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Research Article

Formulation and Evaluation of Fast Dissolving Oral Films of Domperidone

JAMEEL AHMED S MULLA*, UTKARSH A CHOPADE, SURAJ B KUMBHAR, PALLAVI S MARATHE, PRIYANKA V WARE

Department of Pharmaceutics, Shree Santkrupa College of Pharmacy, Ghogaon, Tal:Karad, Dist: Satara, Maharashtra, India

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ABSTRACT

The oral route remains the most preferred for the general population. This system will provide maximum therapeutic efficacy, increased bioavailability and maximum stability by reducing the frequency of dosage. The present work aims to formulate and evaluate fast dissolving oral films of domperidone using HPMC K100 and HPMC E15 as film forming agents by solvent casting method. The prepared films were characterized for weight variation, thickness, tensile strength, folding endurance, surface pH, *in vitro* disintegration time and mouth dissolving time. Polymer ratio and concentration of superdisintegrants played important role in disintegration and mouth dissolving time. *In vitro* drug release profile exhibited that formulation with higher concentration of superdisintegrants dissolves the oral films faster than the others.

INTRODUCTION

Fast dissolving oral films provide the opportunity to administer medicines and avoid first-pass metabolism [1]. Fast dissolving oral films may also be used in children [2, 3], patients with dysphasia [4], and elderly patients [5]. Although certain products such as paracetamol are available as oral suspension, these contain additives and sugar, which may not be advisable for children [6]. In addition, administrating oral liquid formulations to children is challenging by using syringes [7]. These concerns are triggers for the development of more number of fast dissolving oral films formulations. A fast dissolving oral film has been successfully used to deliver medicines to patients having difficulty in swallowing, those with oral pain due to mucositis or after oral surgery, or those with nausea [8].

The oral route is one of the most preferred routes of drug administration as it is more convenient, cost effective, and ease of administration lead to high level of patient compliance. Recently, fast dissolving films are gaining interest as an alternative of fast dissolving tablets. The films are designed to dissolve upon contact with a wet surface, such as the tongue, within a few seconds, meaning the consumer can take the product without need for additional liquid. It gives quick absorption and instant bioavailability of drugs due to high blood flow and permeability of oral mucosa is 4-1000 times greater than that of skin. This convenience provides both a marketing advantage and increased patient compliance. As the drug is directly absorbed into systemic circulation, degradation in gastrointestinal tract and first pass effect can be avoided. These points make this formulation most popular and acceptable among paediatric and geriatric patients and patients with fear of choking. Over-the-counter films for pain management and motion sickness are commercialized in the US markets.

Fast dissolving films are useful in patients such as paediatric, geriatrics, bedridden, emetic patients, diarrhoea, sudden episode of allergic attacks, or coughing for those who have an active life style. It is also useful whether local action desired such as local anaesthetic for toothaches, oral ulcers, cold sores or teething.

Advantages of fast dissolving films include; Convenient dosing, No water needed, No risk of chocking, Taste masking, Enhanced stability, Improved patient compliance, The drug enters the systemic circulation with reduced hepatic first pass effect, Site specific and local action, Availability of large surface area that leads to rapid disintegration and dissolution within oral

Author for Correspondence:
Email: jameelahmed5@rediffmail.com

cavity and Dose accuracy in comparison to syrup [9-11].

Gastroesophageal reflux disease (GERD) is a digestive disorder that is caused by gastric acid flowing from the stomach into the esophagus [12]. GERD is very common in infants, though it can occur at any age. It is the most common cause of vomiting during infancy. The lower oesophageal sphincter is closed in the normal physiological condition. When it opens, it allows the stomach content to enter in the esophagus which produces extensive heartburn. In certain complications, the esophageal path becomes extremely narrow, i.e. erosive esophagitis, esophageal stricture and Barrett's esophagus [13].

Domperidone is an antiemetic drug to prevent vomiting and nausea in chemotherapy treated cancer patients. According to the Medicines and Healthcare Products Regulatory Agency it should be used at the lowest effective dose for the shortest possible time due to cardio toxic effects. Additionally, most of the patients have problems swallowing tablets and suffer from dysphagia [14]. Thus, fast dissolving oral films, which can be administered directly to the oral mucosa, represent an interesting option for systemic delivery of active candidates to cancer patients.

