

Formulation and *In-Vitro* Evaluation of Darifenacin Hydrobromide as Buccal Films

Ishraq K. Abbas^{*1}, Nawal A. Rajab^{**} and Ahmed A. Hussein^{**}

^{*} Faculty of Pharmacy, Al-Rafidain University College, Baghdad, Iraq.

^{**} Department of Pharmaceutics, College of Pharmacy, University of Baghdad, Baghdad, Iraq.

Abstract

Overactive bladder (OAB) affects about 16% of the adults and rises with increasing age. OAB lead to various symptoms such as urgency, incontinence, urinary frequency and nocturia. Darifenacin hydrobromide (DH) is the more recent uroselective M3 receptor antagonist for treating uncomplicated OAB.

Fast dissolving buccal films are the most innovative oral solid dosage form because of their flexibility and comfort. This study aims to formulate DH as fast dissolving buccal films (FDBFs) using a solvent casting method to increase its bioavailability by reducing the effect of first pass metabolism in the liver.

Films were prepared by using polyvinyl alcohol as a film forming polymer, glycerol and tween 80. Different types and concentrations of superdisintegrants (croscarmellose sodium, sodium starch glycolate, indion 414) were used to select the best formula by studying the physicochemical properties of the films, disintegration time (DT) and percent drug release.

The results revealed that formula (F9) that containing 7.5mg DH, 2%w/v PVA, 30%w/w glycerol, 0.5%w/v tween 80, 4%w/w indion 414 was the preferred formula. F9 showed the shortest *in-vitro* disintegration time (31.28sec). *In-vitro* dissolution profile showed the lowest T_{80%} of the drug in 3.05 min and the highest release of the drug (94%) within 5 min (D_{5min} %).

It was concluded that the FDBFs of DH could be considered as a promising drug delivery system with an enhanced disintegration and dissolution rate and better patient compliance.

Keywords: Darifenacin hydrobromide, Overactive bladder, Fast dissolving buccal films.

صياغة وتقييم خارج الجسم لهيدروبروميد الداريفيناسين كشرائح فموية
إشراق كاظم عباس^{*}، نوال عيَّاش رجب^{**} و أحمد عباس حسين^{***}

^{*} كلية الصيدلة، كلية الرافدين الجامعة، بغداد، العراق.

^{**} فرع الصيدلانيات، كلية الصيدلة، جامعة بغداد، العراق.

الخلاصة

المثانة المفرطة النشاط (OAB) تؤثر على حوالي ١٦٪ من البالغين وترتفع هذه النسبة مع تقدم العمر. OAB تؤدي إلى أعراض مختلفة مثل الحاح التبول وسلس البول وتكرار التبول والتبول الليلي. هيدروبروميد الداريفيناسين (DH) هو أحدث مضادات مستقبلات اليوريا الانتقائية M3 لعلاج OAB غير المعقد.

الشرائح الفموية سريعة الذوبان هي الشكل الأحدث ابتكارا للجرع الصلبة عن طريق الفم بسبب مرونتها وراحتها. تهدف هذه الدراسة إلى صياغة DH كشرائح فموية سريعة الذوبان باستخدام طريقة صب المذيبات لزيادة التوافر الحيوي للدواء عن طريق تقليل التمثيل الغذائي الأولي في الكبد. تم تحضير الشرائح باستخدام بوليمر كحول البولي فينيل والجلسرين وتوين ٨٠. تم استخدام أنواع وتركيزات مختلفة من المفتتات الفائقة (كروسكارميلوز الصوديوم، جليكولات نشا الصوديوم، indion 414) لتحديد أفضل صيغة من خلال دراسة الخصائص الفيزيائية والكيميائية للأفلام، ووقت التفكك والنسبة المئوية لتحرر الدواء.

أظهرت النتائج أن الصيغة F9 التي تحتوي على ٧,٥ ملغ من DH و ٢٪ من PVA و ٣٠٪ من الجلسرين، و ٠,٥٪ من توين ٨٠، و ٤٪ من indion 414 وكانت هي الصيغة المفضلة. أظهرت F9 أقصر وقت تفكك خارج الجسم (٣١,٢٨ ثانية). أظهر تحليل الدواء خارج الجسم أدنى وقت لاطلاق ٨٠٪ من الدواء (T₈₀٪) في ٣,٠٥ دقيقة وأعلى إطلاق للدواء (٩٤٪) في غضون ٥ دقائق (D_{5min}٪).

يمكن الاستنتاج بأن أن شرائح DH الفموية سريعة الذوبان يمكن اعتبارها كنظام تحرير أدوية واعد مع تحفيز لمعدل التفكك ولنسبة التحلل بالإضافة إلى تحسين امتثال المرضى.

الكلمات المفتاحية: داريفيناسين هيدروبروميد، فرط نشاط المثانة، أفلام فموية سريعة الذوبان.

Introduction

In the past few decades, development and imagination have ended up basic competence for making progress in the development of novel dosage forms. But, every dosage form has shown some drawbacks like pain of the parenteral dosage form and chocking of tablets and capsules⁽¹⁾.

The oral solid dosage forms are characterized by ease of administration and exact dosing, but it is

sometimes problematic because of decline in bioavailability, long onset time of action and swallowing difficulty especially for pediatric and geriatric⁽²⁾. Most of pharmaceutical manufacturers have focused in their researches on developing new dosage form to achieve patient convenience. Among many drug delivery systems, the fast dissolving films are incredibly prominent among pediatrics and

¹Corresponding author E-mail:ishraqalmualla@yahoo.com

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geriatrics and have started gaining big popularity for their rapid disintegration or dissolution, self-administration even without water or chewing⁽³⁾. The oral cavity is a preferred site for drug administration because of easily drug application by patient and avoidance of possible drug degradation in the GIT in addition to bypassing first-pass hepatic metabolism⁽¹⁾. Oral mucosa is the lining of the oral cavity. The membrane of mucosa cells is hydrophobic in nature and might be selective for hydrophobic molecules only, while the hydrophilic molecules pass the oral mucosal membrane through the para-cellular pathway since the cytoplasm and intercellular spaces are hydrophilic in nature. After absorption, the drug is transported through facial vein, which then drains into general circulation, bypassing the liver, therefore warn off drug from first pass metabolism⁽⁴⁾.

Overactive bladder (OAB) is a common and distressing disorder characterized by incontinence, urinary frequency and nocturia. The symptoms of OAB have been attributed to involuntary contractions of the bladder muscle. This supports the rationale for using a drug that antagonizes the M3-mediated parasympathetic excitation of the detrusor smooth muscle contraction⁽⁵⁾.

Darifenacin hydrobromide (DH) is the first M3-selective receptor antagonist. It has a higher selectivity for muscarinic receptors of the bladder. It was approved by FDA to be used for the symptomatic treatment of OAB in 2004⁽⁶⁾. DH molecular weight is 507.472 g/mol. It is slightly soluble in water (6.03mg/ml). Its melting point is 228-236 °C⁽⁷⁾. It is subjected to extensive first-pass metabolism after oral administration. The absolute bioavailability of DH from 7.5mg and 15mg prolonged release tablet was estimated to be 15.4 % and 18.6% respectively⁽⁸⁾. This study is aimed to prepare DH as fast dissolving buccal films (FDBFs) to enhance patient's compliance.

