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Formulation and Evaluation of Metoclopramide Fast Dissolving Film (FDF)

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ABSTRACT

The fast dissolving film (FDF) is a solid dosage form which disintegrates rapidly when placed in the mouth. The FDF releases its active ingredient(s) allowing for oral mucosal or gastrointestinal absorption to be achieved.

Metoclopramide (MP) is a potent antiemetic drug used for the treatment of nausea and vomiting. Many trials were made to prepare a satisfactory MP FDF using solvent-casting method.

Nine formulations of MP FDF were prepared (F1-F9). The effect of variable formulation factors on both mechanical and physical attributes of Mp FDF, in addition to the drug release profile, were evaluated.

It was found that the prepared MP FDF that contains hydroxyl propyl methyl cellulose (HPMC) showed the fastest in-vivo disintegration time in the mouth among other investigated polymers. The results showed also that as the concentration of HPMC was increased, both the disintegration time in the mouth and the mechanical strength were accordingly increased.

The MP FDF formula (F7) which contained MP (5 mg), HPMC (340 mg), glycerin (0.35 ml) and Tween 80 (0.15 ml) showed fast disintegration time in the mouth (23 sec) and satisfactory mechanical properties (folding endurance of 150) when a minimal amount of surfactant and plasticizer were used. In addition, formula F7 gave faster dissolution rate as compared with conventional MP tablet (Meclodin®).

The overall findings suggested that the current MP FDF can be given orally when fast action is the target.

Keywords: fast dissolving film, orodispersible, metoclopramide, HPMC.

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INTRODUCTION

The oral route of administration is the most popular. About 50 to 60% of all dosage forms are given orally because of ease of swallowing, no pain, versatility, and high patient compliance. Oral solid drug delivery systems do not necessitate sterile conditions and hence, are more economic industrially [(1)].

Many pharmaceutical products are given in the form of tablets and capsules. However, patients, especially geriatrics and pediatrics, may exhibit difficulty in taking such dosage forms [(2)].

It is reported that some geriatrics and pediatrics are unwilling to swallow these solid dosages due to fear of dysphasia [(3)]. It is reported that 50 per cent of community is negatively affected by dysphasia, which in turn leads to high incidence of non-compliance and failure of therapy [(4)].

In overcoming this problem, orally disintegrating tablets were formulated. These products are also called rapid dissolving, fast dissolving, rapid melting and quick disintegrating tablets. The orally disintegrating tablets can be defined as "A solid dosage form containing active ingredient which disintegrates rapidly, usually within a second, without water when used in the mouth" [(5)].

However, large numbers of oral disintegrating tablets are brittle and fragile, which required a special package for protection during transportation and storage [(6)].

The fast dissolving film (FDF) may be defined as an oral solid dosage form that uses a water soluble polymer which allows the product to rapidly hydrate by saliva, stick to mucosa, disintegrate within seconds, dissolve and release the active ingredient(s) for oro-mucosal absorption when placed in the mouth. The sublingual mucosa is mostly permeable due to thin membrane and good blood supply. This usually gives fast absorption of drugs and rapid bioavailability due to high blood circulation [(7)].

The FDF are not as fragile as oral disintegrating tablets, and they possess such features as ease of transportation, handling and storage. The FDF are one of the most advanced forms of fast dissolving products due to more comfort and flexibility. They improve the performance of medications because they require less saliva to dissolve as compared to fast dissolving tablets or capsules [(7, 8)].

Different terms are found in the literatures for FDF, e.g., quick dissolving films, flash release wafers, thin strips, and melting films. The "melting film" is somewhat inappropriate term as the film is not "melting" but "dissolving", or at least disintegrating in the mouth. Therefore, the term "soluble film" is more acceptable by the FDA, whereas the European Medicines Agency is preferring "orodispersible film" [(9)].

Materials and Methods

Materials

The following materials were used in this study: Hydroxy Propyl Methyl Cellulose (HPMC) and Poly Vinyl Pyrrolidone (PVP) (Sigma Chemical co., USA). Metoclopramide hydrochloride (Samara Drug industries, Iraq). Hydrochloric acid and Tween 80 (Thomas Baker chemicals, India). Glycerol (BDH, England). Citric acid (Gainland chemical company, U.K.). Meclodin® tablet (SDI, Iraq).