The aim of the present works is to prepare and evaluate fast dissolving oral films of domperidone for better patient compliance and instant bioavailability.

MATERIALS AND METHODS

Materials

Domperidone was procured from Ipca Laboratories, Mumbai. HPMC K100 was purchased from Research-Lab Fine Chem Industries, Mumbai. HPMC E15 and sodium starch glycolate extra pure were obtained from Loba Chemie, Mumbai. PEG 400 was procured from Molychem, Mumbai. All the other chemicals, excipients and solvents used are of laboratory grade and analytical grade procured from reliable sources.

Preparation of Film by Solvent Casting Method

Fast dissolving oral films were prepared by solvent casting method. Briefly, HPMC K100 and HPMC E15 as film forming agent (1:1, 1:2, 2:1) were dissolved in distilled water, then the solution was stirred continuously for 1 hr using magnetic stirrer. To this, drug solution and plasticizer were added. Later, citric acid, superdisintegrant, sweetening agent, coloring agent were dissolved and kept aside for 1 hr to remove air bubbles entrapped. The formulation was casted on a suitable platform like petri plate and dried. Then the film was carefully removed and cut into suitable size.

Characterization of fast dissolving oral films

Weight variation of the film

Three films of size (2×2cm^2) from every batches of fast dissolving oral film were weighed on an electronic balance and the average weight and standard deviation was calculated [15].

Thickness of the film

The thickness of the polymer films was measured by using screw gauge. The thickness of each film at 3 different areas was determined and standard deviation was calculated [16].

Tensile strength

Film strip of dimension 2 X 2 cm^2 and free from air bubbles or physical imperfections was held between two clamps positioned at a distance of 3 cm apart. A cardboard was attached on the surface of the clamp via a double sided tape to prevent the film from being cut by the grooves of the clamp. During measurement, the strips were pulled at the bottom clamp by adding weights in pan till the film breaks. The force was measured when the films broke [17]. Tensile strength was calculated by using following formula:

$$\text{Tensile strength (kg/mm}^2\text{)} = \frac{\text{Force at Break}}{\text{Initial cross sectional area of the film}}$$

Folding endurance

This parameter was determined by repeatedly folding one film at the same place till it broke. The number of times the film could be folded at the same place without breaking/cracking gave the value of folding endurance [14].

Surface pH

The surface pH of the films was determined in order to investigate the possible side effects due to change in pH *in vivo*, since an acidic or alkaline pH may cause irritation to the buccal mucosa. The film to be tested was placed in a Petri dish and was moistened with 0.5 ml of distilled water and kept for 1 h. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibrating for 1.0 min [17]. The average of three determinations for each is shown in Table 2.

Table 1: Formulations of Fast Dissolving Oral Films of Domperidone

	F1	F2	F3	F4	F5	F6	F7	F8	F9
Domperidone (mg)	10	10	10	10	10	10	10	10	10
HPMC K100 (mg)	150	150	150	100	100	100	200	200	200
HPMC E15 (mg)	150	150	150	200	200	200	100	100	100
PEG 400 (ml)	10	10	10	10	10	10	10	10	10
Sodium starch glycolate (mg)	2	4	6	2	4	6	2	4	6
Citric acid (mg)	50	50	50	50	50	50	50	50	50
Sucrose (mg)	125	125	125	125	125	125	125	125	125
Vanilla (mg)	50	50	50	50	50	50	50	50	50
Quinolin yellow color (mg)	2	2	2	2	2	2	2	2	2
Ethanol (ml)	2	2	2	2	2	2	2	2	2
Distilled water (q.s.)	20	20	20	20	20	20	20	20	20