Materials and methods

Materials

DH supplied by Hyperchemical comp., China. Polyvinyl alcohol (AVONCHEM, UK), glycerol (Fluka Chemi AG, Switzerland), tween 80 (SD Fine-Chem. Limited, Mumbai, India), croscarmellose sodium and sodium starch glycolate (Hyperchemical comp. China), indion 414 (Ion Exchange India Ltd, Mumbai).

Methods

Preparation method of darifenacin hydrobromide fast dissolving buccal films

Solvent casting technique was used in the preparation of DH FDBFs by using 9 cm diameter petri dishes. 2%w/v of PVA solution was prepared by dissolving the polymer in deionized water with constant stirring (120rpm) by magnetic stirrer to form a homogenous polymeric solution. To this polymer solution, excipients were added separately. DH was dissolved, in 30 ml absolute ethanol at 60

°C with stirring to form a clear solution. Then the two mediums were mixed together using magnetic stirrer. The mixture (63ml) was set aside to ensure air bubbles removal, then casted in a petri dish (9 cm diameter) and kept in an oven at 50°C overnight. The dried film was then removed and cut into (2cm×2cm) films⁽⁹⁾.

Nine formulas (F1-F9) were prepared using different superdisintegrants types {croscarmellose sodium (CCS), sodium starch glycolate (SSG) and indion 414} and concentrations (2%, 3% and 4%) to select the best formula (Table 1).

Evaluation of darifenacin hydrobromide fast dissolving buccal films:

Physical appearance of the prepared films

Physical appearance was evaluated by visual inspection for homogeneity, clearness and surface texture.

Weight variation

It was done by weighing ten films individually, and average weights were calculated. The accepted film weight should not significantly deviate from weight average⁽¹⁰⁾.

Thickness of the films

It was measured by using a standard Vernier caliper. Six films were measured at five positions, and average thickness was calculated⁽¹¹⁾.

Drug content uniformity

Three films were placed in 100 ml phosphate buffer (pH6.8) solutions individually and kept on a magnetic stirrer for 30min. The solution was filtered by filter syringe (0.45µm), and DH amount was measured spectrophotometrically⁽¹²⁾.

Folding endurance (FE)

FE was determined by manual repeated folding of film at specified site until it breaks or cracks, and average values were calculated and reported. FE of more than 300 gives a good idea about the flexibility and toughness of the formulation⁽¹¹⁾.

In-vitro disintegration time (DT)

It was measured visually by using a petri dish method. The test was done by taking three films of each patch in a petri dish (5cm diameter) separately, and after adding 2 ml of deionized water for each film, the petri dish was shaken smoothly and continuously, then measure the time at which the FDBFs start to break down or disintegrate⁽¹¹⁾.

Determination of surface pH

This is essential to investigate the opportunity of side effects when using the films *in-vivo*, because sharp acidic or basic pH may irritate the mucosal membrane of the oral cavity. To measure the pH value; three films were allowed to dissolve in 2 ml of deionized water separately, and the pH of the obtained solution is determined using pH-meter⁽¹¹⁾.

Table 1. Composition of darifenacin hydrobromide fast dissolving buccal films (4cm²)

Formula no.	Darifenacin Hydrobromide (mg/Film)	polymer (mg/Film)	Plasticizer mg/Film	Surfactant (mg/Film)	Superdisin tegrant mg/Film			Flavoring Agent	Sweetenin g_agent	Saliva stimulant
		PVA	Glycerol	Tween 80	Croscarmellose Sodium	Sod. Starch glycolate	Indion 414	Vanilla	Sod. saccharin	Citric acid
F 1	7.5	41	12	10	1.6			2.5	2.5	2.5
F 2	7.5	41	12	10	2.3			2.5	2.5	2.5
F 3	7.5	41	12	10	3.1			2.5	2.5	2.5
F 4	7.5	41	12	10		1.6		2.5	2.5	2.5
F 5	7.5	41	12	10		2.3		2.5	2.5	2.5
F 6	7.5	41	12	10		3.1		2.5	2.5	2.5
F 7	7.5	41	12	10			1. 6	2.5	2.5	2.5
F 8	7.5	41	12	10			2. 3	2.5	2.5	2.5
F 9	7.5	41	12	10			3. 1	2.5	2.5	2.5

In-vitro dissolution stud

It was done by using USP type II (paddle apparatus) with 300 ml of Phosphate buffer (pH 6.8). The medium was adjusted to rotate at 50 rpm, and the temperature was maintained at 37±0.5°C. 5 ml Samples were taken by using a syringe at regular intervals (1, 2, 3, 4, 5, 10, 15 and 20min) replaced with 5ml buffer medium to maintain sink condition. Then before analyzing the withdrawn samples using UV-spectrophotometry at DH λ_{max}, they were filtered by filter syringe (0.45 μm). Then the dissolution profile of the drug is constructed by plotting the percent of accumulative drug release against the time ⁽¹³⁾.

T_{80%}(min) which is the time needed to release 80% of the drug and D_{5min}(%) which represent the percentage of drug released in 5 min was used to study the effect of different factors on the dissolution profile ⁽¹⁴⁾.

Effect of superdisintegrant type and concentration

Three formulas (F1, F2 and F3) were developed to illustrate CCS effect at different concentrations (2%, 3% and 4%w/w of total dry constituents of the film) on the mechanical, physical properties and dissolution profile of DH films. SSG with 2%, 3% and 4% concentrations used to study its effect on F4, F5 and F6. The last superdisintegrant used was indion 414, also with same concentrations in F7, F8 and F9.

Characterization of selected formula:**Percentage moisture loss (PML)**

This was done to determine physical stability of films. It was detected by putting three accurately weighed films in a desiccator that containing silica gel beads. After 72 hours; films were taken and weighed again ⁽⁹⁾.

$$PML = \frac{(\text{Initial weight} - \text{Final weight}) \times 100}{\text{Initial weight}}$$

Percentage moisture absorption (PMA)

PMA was used to check the physical stability of films at high humid condition. It was identified by keeping three accurately weighed films in a desiccator containing a saturated solution of calcium chloride, at 25°C for 72 hours, then after three days, films were reweighed.

$$PML = \frac{(\text{Final weight} - \text{Initial weight}) \times 100}{\text{Initial weight}}$$

Evaluation of mechanical property of the films:**Tensile strength (TS)**

It is maximum force required for breakdown of the film. The film were cut around a standard 9×2 cm² template (dumbbell) and put between two clamps of tensometer and pulled at a rate of 5 mm/min. TS was measured by mega Pascal (MPa) ⁽⁹⁾. Tensile strength= Load at break (N)*100/Width× Thickness (mm²).