METHODS

Preparation of MP FDF

Nine formulations of MP FDF were formulated (F1-F9), as shown in table (1), by the use of solvent-casting method. Each FDF with a surface area of 4 cm^2 is loaded with 5 mg of MP. The number and area of FDF formulated for each batch was calculated as follow:

Diameter of petri dish = 8.46 cm
Petri dish total area = 56 cm^2
Each FDF area = 2×2 = 4 cm^2

Number of FDF in batch =56/4 =14
Total drug load = 5×14 = 70 mg.
One can summarize the above procedure as follow [10-12]:
The HPMC was dissolved in 15 ml of distilled water (D.W.) to prepare an aqueous dispersion of film-forming polymer. To this polymeric dispersion, 70 mg of MP and all other excipients were added. The dispersion was stirred for 30 minutes and was used after at least 24 hours of rest to allow the entrapped air bubbles to be removed. Then, the dispersion was cast onto 8.46 cm-diameter petri dish and was dried in oven (Gallenhamp BS, W. Germany) at 40 ºC for 24 hours as shown in figure (1).
The prepared MP FDF were collected carefully from petri dish, visually checked for any imperfections (if any) and divided into the required measurement (2 x 2 cm) to ensure the equivalent dose of MP for each film. The prepared MP FDF were stored for further investigations [10-12].

Table (1): Composition of FDF Formulations.

Formulations	HPMC (mg)	PVP (mg)	Glycerol (ml)	Tween 80 (ml)	Citric acid (mg)
F1	68.6	—	0.2	0.1	2.85
F2	102.96	—	0.3	0.15	42.7
F3	272	—	1	0.5	11.2
F4	340	—	1	0.5	14
F5	340	—	0.5	0.25	14
F6	340	—	0.4	0.2	14
F7	340	—	0.35	0.15	14
F8	510	—	1	0.5	21
F9	—	600	0.35	0.15	14