Table 2: Characterization of Domperidone-loaded Fast Dissolving Oral Films

	Weight variation of the film (mg)	Thickness of the film (mm)	Tensile strength (kg/mm^2)	Folding endurance	Surface pH	*In vitro* Disintegration time (sec)	Mouth dissolving time (sec)	Drug Content (%)
F1	56.46±0.25	0.733±0.015	2.37±0.070	98.66±2.51	6.53±0.152	52.33±2.51	57.66±2.51	95.93±0.472
F2	58.43±0.15	0.730±0.010	2.68±0.030	99.33±6.65	6.76±0.057	44.66±1.52	53.66±4.04	95.93±0.251
F3	55.66±0.25	0.673±0.020	2.37±0.025	107.33±4.04	6.63±0.152	39.66±1.52	46.66±2.08	94.76±0.450
F4	56.56±0.41	0.730±0.020	2.57±0.020	93.33±4.16	6.53±0.152	64.66±1.52	73.66±4.04	93.36±0.378
F5	61.46±0.25	0.730±0.010	2.34±0.010	86.33±3.05	6.73±0.152	60.33±1.52	67.66±2.51	94.53±0.305
F6	60.50±0.30	0.693±0.015	2.45±0.025	92.66±2.08	6.66±0.152	54.66±2.51	63.33±3.51	95.86±0.251
F7	57.53±0.32	0.726±0.020	2.31±0.072	116.33±5.13	6.73±0.152	82.33±2.51	88.33±3.51	97.66±0.472
F8	55.60±0.20	0.656±0.020	2.83±0.020	85.33±4.04	6.83±0.057	75.66±2.08	84.33±4.04	92.63±0.152
F9	57.40±0.20	0.703±0.015	2.72±0.020	96.66±2.08	6.66±0.11	70.66±2.08	78.33±3.05	93.10±0.871

The values are expressed as mean±SD, n=3

In Vitro Disintegration Time

The film of (2x2 cm^2) size (unit dose) was placed on a petridish containing 10 ml of distilled water. The time required for the film to break was noted as cursive *in vitro* disintegration time [18].

Mouth Dissolving Time

The mouth dissolving time was determined by placing the film manually into a beaker containing 50 ml of 6.8 pH phosphate buffer. Time required by the film to dissolve was noted [19].

Content Uniformity

The films were tested for content uniformity. Films of 2x2 cm^2 was cut, placed in 100 ml volumetric flask and dissolved in methanol, volume was made up to 100 ml with methanol. Solution was suitably diluted. The absorbance of the solution was measured at 282 nm [19].

FTIR (Fourier Transform Infrared) Studies

FTIR studies were carried out for detection of drug-polymer interaction. In the present study the IR study of pure drug domperidone and drug loaded fast dissolving oral films were carried out to study the compatibility between them [20].

Differential Scanning Calorimetry (DSC) Studies

DSC thermograms of the pure domperidone and domperidone containing films were recorded on a thermal analyzer (Shimadzu DT-60, Kyoto, Japan) by heating the samples from 30 to 300° C at a rate of 10° C/min in an inert nitrogen atmosphere [21].

In Vitro Dissolution Studies

Dissolution study was carried out using USP type I (basket apparatus) with 300ml of pH 6.8 Phosphate buffer as dissolution medium maintained at 37 ± 0.5 °C. Medium was stirred at 50 rpm for a period of 20 minutes. Samples were