Percent of elongation (%E)

%E is the stretching and distortion of the film when a force is applied on it ⁽¹¹⁾.

$\%E = \frac{\text{Final length} - \text{initial length}}{\text{Initial length}} \times 100$

Young's modulus (YM)

It is defined as the measure of the stiffness of film. So rigid and fragile films exhibit high TS and YM with small %E ⁽¹¹⁾.

$YM = \frac{\text{Slop} \times 100}{\text{Strip thickness} \times \text{Cross-head speed}}$

Drug-polymer compatibility study

It was examined by Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetric Studies (DSC) and X-Ray Powder Diffraction (XRPD).

Fourier transform infrared spectroscopy

FTIR confirmed the compatibility of the drug and the formulation. Spectra of pure drug and formulations were determined by potassium bromide (KBr) disc method. The spectrum was recorded for the drug, polymer, 1:1 physical mixture of polymer and drug and the selected formula. Samples and KBr were mixed and pressed in the form of a disc, then it was analyzed by FTIR spectroscopy from 4000 - 400 cm^{-1} ⁽⁹⁾.

Differential Scanning Calorimetric Studies (DSC)

DSC scans were done for the drug, polymer, 1:1 physical mixture of drug and polymer and for the selected film. A certain amount of the sample was introduced in a typical aluminum pans and increasing the temperature at a constant rate (10°C/min), at a temperature range of 8 °C up to 300 °C ⁽⁹⁾.

X-Ray powder diffraction (XRPD)

XRPD study can be used to confirm the crystalline nature of materials. The diffractograms of DH, polymer and the selected formula were studied. The study was approved by using Shimadzu XRD-6000 powder XRPD at continuous scan range of 5°- 60° of 2 θ . The operating voltage was 40 (kV) and current 30 mA ⁽¹¹⁾.

Stability studies

Stability study was performed by storing the selected DH formula films in an aluminum foil in sealed container and placed them in three ovens that maintained at three temperatures of 40°C, 50°C, and 60°C for three months. Then the films were withdrawn every 14 days and examined them for physical, mechanical properties and drug content ⁽⁹⁾.

Statistical analysis

The results were demonstrated as a mean of triplicate models $\pm$ standard deviation (SD) and were tested by the one-way analysis of variance (ANOVA) to determine if the changes in the applied factors are statistically significant ($P \leq 0.05$) or non-significant ($P > 0.05$).

Results and Discussion**Evaluation of darifenacin hydrobromide fast dissolving Buccal Films****Physical appearance**

All prepared films showed colorless, translucent, and homogenous smooth surface properties.

Weight variation

The average weights were between 0.08 ± 0.007 to 0.102 ± 0.01 (Table2). Weight variations was due to variation in excipients concentration of each formula while low SD from the mean demonstrates that films were uniform.

Thickness of the films

The average thickness was between 0.164 ± 0.02 to 0.21 ± 0.02 mm (Table2). A very low SD indicates that the method used for the formulation was applicable.

Drug content uniformity

The formulated DH films showed a drug content ranged from $90.8\% \pm 2$ to $102\% \pm 0.35$ (Table2). The accepted range of content uniformity labeled in the United States Pharmacopeia (USP) is varied from 90% to 110% ⁽²⁵⁾. On this basis, it was concluded that DH was distributed uniformly throughout the films.

Folding endurance (FE)

All formulations resisted cracking for more than 300 folding times (Table2). This result is consistent with research was done by Londhe and Umalkar in 2012 ⁽¹⁵⁾.

In-vitro disintegration time

DT was studied in triplicate, and results were ranged between 31.28 ± 1.45 - 44.97 ± 3 secs (Table2).

Determination of surface pH

Measurement of prepared films showed an acceptable surface pH value (4.1 ± 0.06 - 5.1 ± 0.28) (Table2). Since films surface pH did not deviate sharply from the neutral pH, there will not be any irritation to the mucosal lining of the oral cavity.

Table 2. Physical evaluation parameters of darifenacin hydrobromide fast dissolving buccal films (4cm²).

F No.	Weight Variation n= 10	Thickness (mm) n=6	Drug content (%) n=3	Folding Endurance n=3	In vitro DT(sec) n=3	Surface pH n=3
F 1	0.08 ± 0.007	0.18 ± 0.009	99 ± 0.007	> 300	39.3±0.95	4.4 ± 0.06
F 2	0.09 ± 0.09	0.19 ± 0.01	98.1 ± 0.04	> 300	37.3 ± 2.5	4.2 ± 0.06
F 3	0.102 ± 0.01	0.21 ± 0.02	90.8 ± 2	> 300	35.73 ±0.8	4.1 ± 0.06
F 4	0.095 ± 0.03	0.164 ± 0.02	97.44 ± 0.04	> 300	44.97 ± 3	4.2 ± 0.15
F 5	0.1 ± 0.01	0.175 ± 0.02	102 ± 0.35	> 300	43.33 ± 3	4.5 ± 0.0
F 6	0.17 ± 0.01	0.195 ± 0.02	96.9 ± 1	> 300	40.59± 4.35	4.1 ± 0.2
F 7	0.09 ± 0.008	0.17 ± 0.01	95.36 ± 0.04	> 300	38.88 ± 3.2	5.1 ± 0.28
F 8	0.095 ± 0.01	0.18 ± 0.02	98.1 ± 2	> 300	37.33 ± 1.15	4.8 ± 0.0
F 9	0.097 ± 0.01	0.195 ± 0.01	99 ± 0.1	> 300	31.28 ± 1.44	4.9 ± 0.05

Mean ± SD

Effect of superdisintegrant

Superdisintegrants, are poor water solubility substances with functional hydration capacity that can facilitate disintegration with a smaller quantity of them either by swelling action, capillary (wicking) action or combination of both mechanisms⁽¹⁶⁾.

Effect of superdisintegrant concentration

All formulas (F1-F9) had acceptable mechanical properties with FE > 300 as seen in table 2. Films of F1, F2 and F3 were prepared with 2%, 3% and 4%w/w of CCS respectively to study its effect on *In-vitro* DT and release profile of the prepared films.

Table3 and figure1 showed that films DT declined from 39.31sec to 37.3sec, and 35.73sec with increasing in CCS concentration from 2% to 3%, and to 4%, with a significant variation ($p < 0.05$) between F1-F3, while there is no significance ($p > 0.05$) between F1-F2 and F2-F3.

There was significant changes ($p < 0.05$) in the dissolution profiles between F1 and F3 in $T_{80\%}$ and $D_{5min}(\%)$ that was (8.9 min and 65%) for F1 and (4.3 min and 87.5%) for F3, whereas the difference was non-significant ($p > 0.05$) between F1 and F2. There were also significant changes ($p < 0.05$) between F2 and F3 (Table4 and Figure2). Similar results noticed by by Xu *et al.*⁽¹⁷⁾.

