2, F11, and F12) are shown in the table (4), which shows that the increase in the plasticizer concentration produced a decrease of the Young's modulus (YM), and the tensile strength (TS). The decrease in tensile strength as a function of plasticizer concentration increase may be due to the weakening of the intermolecular forces between polymer chains, thus leading to decrease the rigidity of three-dimensional structure formed upon drying the film, this leads to a less force to break the film. Moreover, it was seen that the increasing the concentration of plasticizer leading to increasing the percentage of elongation (%E). These results can be explained by the fact that the plasticizers act as an interior emollient and enhance movement of the polymer chains (lubricity theory) [41].

From the release profile of bromocriptine mesylate from formulas (F2, F11, and F12) which contain 20, 15 and 25% of PEG 400 respectively that shown in (fig. 10), it was observed that the drug release rate increased significantly ($p<0.05$) as the concentration PEG 400 was increased; Here the role of PEG 400 may be a dissolution facilitating agent, therefore increasing concentration will increases the drug release rate [42].

The time needed for 80% of medication to be released (T80%) and percent medication dissolved in 2 min (D2 min) from the formulated films (F2, F11and F12) are listed in the table (8).

The dissolution parameters showed that F12 prepared with 25% PEG400 had the best drug release profile among other formulas prepared with less concentration of PEG400, so F14 was chosen for the design of the subsequent formulas through the study.

Table 8: *In vitro* dissolution parameters from the prepared oral films (F2, F11, and F12)

Formula code	T80%(min) mean±SD	D2 min(%) mean±SD
F2	2.6±0.5	71.6±0.2
F11	3.14±0.3	65.4±0.8
F12	2.06±0.25	77.4±0.65

SD-Standard deviation; n=3; T80%-time required for 80% of drug to be released; % D2 min-cumulative percentage release of drug at 2 min.

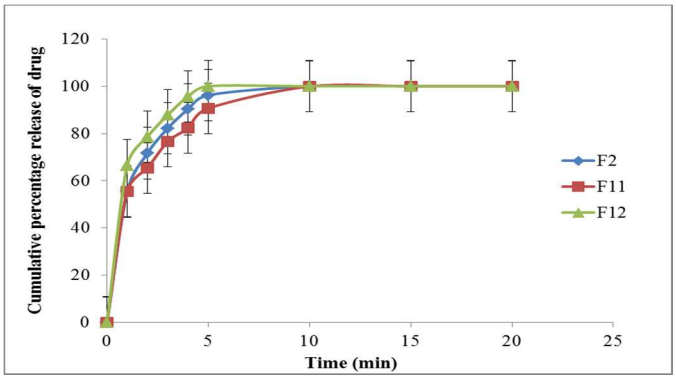


Fig. 10: Cumulative percent of bromocriptine mesylate release from formulas prepared with the different concentration of PEG400 in phosphates buffer (pH 6.8) at 37 °C, (All the values were calculated as mean±standard deviation; n=3)

Effect of super-disintegrant (crospovidone) concentration

Incorporation of super-disintegrant (crospovidone) to the best formula (F12),from the previous study, in different concentrations (1 and 3% w/w) of the total dry weight of the film represented by (F13 and F14) respectively to study its effect on the physical, mechanical properties and the release profile of bromocriptine mesylate from the film.

The physical properties in the table (3) showed an enhancement in the disintegration time also shown in fig. (11) with the addition of crospovidone to the prepared formula also the disintegration time was more enhanced with increasing the concentration of crospovidone from 1% to 3% w/w as shown in (F13 and F14) respectively. This disintegration enhancement is caused by the ability of crospovidone to wick saliva quickly into the film that leads to generate the volume expansion and hydrostatic pressures necessary to provide rapid disintegration in the mouth, the major mechanism of disintegration for crospovidone is wicking mechanism in addition to the swelling mechanism [43].