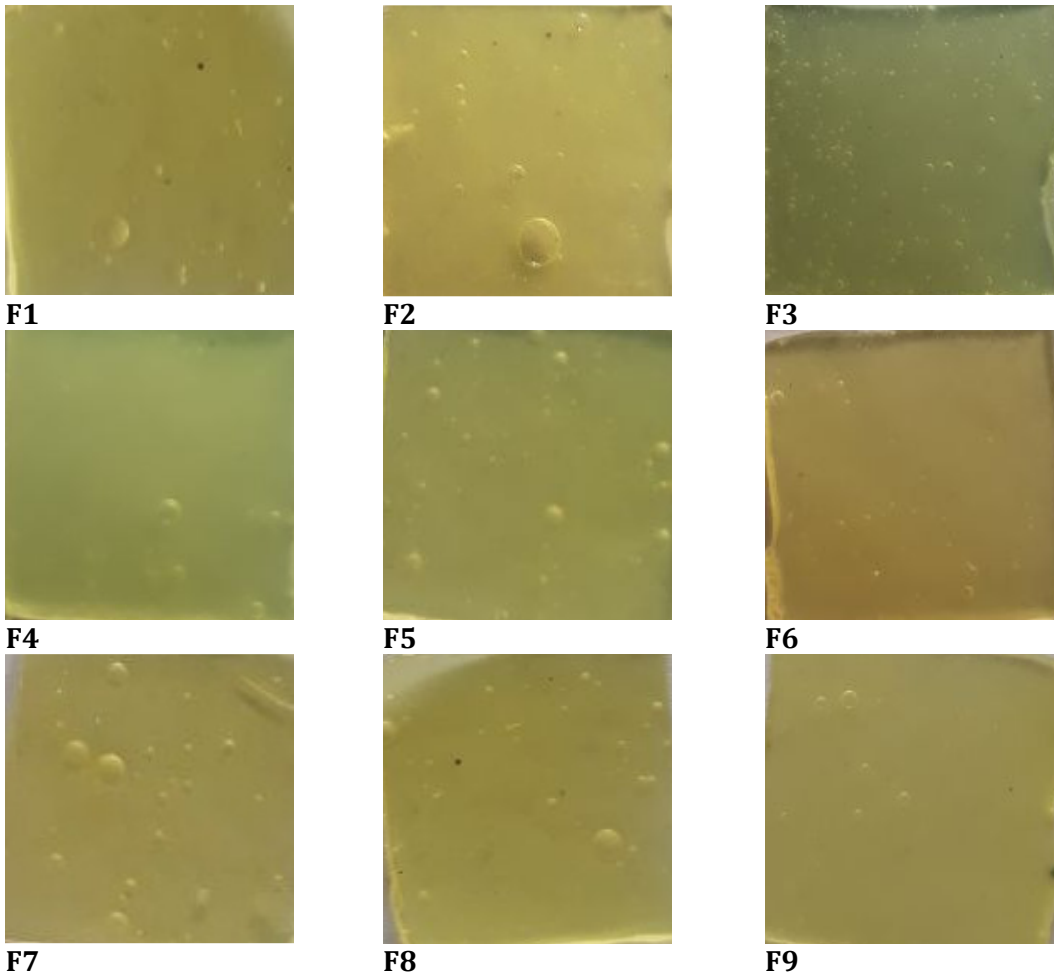

Figure 1: Photographs of Domperidone-loaded Fast Dissolving Oral Films

withdrawn at every 1, 2, 3, 4, 5, 10, 15 and 20 min interval, replacing the same amount with the fresh medium. Samples were suitable diluted with pH 6.8 and analyzed for drug content at 282 nm [19].

RESULTS AND DISCUSSION

Domperidone loaded fast dissolving oral films were successfully prepared by solvent casting method. Photographs of all the formulations are shown in the Table 2.

Weight Variation of the Film

Weights of all the fast dissolving oral films were performed and they are found between the ranges of 55.60±0.20 to 61.46±0.25 mg. The results are tabulated in Table 2 and Fig. 2.

Thickness of the Film

Thicknesses of all the fast dissolving oral films were performed and they are found between the ranges of 0.656±0.020 to 0.733±0.015 mm. The results are tabulated in Table 2 and Fig. 3.

Tensile Strength

Tensile strengths of all the fast dissolving oral films were performed and they are found between the ranges of 2.31±0.072 to 2.83±0.020 kg/mm^2. The results are tabulated in Table 2 and Fig. 4.

Folding Endurance

Folding endurances of all the fast dissolving oral films were performed and they are found between the ranges of 85.33±4.04 to 116.33±5.13. The results are tabulated in Table 2 and Fig. 5.

Surface pH

Surface pH of all the fast dissolving oral films were performed and they are found between the ranges of 6.53±0.152 to 6.83±0.057. The results are tabulated in Table 2 and Fig. 6.

In Vitro Disintegration time

In vitro disintegration time of all the fast dissolving oral films, were performed and they are found between the ranges of 39.66±1.52

to82.33±2.51 seconds. The results are tabulated in Table 2 and Fig. 7.

Mouth Dissolving Time

Mouth dissolving time of all the fast dissolving oral films was performed and they are found between the ranges of 46.66±2.08 to 88.33±3.51seconds. The results are tabulated in Table 2 and Fig. 8.

Drug Content

Drug contents of all the fast dissolving oral films were performed and they are found between the ranges of 92.63±0.152 to 97.66±0.472 %. The results are tabulated in Table 2 and Fig. 9.