These results may be related to CCS wicking effect that provide pathways in the film just like capillaries in which liquid is drawn up and rupture the inter-particulate bonds causing the film to break apart⁽¹⁸⁾. Gissinger and Stamm⁽¹⁹⁾ reported that the disintegration and dissolution could not be only explained by the formation of the porous capillary network and other factors like swelling force are also essential for disintegration especially for CCS.

Films of F4, F5 and F6 were prepared with 2%, 3% and 4% of SSG. DT measurement revealed that F6 had lowest time (40.97sec) (Table3 and Figure1), but with no significance between the three formulas ($p > 0.05$). Decrease in DT by using 4% SSG was observed by Sharma that prepared salbutamol sulfate fast disintegrating tablet with different concentration of SSG; 1%, 2%, 4%, 6%, 8% and 10% where the lowest disintegration time was by using 4% of SSG⁽²⁰⁾.

Table3 and figure2 showed that lowest $T_{80\%}$ time and $D_{5min}(\%)$ (4.31min, 85.6%) was in F6 with a non-significant difference ($p > 0.05$) when compared with (8.63min, 53.57%) and (7.05min, 60.87%) of F4 and F5 respectively. These results correspond to research findings of Haque and Sheela⁽²¹⁾.

SSG effects may be due to swelling property of SSG that involves rapid absorption of water leading to an enormous increase in films volume that overcomes interconnection bond of other ingredients resulting in fast disintegration and fast release of drug⁽²¹⁾.

Last type used was indion in 2%, 3% and 4%w/w concentrations of F7, F8 and F9 respectively. Concerning DT; F9 showed 31.28sec with significant variation ($p < 0.05$) when compared with F8 and F7 (37.33sec and 38.88sec) respectively (Table3 and Figure1).

Indion effects (Table4 and Figure2) reveals that F9 showed 3.05min $T_{80\%}$ and 94% $D_{5min}(\%)$ with significant difference ($p < 0.05$) of both parameters when compared with F8 (5.3min, 77.8%) and F7 (7.4min, 68.71%). Chandira *et al.*, (2008) showed similar results⁽²²⁾.

These effects could be due to indion ability to swell upon contact with water without lump formation and without adhesive tendency that causes uniform film disintegration and then dissolution^(18,23).

In this study, by using range of 2% to 4% of Superdisintegrants, it was clear that the more concentrated superdisintegrant, the lower *In-vitro* DT, the shorter $T_{80\%}$ and the higher D_{5min} for all types of Superdisintegrants.

Effect of superdisintegrant type

All Superdisintegrants used had a positive effect on DT and increasing the release of the drug from the formulas in a shorter time, but it was clear that indion was the best one followed by CCS then

SSG with significant difference ($p < 0.05$) (Tables 3,4 and Figures 1,2). This may be related to prompt swelling tendency of indion on wetting, thus causing rapid disintegration⁽²³⁾.

Amin *et al.*, formulated roxithromycin, dicyclomine hydrochloride and montelukast with four superdisintegrants (indion, CCS, SSG and crospovidone), the optimized formulas were containing indion for all drugs. These results reconcile with current research⁽²³⁾.

Table 3. Disintegration time of darifenacin hydrobromide fast dissolving buccal films .

F no. N=3	95% Confidence Interval for Mean		
	DT (sec) Mean $\pm$ Std. Error	Std. Deviation	Std. Error
F1 (2%CCS)	39.31 $\pm$ 0.55	0.95	0.55
F2 (3%CCS)	37.30 $\pm$ 1.47	2.56	1.47
F3 (4%CCS)	35.73 $\pm$ 0.45	0.77	0.44
F4 (2%SSG)	44.97 $\pm$ 1.73	3.00	1.7
F5 (3%SSG)	43.33 $\pm$ 1.76	3.05	1.76
F6 (4%SSG)	40.59 $\pm$ 2.5	4.35	2.51
F7 (2%indion)	38.88 $\pm$ 1.84	3.20	1.84
F8 (3%indion)	37.33 $\pm$ 0.66	1.15	0.66
F9 (4% indion)	31.28 $\pm$ 0.83	1.44	0.83

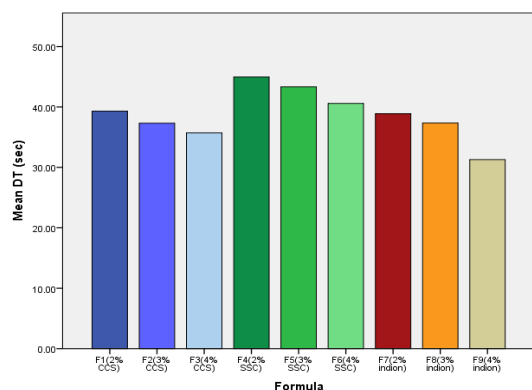


Figure 1. Disintegration time of darifenacin hydrobromide fast dissolving buccal films.

Table 4. Dissolution parameters of darifenacin hydrobromide fast dissolving buccal films

Formula no.	$D_{5min}(\%)$	$T_{80\%}(\text{min})$
F1 (2%CCS)	65	8.9
F2 (3%CCS)	70.27	6.95
F3 (4%CCS)	87.5	4.13
F20 2%SSG	53.57	8.63
F21 3%SSG	60.87	7.05
F22 4%SSG	85.6	4.31
F23 2%Indion	68.71	7.4
F24 3%Indion	77.8	5.30
F25 4%Indion	94	3.05

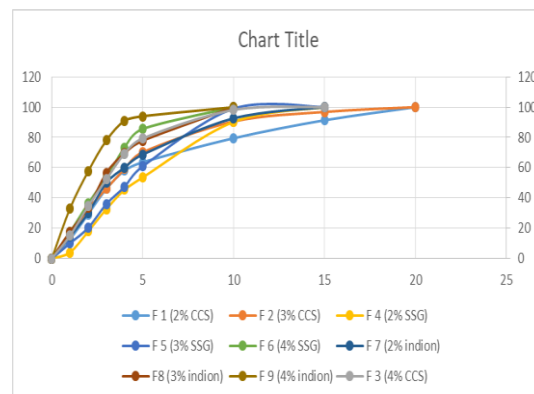


Figure 2. Dissolution profile of darifenacin hydrobromide fast dissolving buccal films

Characterization of selected formula

F9 that composed of 2%w/v PVA, 30%w/w glycerol and 4%w/w of indion showed shortest DT of 31.28sec and superior dissolution profile with $T_{80\%}$ time of 3.05min and D_{5min} of 94% was selected as the best formula.

Percent moisture loss (PML)

F9 showed PML of $6.41 \pm 0.9\%$. The obtained value was close to that reported by Jasim in 2006⁽²⁴⁾.

Percent moisture absorb (PMA)

F9 PMA was 3.5 ± 0.7 which was very close to the PMA for PVA films investigated by Tamer in 2018⁽¹¹⁾.

Evaluation of mechanical property of the films

Mechanical property can be expected by studying some parameters like FE, TS, %E and YM. FE results were mentioned previously and listed in table 2.