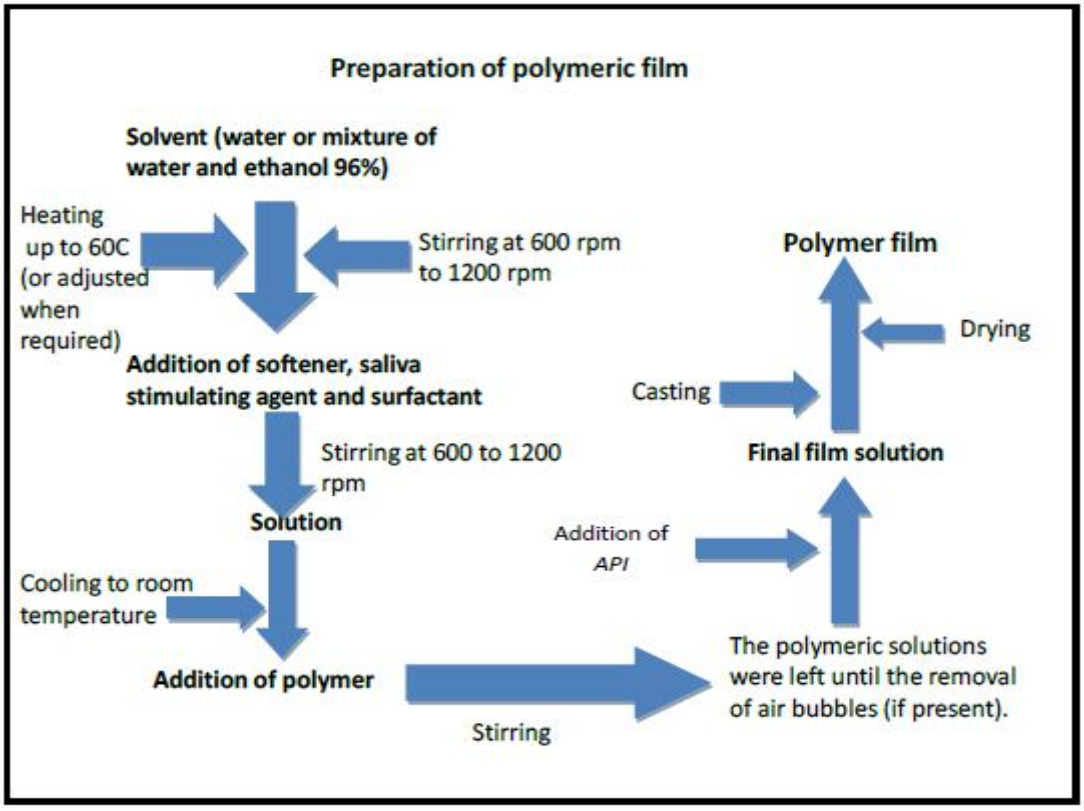


Figure 1: Formulation scheme of FDF [13].

Variables Affecting the Formulation of MP FDF

Effect of Different Types and Concentrations of Film Forming Polymers

Formulations F1-F9 (table 1) were used to study the effect of type of polymer (HPMC, PVP) with different polymer concentrations on the mechanical and physical properties of MP FDF. This study was done to investigate the potential differences between the used polymers in order to choose the best film forming polymer.

Effect of Plasticizer and Surfactant concentrations

Different formulations were utilized to study the effect of plasticizer (glycerol) and surfactant (Tween 80) concentrations on the mechanical properties of MP FDF (table 1).

Evaluation of MP FDF

Visual Inspection

The surface texture, color, homogeneity and transparency of the MP FDF are properties that were tested for the selected films.

Weight Variation

The variation of weight of MP FDF was done by weighting individually 20 films and the average weight of them was determined. To pass the test successfully, the calculated weight of not more than 2 FDF should not deviate from the average weight by more than 7.5% and no one exceed 15% [14].

Thickness Measurement

The thickness of all MP FDF was determined at different points (center and all corners) by the use of vernier caliper as micrometer (GUO GEN, China).

Folding Endurance

The folding endurance of all MP FDF formulations was determined by folding a strip at the same place repeatedly until breaking or folding as maximum as 250 times [15].

Surface pH Measurement

The pH of surface of MP FDF was investigated in order to find out the probability of local irritation of the oral mucosa since an alkaline or acidic pH may be harmful. All MP FDF formulations was wet with the aid of D.W., then a pH meter (Werk GMBH, Germany) was used to measure the surface PH [15].

Disintegration Time in the Mouth (in vivo test)

Five healthy volunteers were subjected to the measurement of time of disintegration in the mouth of all MP FDF formulations. Before test, volunteers got detailed information on this test.

The volunteers were asked to wash their mouth with distilled water. The prepared MP FDF were put on the tongue and a stopwatch was started immediately. Volunteers were allowed to move the MP FDF into the upper palate of the mouth and to perform a gentle tumbling on the FDF without biting on it or tumbling it from one side to another.

When the last detectable fragment or granule had disintegrated, the stopwatch was stopped and the time was reported. The swallowing of saliva was prevented during the procedure, and it was washed from the mouth after each test [12].

Dissolution Test

The in-vitro dissolution test was done for the best FDF formula (F7) in a basket dissolution apparatus (Copley scientific, UK) [16, 17]. A 4-cm^2 sample of MP FDF was weighed accurately. The dissolution medium was 500 mL of 1.2N HCl at a rotation speed of 50 rpm at 37±0.5°C. A dissolution sample of 5 ml was withdrawn at specific time intervals and replenished with another 5 ml of fresh medium. The release profile of MP was determined by spectrophotometer (Carry 100 UV, Varian, Australia) at 272 nm as the λmax [5].

In addition, the above test was also done for a conventional MP tablet (Meclodin®, SDI, Iraq) as reference. The testing conditions were the same as above.

RESULTS AND DISCUSSION

Evaluation of MP FDF

Visual Inspection

The films were round (takes the shape of the petri dish), transparent, clear, soft, without air bubbles, uniform in thickness, colorless, thin, easily removed from the petri dish and had a good texture from all edges (figure 2).

Figure (2): The prepared MP FDF.