FTIR (Fourier Transform Infrared) Studies

Fig. 10 displays the FTIR spectra of pure drug and drug-loaded fast dissolving oral film. The FTIR of pure drug was characterized by N-H stretching at 3170 cm^{-1} and C=O stretching at 1741 cm^{-1}, for the presence of –CO-NH group (Fig. 10a). Drug-loaded fast dissolving oral film FT-IR spectrum showed characteristic bands as 2937 cm^{-1} for N-H stretching and 1741 cm^{-1} for C=O stretching. This indicates that drug is intact in the formulation.

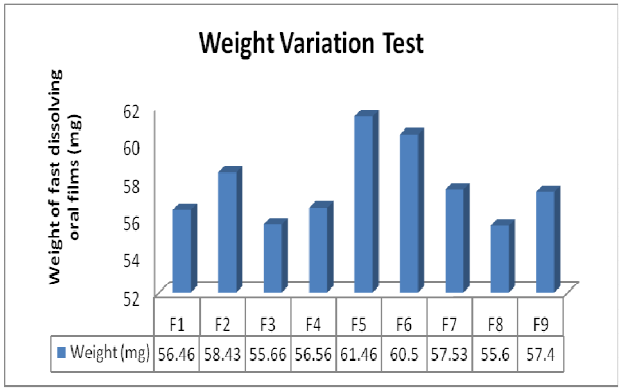

Figure 2: Weight of fast dissolving oral films.

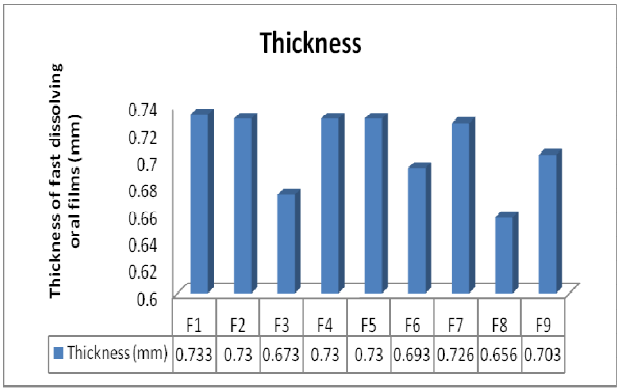

Figure 3: Thicknesses of fast dissolving oral films.

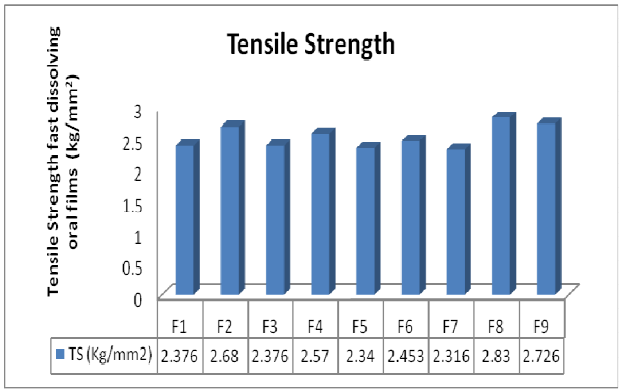

Figure 4: Tensile strengths of fast dissolving oral films.

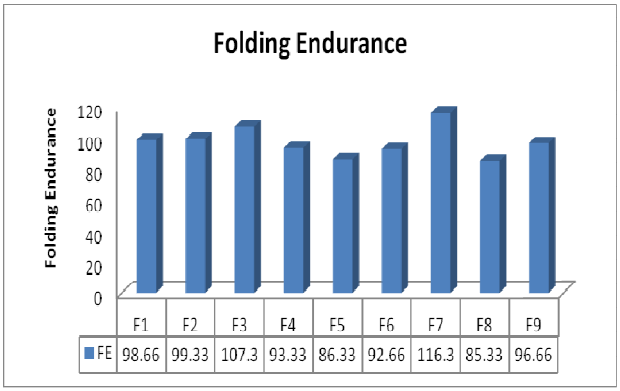

Figure 5: Folding endurances of fast dissolving oral films.