Tensile strength

TS of F9 was 2.089 ± 0.7 MPa. It was close to results of Tamer (2.78 MPa) ⁽¹¹⁾.

Percent elongation

E% value was $62 \pm 2.1\%$ for the F9 which is near to that obtained by Noor ⁽⁹⁾.

Young's modulus

YM was 8.74 ± 0.4 MPa for F9. It is clear from all mechanical properties that the selected film is of excellent flexibility and this corresponds to findings of Arora and Chakraborty (2017) in their review on PVA films ⁽²⁵⁾.

Drug-polymer compatibility Test

There are some parameters that reflect the drug-polymer compatibility like:

Fourier transform infra-red (FTIR)

The FTIR spectrum of the DH, PVA polymer, 1:1 physical mixture (DH and PVA) and

F9 are shown in figures 3, 4, 5, and 6 respectively. The main characteristic peaks of DH at wave numbers (in cm^{-1}) are: 3464 for N-H asymmetric stretching of amide (3500-3400), 3251 and 3205 for N-H symmetric stretching of amide (3300-3180), 1662 for C=O stretching of amide (1695-1630), 1350 for C-N stretching of tertiary amine (1360-1310), 1215 for C-O stretching of furan (1300-1000)..

From FTIR results, it was observed that there was no chemical interaction as well as no changes in the peaks of fingerprint region obtained in DH spectrum to that of physical mixture spectra.

All functional groups in DH spectrum were maintained in the spectrum of F9. The results indicate that no chemical interaction occurred between DH and excipients used in F9.