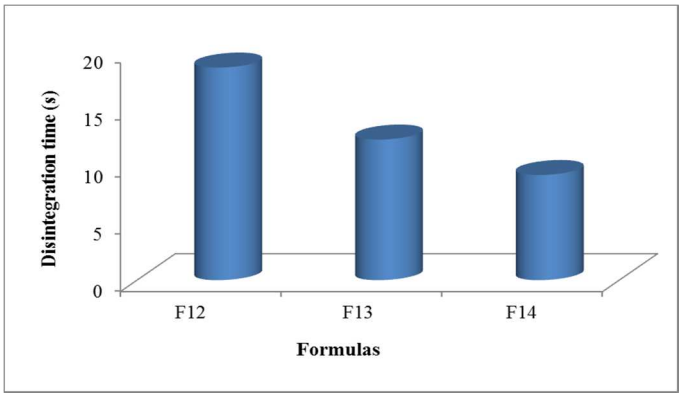


Fig. 11: *In vitro* disintegration time in seconds of formulas prepared with a different concentration of supper disintegrant (crospovidone), (All the values were calculated as mean±standard deviation; n=3)

While the mechanical properties for related parameters (percentage of elongation, tensile strength, and Young's modulus) as shown in the table (4) which revealed that there is no significant difference (P>0.05) with the addition of crospovidone.

On the other hand, adding crospovidone in F13 and F14 (1% and 3% respectively) to the prepared bromocriptine mesylate fast dissolving films show a significant difference (p<0.05) in the dissolution release profile in compares with (F12) prepared without crospovidone as represented by the fig. (12). This result also reported by Deep AK and *et al.* were they got an increase in disintegration and enhance in dissolution release profile of cinnarizine fast dissolving films by increasing the amount of crospovidone [44]. The release of bromocriptine mesylate mainly depends upon the superdisintegrant concentration. It was found that increase in the content of superdisintegrants, increased the drug release [45]. The enhancement in the release of drug from F13 and F14 can be explained by the porous structure of crospovidone in which the crospovidone particles seem to be granular and highly porous when examined under a scanning electron microscope. This unique, porous particle morphology is acting to wick the liquid, and due to its high crosslink density leading to fast swelling of crospovidone in water without gelling [46].

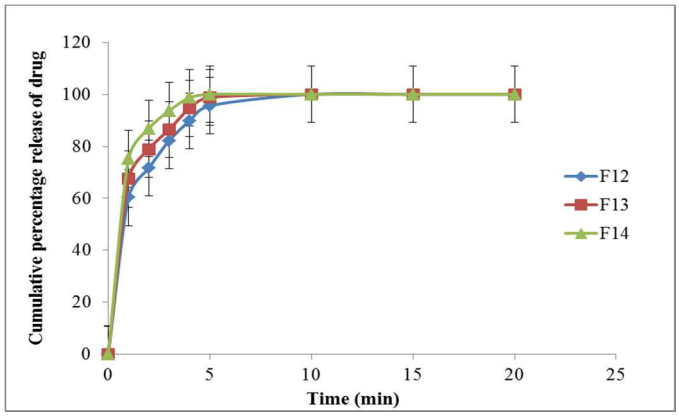


Fig. 12: Cumulative percent of bromocriptine mesylate release from formulas prepared with the different concentration of crospovidone in phosphates buffer (pH 6.8) at 37 °C, (All the values were calculated as mean±Standard Deviation; n=3)

The time needed for 80% of medication to be released (T80%) and percent medication dissolved in 2 min (% D2 min) from the formulated fast dissolving oral films (F12, F13and F14) are listed in table (9), which showed that F14 (3% crospovidone) gave the fastest T80% (1.35±0.3) and the highest %D2 min (86.8±0.1).

Table 9*: In vitro* dissolution parameters from the prepared oral films (F12, F13, and F14)

Formula code	T80% (min) mean±SD	D2 min (%) mean±SD
F12	2.06±0.25	77.4±0.65
F13	2.0±0.1	78.9±0.2
F14	1.35±0.3	86.8±0.1

SD-Standard deviation; n=3; T80%-time required for 80% of drug to be released; % D2 min-cumulative percentage release of drug at 2 min, according to the results above, F14 was selected as an optimized formula for the formulation of bromocriptine mesylate fast dissolving oral film.