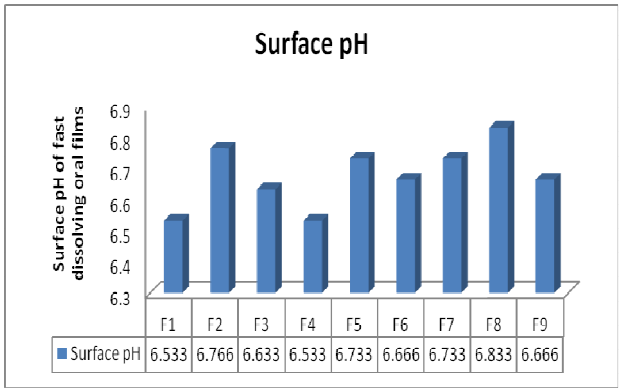

Figure 6: Surface pH of fast dissolving oral films.

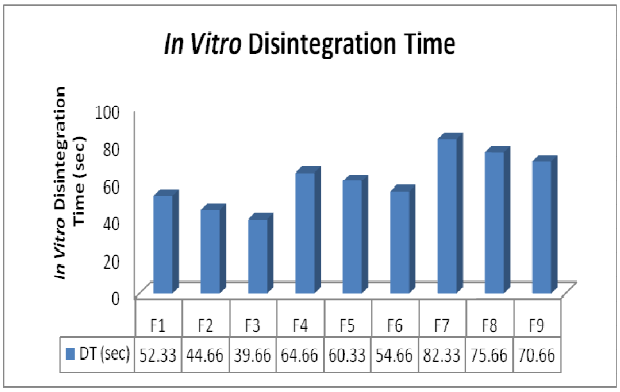

Figure 7: *In vitro* disintegration time of fast dissolving oral films.

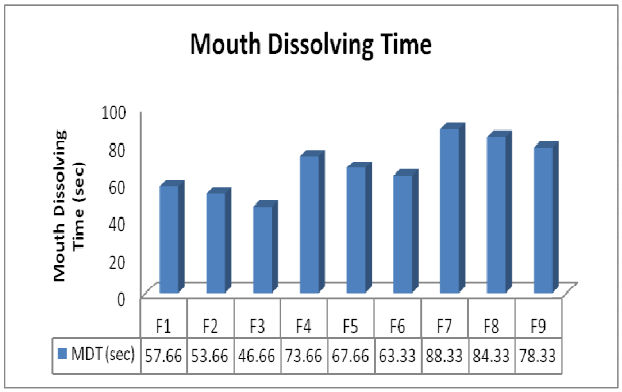

Figure 8: Mouth dissolving time of fast dissolving oral films.

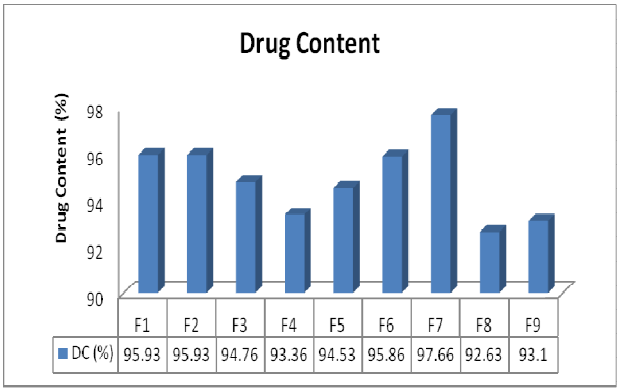

Figure 9: Drug contents of fast dissolving oral films.