Weight Variation

The obtained data revealed that the average weight values for all formulations were acceptable and consistent with the reported values [14]. The weight of MP FDF was found to vary in the range of 130-205mg.

Thickness Measurement

Table (2) shows the average film thickness of all formulations. The MP FDF thickness was found to vary between 0.22-0.77 mm. These values indicate that the casting method that utilized for the preparation of MP FDF was acceptable, reproducible and a uniform thickness of strips can be achieved. Therefore, dose accuracy of MP FDF can be guaranteed.

Folding Endurance

The average folding endurance of MP FDF were given in table (2). The folding endurance values were found to vary between 2-150 times, with the maximum value seen in the formula F7. The folding endurance of the formula F7, 150 times, is quite enough to ensure the mechanical strength of the prepared FDF. Besides, the formula F7 showed fast disintegration time in the mouth (table 2), therefore, it is selected as the best formula.

Surface pH Measurement

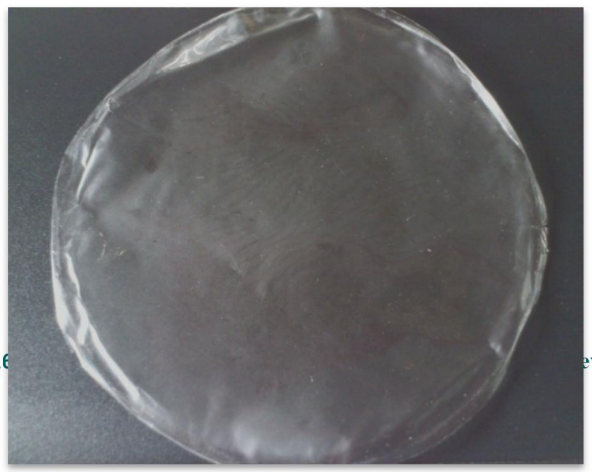
The pH of surface of all formulations (table 2) was found to be 5.9-6.4 that lies within the salivary pH range [18]. This indicates that the MP FDF are not irritant and can be used safely in the mouth.

Disintegration Test in the Mouth

As seen in table 2, the time of disintegration of MP FDF in the mouth (in vivo test) were found to be 6-39 sec which is acceptable according to the criteria of oral dispersible dosage forms [19]. Regarding the selected best formula (F7), the disintegration time was 23 seconds which represents a good result according to literatures [20].

Although it is hydrophilic with suitable wetting property, HPMC amount was inversely proportional to the disintegration time in the mouth (figure 3). This fact may be attributed to the stronger polymer network that formed as result of increasing HPMC concentration which in turn requires more time to be broken [21].

Table (2): The Physical Properties of MP FDF *.



Formulations	Thickness (mm)	Surface pH	Folding Endurance	Mouth Disintegration Time (sec)
F1	0.223± 0.1	6.4± 0.3	2± 0.2	6± 0.7
F2	0.373± 0.1	5.9± 0.5	3± 0.2	7± 1.0
F3	0.604± 0.2	6.1± 0.8	2± 0.1	14.3± 5.2
F4	0.645± 0.1	5.9± 0.6	3± 0.1	24± 6.3
F5	0.528± 0.2	6 ± 0.5	50± 2.1	23± 5.8
F6	0.528± 0.2	5.9± 0.9	90± 4.4	23± 7.4
F7	0.528± 0.1	6.1± 0.7	150± 5.3	23± 6.2
F8	0.770± 0.2	5.9± 0.9	4± 0.1	39± 7.1
F9	——	——	——	——

*Results are expressed as mean ± S.D. (n=3)