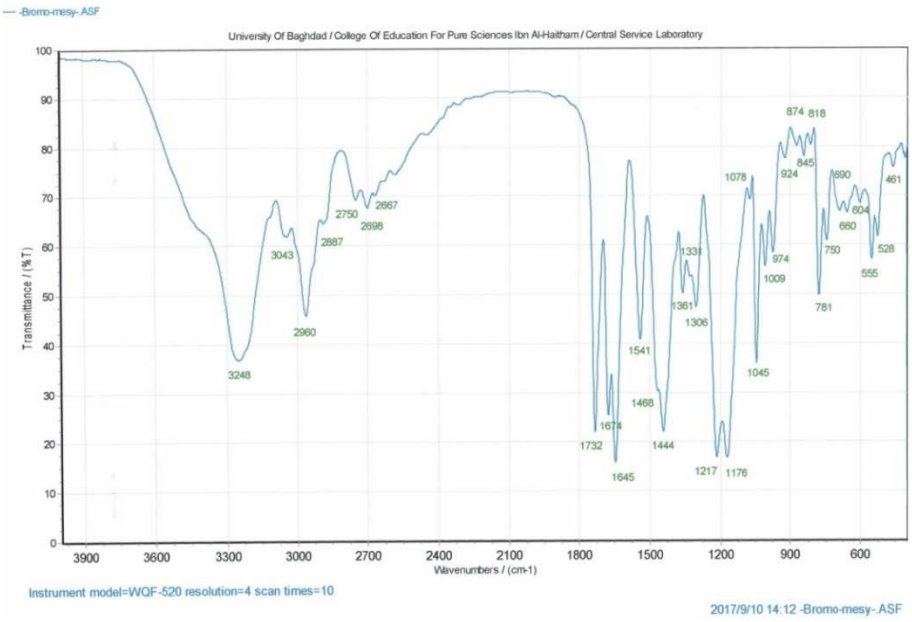


Fig. 13: FTIR spectrum of bromocriptine mesylate

Drug-polymer compatibility study

Fourier transform infrared spectroscopy (FTIR)

The principal peaks of the FT-IR spectrum of bromocriptine mesylate are shown in fig. (13), which is at the wave numbers(in cm-1):1047 for alcohol C-H stretching (1260-1000), 1211 for alkyl halide C-Br wagging band (1300-1150), 1361 for the S=O in sulphonate salt (1372-1335), 1444 for aromatic ring (1500-1400), 1544 for amide N-H (1650-1515), two bands 1726 and 1672 for C=O stretching in the ketone group (1870-1540), and 3261 for amide N-H stretching (3350-3180) [47].

Similar peaks were obtained from the bromocriptine in the physical mixture of the selected formula 14 and in the selected formula (F 14) as a film as shown in fig. 13, 14 and fig. 15 respectively, this indicates the lack the possibility of interaction between drug and excipients used in the preparation.

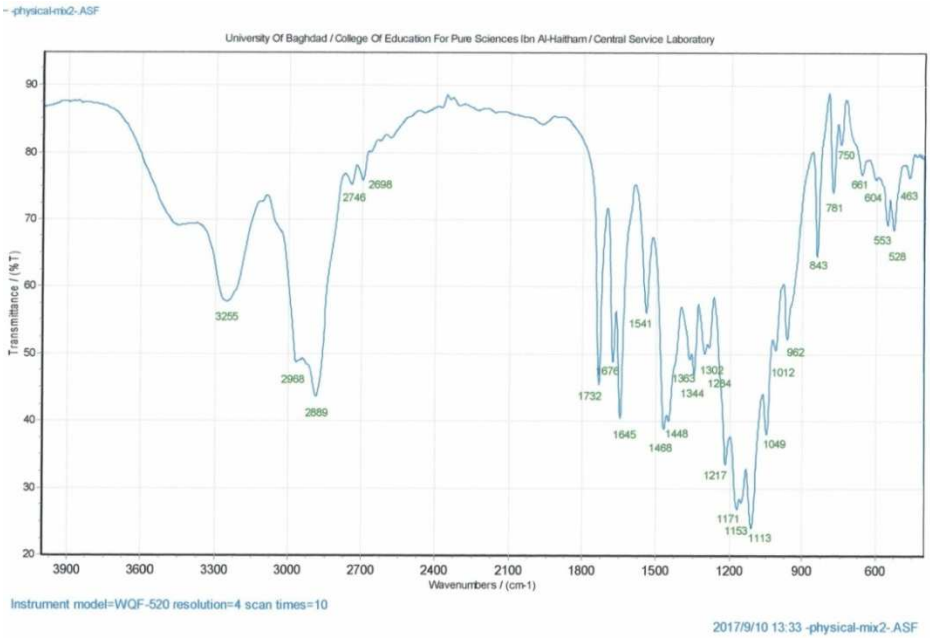


Fig. 14: FTIR spectrum of a physical mixture of the selected formula (F14)