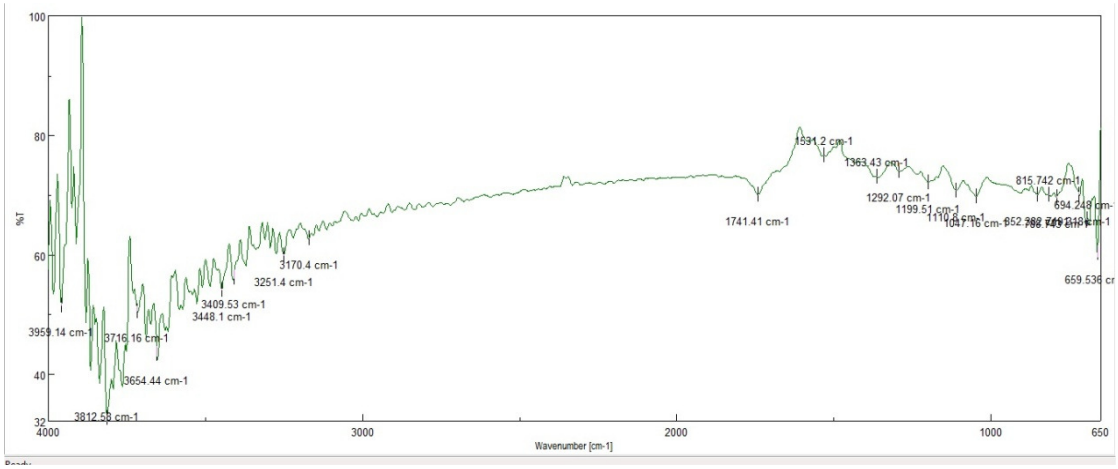

Figure 10a: FTIR of pure drug

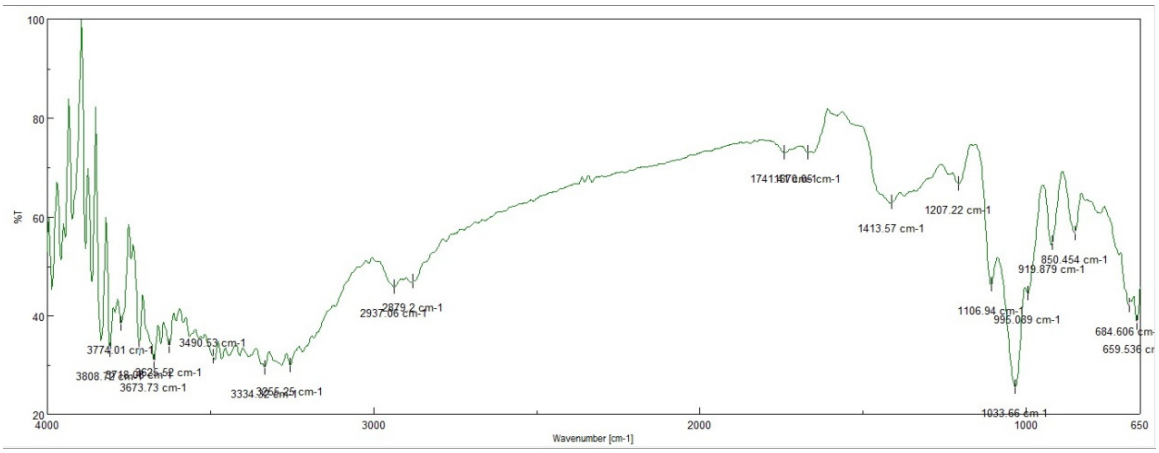

Figure 10b: FTIR of drug loaded fast dissolving oral film

Differential Scanning Calorimetry (DSC) Studies

The DSC thermograms of pure drug and drug-loaded fast dissolving oral films are depicted in Fig. 11. The thermogram of drug was characterized by sharp melting endotherm at 243.19°C. As expected, DSC analysis demonstrated that the domperidone was rendered amorphous in the fast dissolving oral film as indicated by the reduction in the intensity of melting endothermic peak for domperidone at approximately 242.73°C.

In Vitro Dissolution Studies

The *in vitro* drug release study was conducted in pH 6.8 Phosphate buffer as dissolution medium for 25 minutes using USP type I (basket apparatus). The results are illustrated in Figure 12. All fast dissolving oral film with varying ratios of polymers and concentrations of

superdisintegrants showed rapid drug dissolution with an initial burst release of domperidone in the first 5 minutes followed by timed release over 25 minutes.