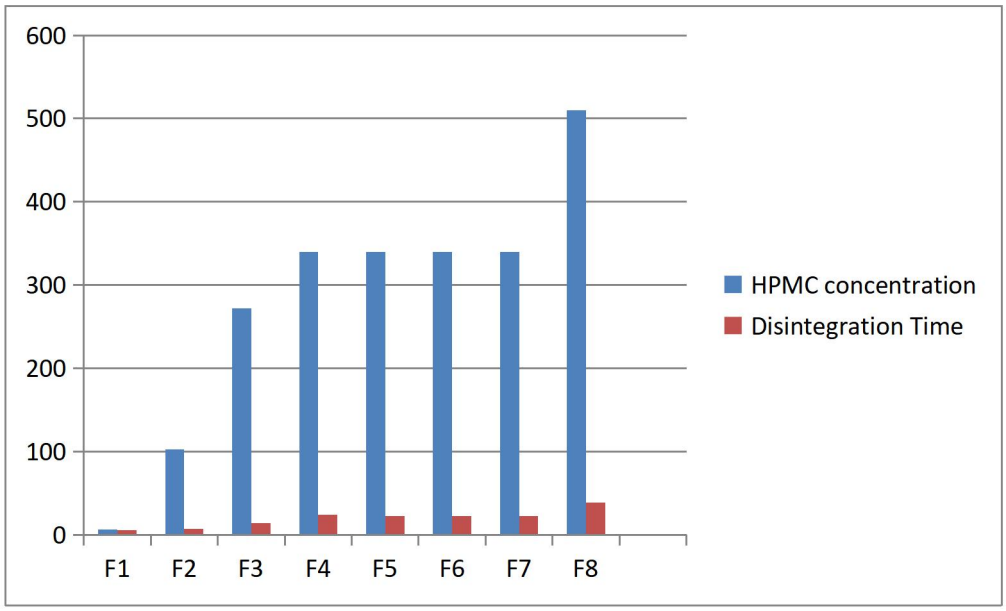


Figure (3): Effect of different concentrations of HPMC on MP FDF disintegration time in the mouth.

Dissolution Test

Dissolution tests are of especial importance if the dissolution step is the rate-limiting in absorption of active ingredient, e.g., dispersible dosage forms containing drugs that show fast absorption [22].

The dissolution test for the selected MP FDF (F7) as well as Meclodin® tablet as a reference was done using 500 ml of 0.1N HCl (pH 1.2) as a dissolution medium at 37 ± 0.5 ^{0}C with constant stirring speed of 50 rpm for 30 min.

As shown in figure (3), it is clear that the FDF (F7) shows faster release profile than Meclodin® tablet which confirm the preference of the prepared film over Meclodin® tablet.

Statistically, there is highly significant difference ($P<0.05$) among samples at 1, 3, 5, and 10 min time intervals (figure 3) between Meclodin® tablet and MP FDF (F7).

Figure (4) indicates that the FDF formula (F7) showed faster release rate than Meclodin® tablet. The time at 75% release (T 75%) of MP FDF (F7) was 10-fold faster than that of Meclodin® tablet. It is worth mentioning that the T 75% is an important parameter in the quality control. According to USP, the oral solid dosage form should comply with the T 75% requirements in order to pass the dissolution test successfully [23].