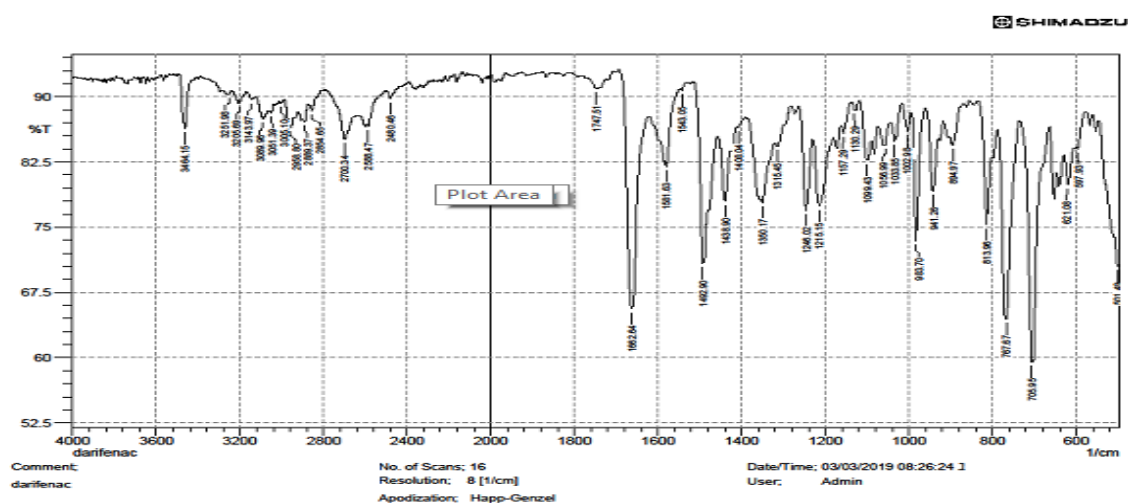


Figure 3. FTIR spectrum of darifenacin hydrobromide

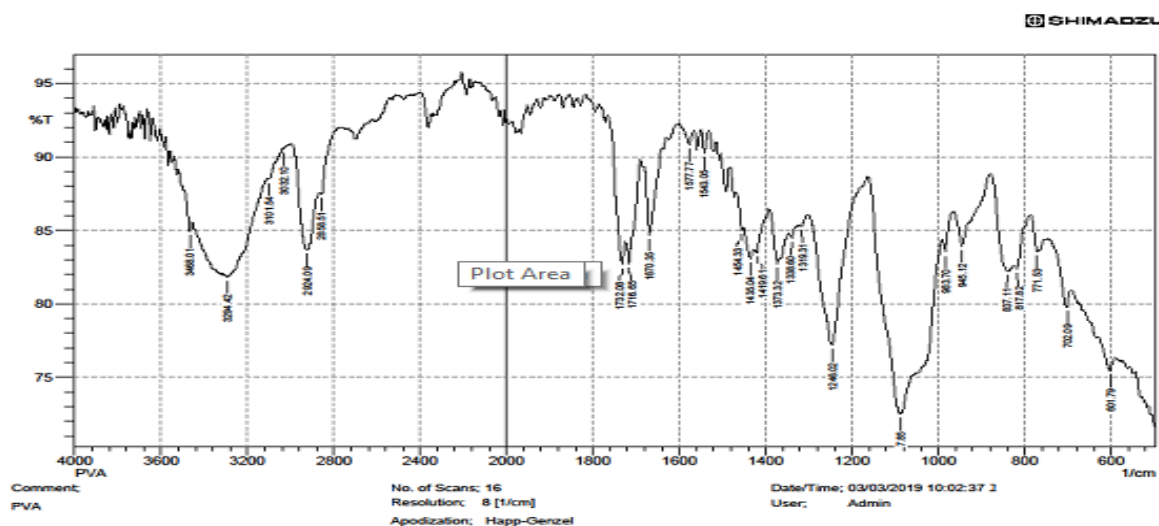


Figure 4. FTIR spectrum of PVA

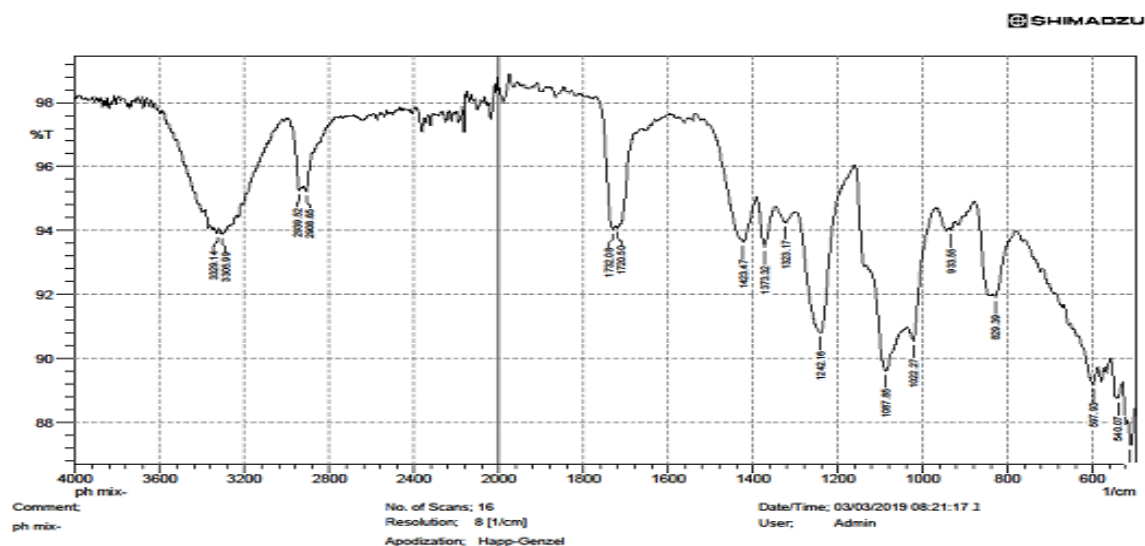


Figure 5. FTIR spectrum of physical mixture

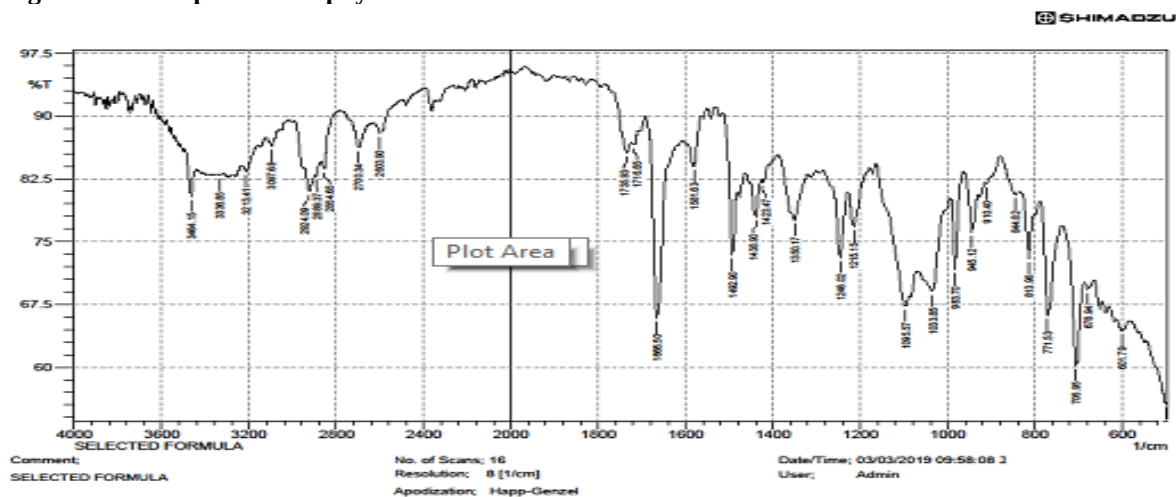


Figure 6. FTIR spectrum of (F9)

Differential scanning calorimetry (DSC)

DSC Technique has been performed to investigate thermal stability of DH and excipients. DSC of DH, PVA, (1:1) physical mixture of DH with PVA and F9 has been shown in figures 7, 8, 9 and 10 respectively.

A single peak confirming melting point of DH was detected at 235.8 °C, indicating a crystal DH form. The peak of physical mixture revealed two peaks; one specific for DH and the other for PVA indicating that there was no interaction between them.

F9 showed a broad peak indicating complete disappearance of DH peak and proposing the dispersion of DH in amorphous form in the film

and/or there was a complete homogeneous dissolution of DH in the polymer lattice.