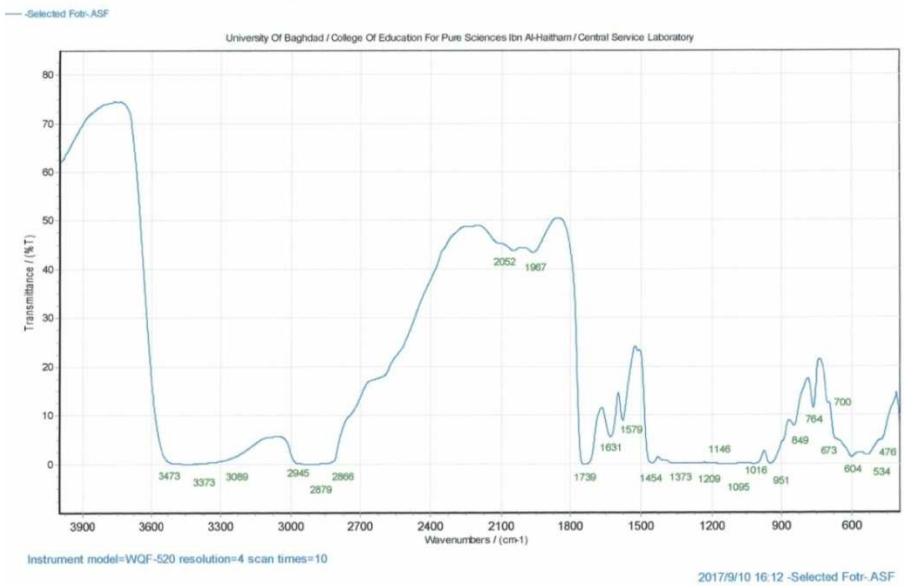


Fig. 15: FTIR spectrum film of the selected formula (F14)

X-Ray diffraction

The x-ray diffractogram of bromocriptine mesylate confirms its crystalline nature, as evidenced by the number of sharp and intense peaks as shown in fig. (16). However, the diffraction pattern of selected formula F14 represents disappearance of crystalline peaks of the drug, and these findings suggest the improvement of drug solubility by the formation of an amorphous form of the drug. Similar results were observed by Reddy PB *et al.* [48].

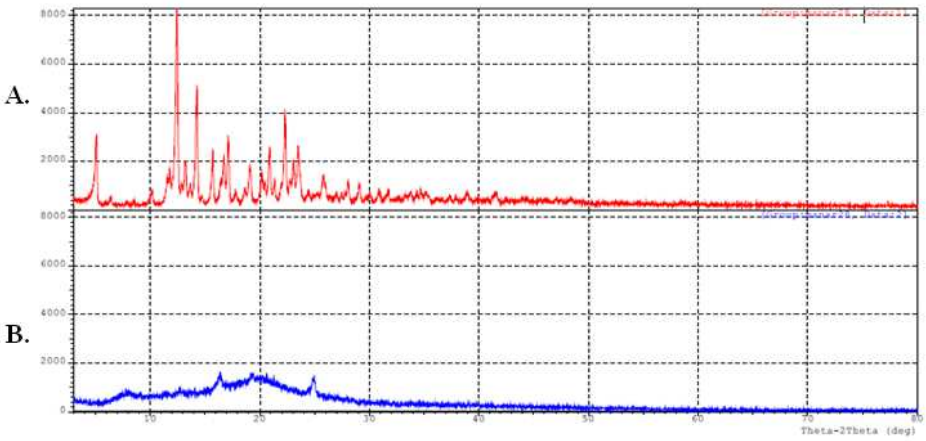


Fig. 16: A. X-Ray diffraction of pure bromocriptine mesylate, B. X-Ray diffraction of the selected formula F14

CONCLUSION

By the results obtained; hydroxypropyl methylcellulose showed the fastest *in vitro* disintegration time. In addition, acceptable mechanical properties and dissolution behaviour were achieved. Also, PEG400 was the best plasticizer as it showed an improvement in mechanical and physical characteristics of the bromocriptine mesylate oral film. Formula (F14) which composed from 50% w/w HPMC E5 as a film forming polymer, 25% PEG400 as a plasticizer, 5% poloxamer 407 as a surfactant and 3% crospovidone as superdisintegrant regarded as an optimized formula with a low disintegration time (9.2±0.1 seconds), 80% of drug released within (1.35 minute).

Bromocriptine mesylate administered in the form of fast dissolving films will be a potential novel drug dosage form for geriatric and also for the general population with DM type II by providing faster release and better patient compliance.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

Declared none

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