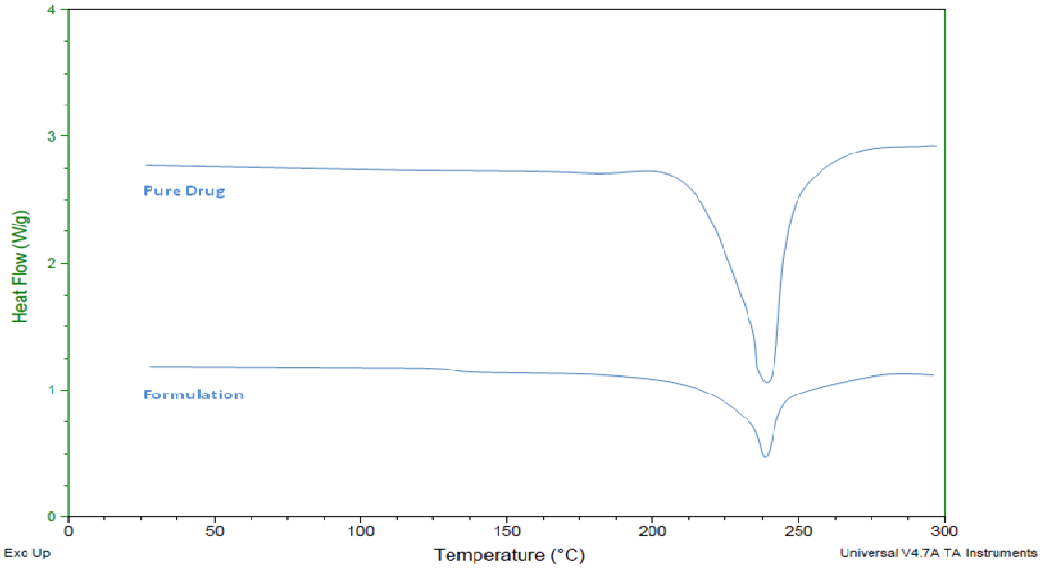

Figure 11: DSC analysis of pure drug and drug-loaded fast dissolving oral film

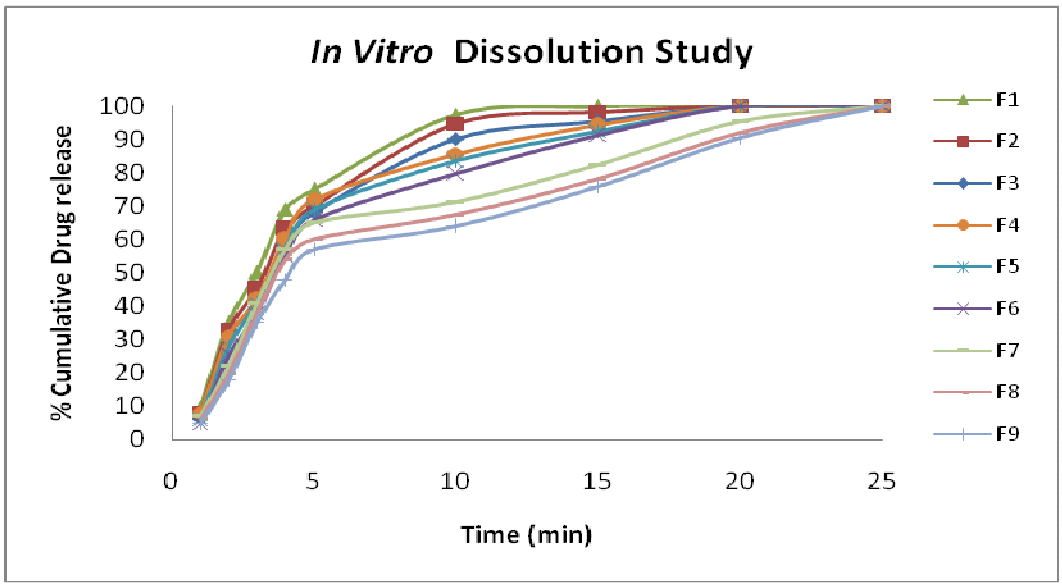

Figure 12: *In vitro* dissolution study of fast dissolving oral films.

CONCLUSIONS

Domperidone-loaded fast dissolving oral films were successfully prepared by solvent casting method. All formulations are uniformly prepared with minimum weight variation, thickness and surface pH. Polymer ratio and concentration of superdisintegrants played important role in disintegration and mouth dissolving time. *In vitro* drug release profile exhibited that formulation with higher concentration of superdisintegrants dissolves the oral films faster than the others.

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