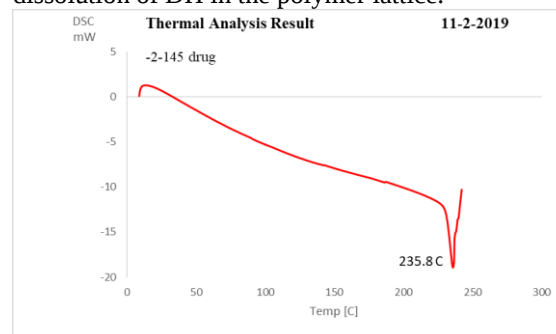


Figure 7. DSC of darifenacin hydrobromide

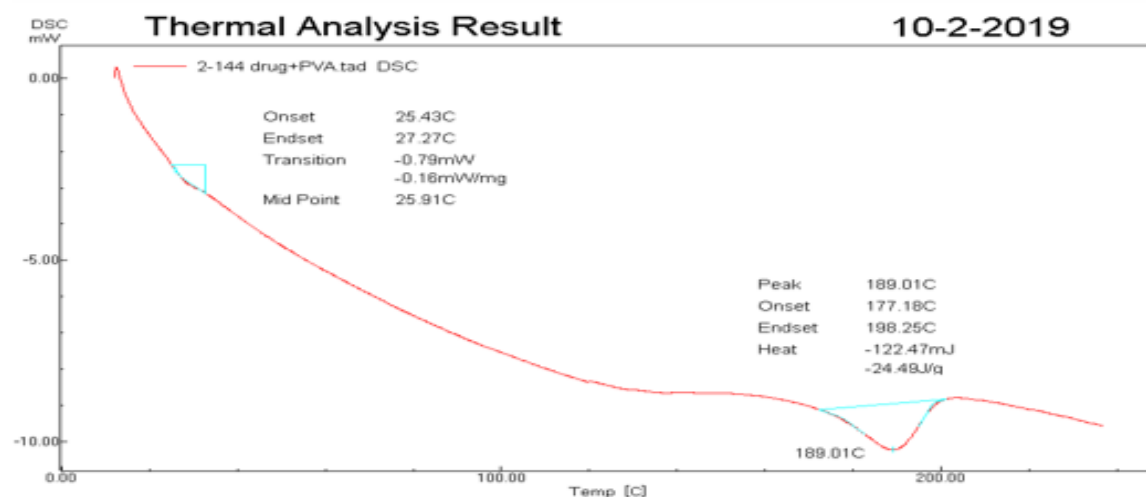


Figure 8. DSC of PVA

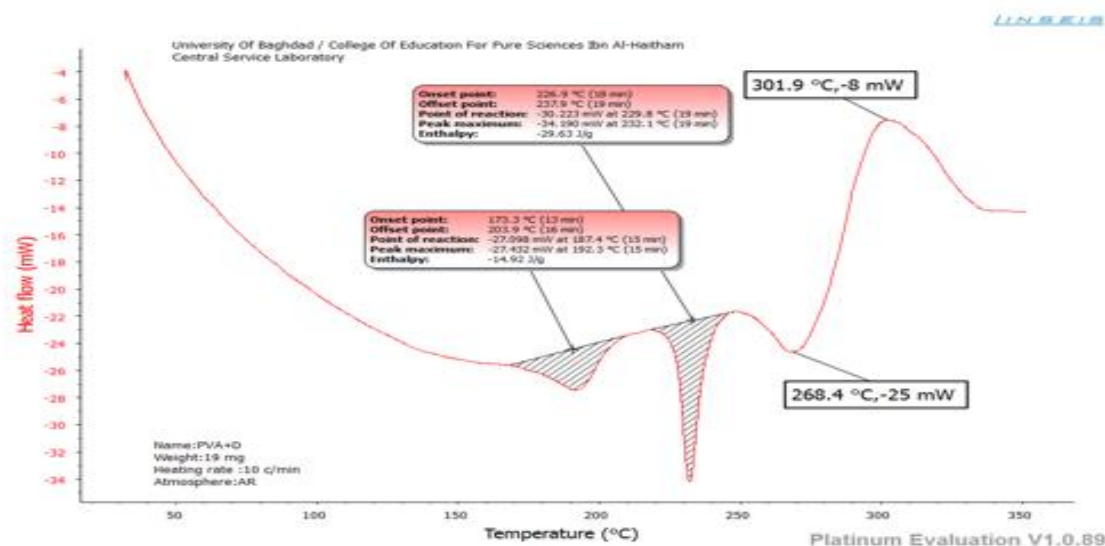


Figure 9. DSC of physical mixture

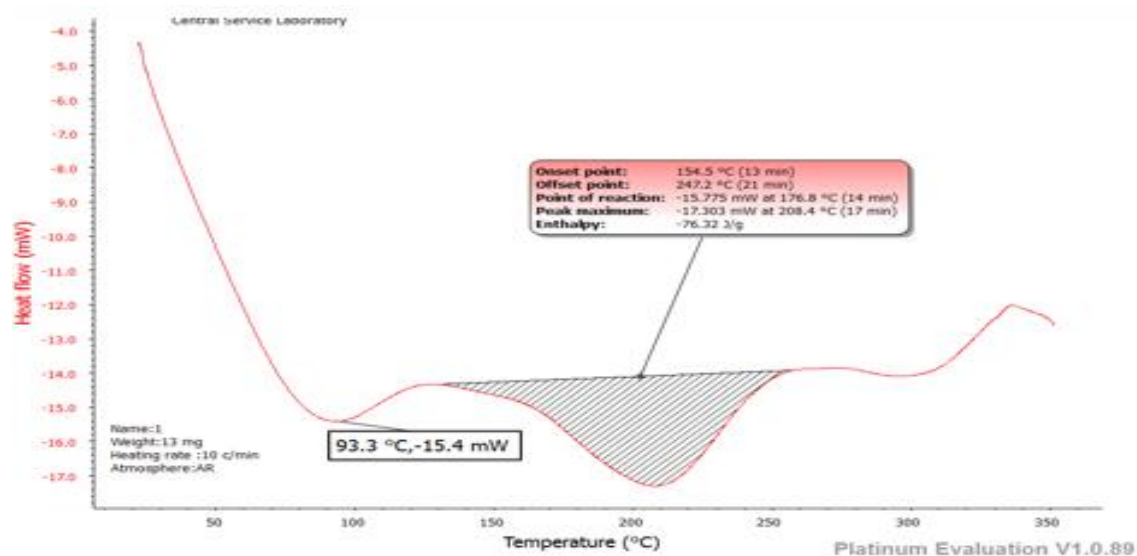


Figure 10. DSC of F9

X-Ray powder diffraction

XRPD of DH, PVA, and F9 are presented in figures 11, 12 and 13.

XRPD of DH showing a typical crystalline pattern, that can be noticed by several sharp peaks (11.682, 18.426 and 20.426).

The XRPD of PVA has distinct peaks at 19.265, 19.863 and 21.408. However, XRPD of F9 represents an absence of all characteristic peaks of DH and PVA. These findings suggest that DH and PVA converted from crystalline to amorphous form.

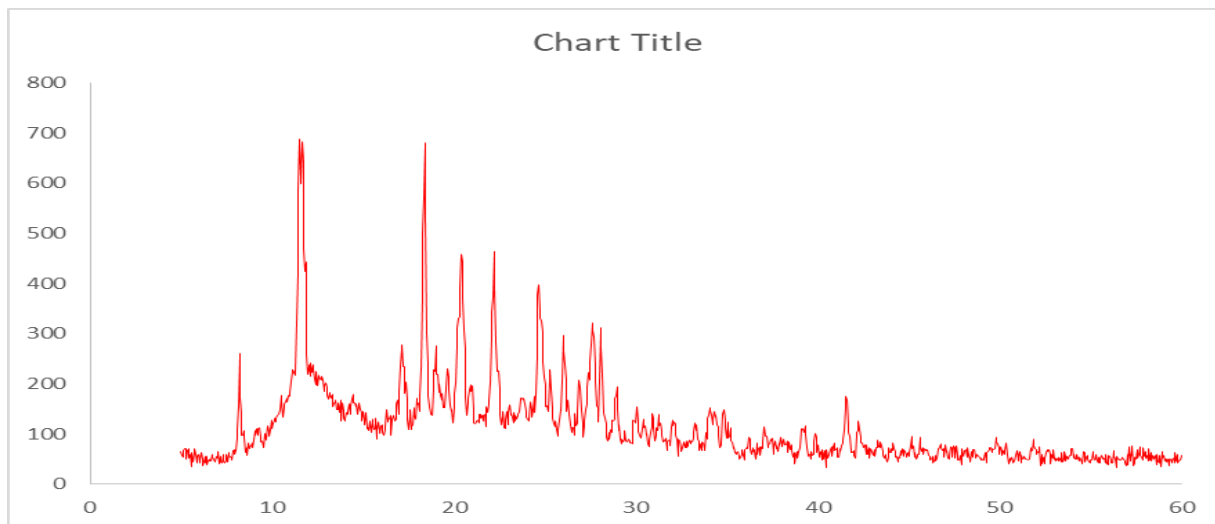


Figure 11. XRDP of pure darifenacin hydrobromide

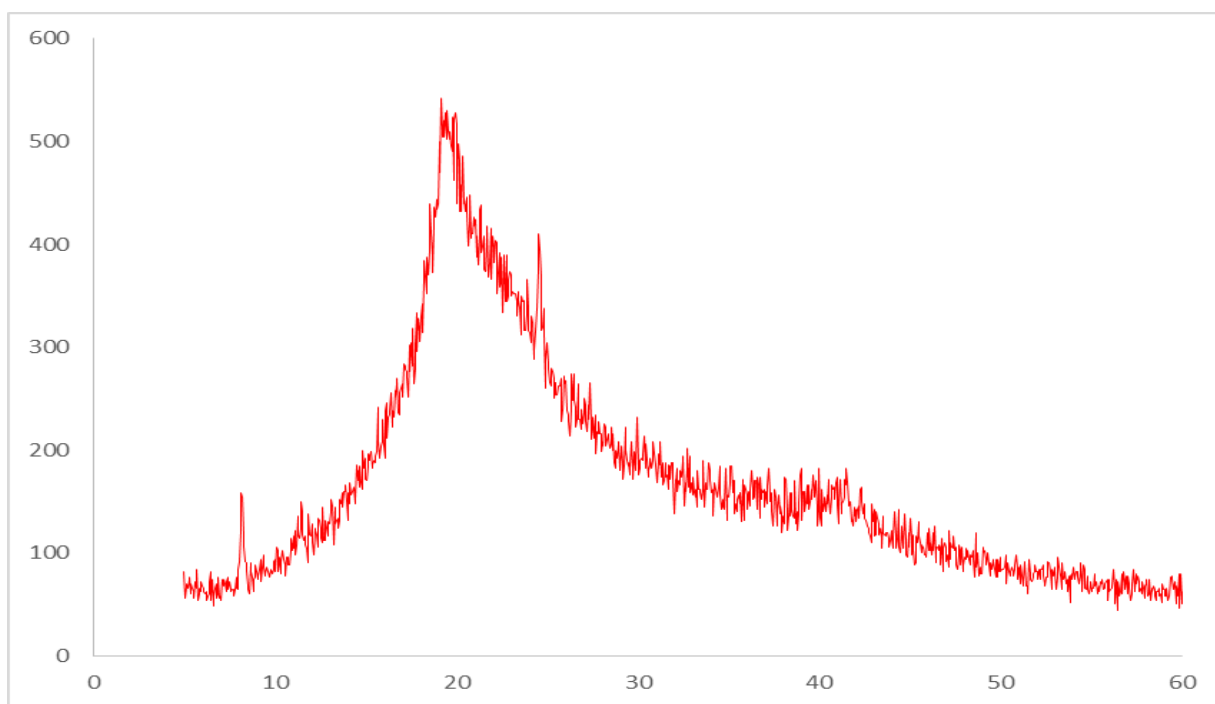


Figure 12. XRDP of PVA

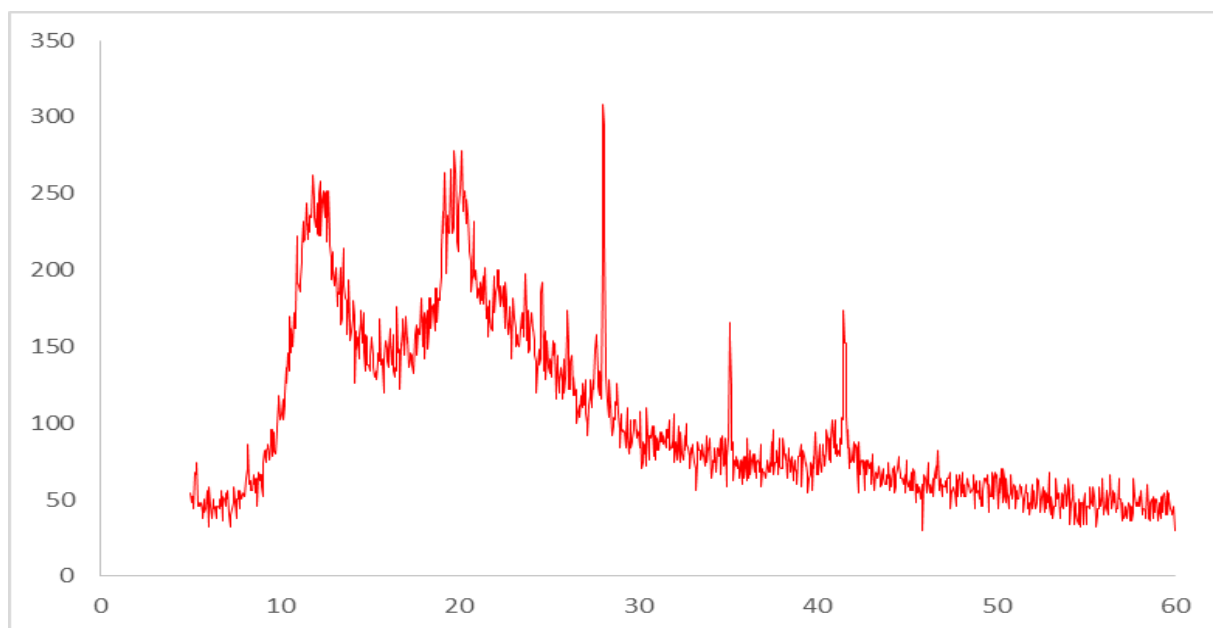


Figure 13. XRPD of F9

Stability

F9 stability was studied at three temperatures, 40 °C, 50 °C and 60 °C for three months. Figure 14 shows plot of logarithm percent remaining of DH versus time in weeks at different temperatures. The obtained profiles were linear indicating that DH degradation follows first order kinetics.

The degradation rate constant (K) at every temperature was calculated from the slope of every line ⁽²⁶⁾

$$K = -\text{slope} \times 2.303 \quad (6)$$

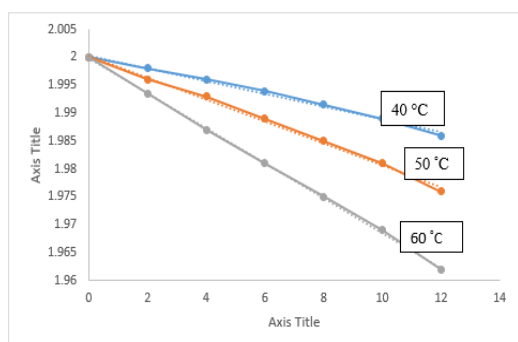


Figure 14. Degradation profile of darifenacin hydrobromide in F9 at 40°C, 50°C and 60°C

The values of K for each temperature are summarized in table 5.

Table 5. Degradation rate constants (K) of darifenacin hydrobromide in F9 at 40 °C, 50 °C, and 60°C

Temperature (°C)	K(week ⁻¹)
40	2.76x10 ⁻³
50	4.7x10 ⁻³
60	7.1x10 ⁻³

Expiration date was calculated from degradation rate constant at 25°C (K₂₅) using Arrhenius plot equation (7) as shown in figure (15).

$T_{90\%} = 0.105/k_{25}$ (7) At temperature 25°C;

$K = 0.00126 \text{ week}^{-1} (1.26 \times 10^{-3} \text{ week}^{-1})$;

$T_{90\%} = 83.4 \text{ weeks} = 1.6 \text{ years}$.

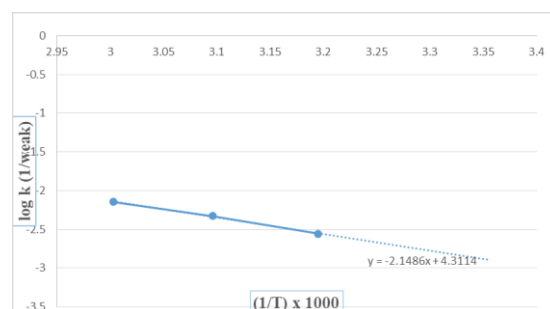


Figure 15. Arrhenius plot of darifenacin hydrobromide in F9 for expiration date estimation

Conclusion

Based on obtained results; it was clear that the more concentrated superdisintegrant, the better disintegration rate and drug release, with superiority to indion 414 superdisintegrant and the FDBFs is a

promising dosage form for releasing Darifenacin hydrobromide.

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