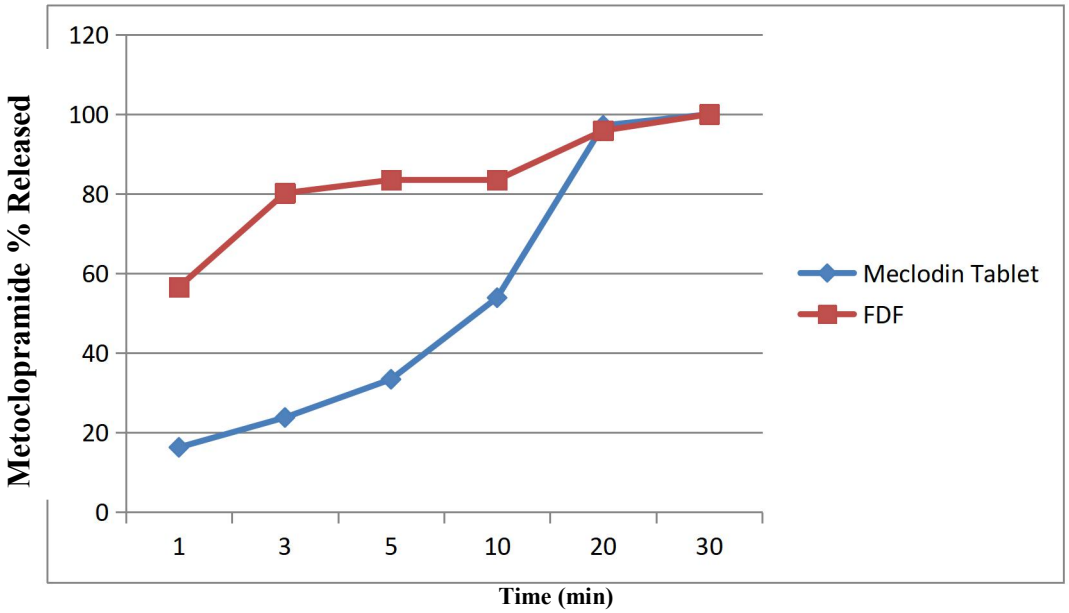


Figure (3): The release profiles of MP from the FDF (F7) and Meclodin® tablet in 0.1N HCl (pH 1.2) at 37± 0.5 ^{0}C.

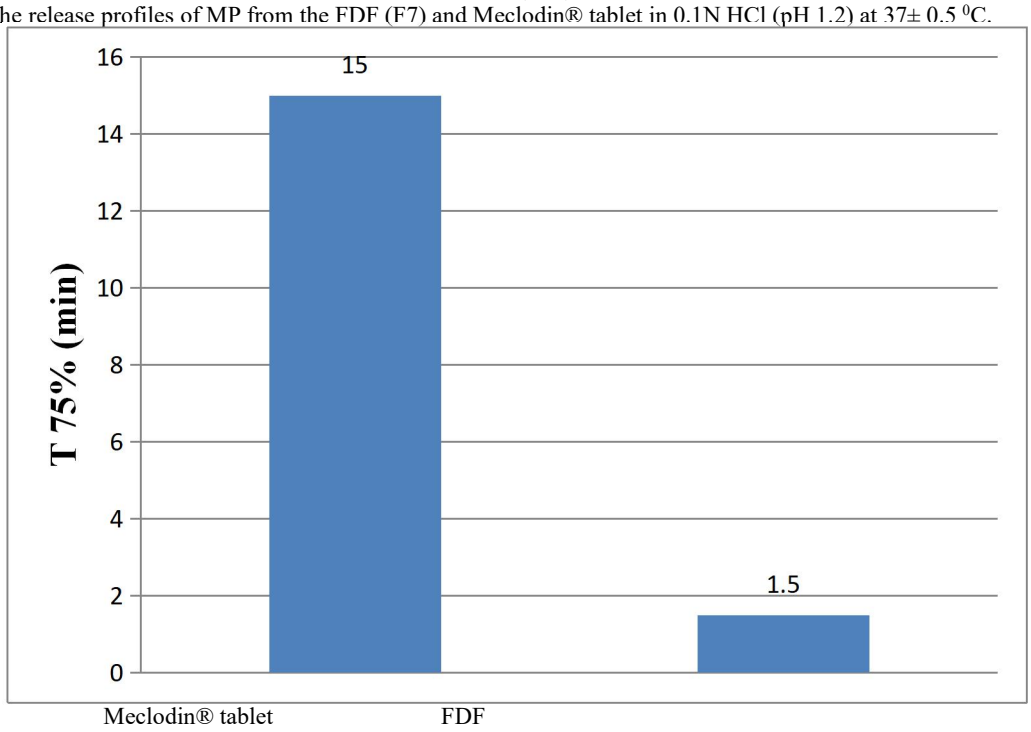


Figure (4): T 75% release of MP from Meclodin® tablet and FDF (F7) in D.W at 37±0.5 ^{0}C.

Variables Affecting the Formulation of MP FDF

Effect of Different Types and Concentrations of Film Forming Polymers

Formulations F1-F9 (table 1) were used to study the effect of type of polymer (HPMC, PVP) with variable concentrations on the mechanical and physical properties of MP FDF. This study was done to investigate the potential differences between the used polymers to choose the best film forming polymer.

Table (2) revealed that the FDF made of HPMC, as represented by the formula F7, showed fast disintegration time in the mouth, fast dissolution profile with good mechanical properties (folding endurance of 150).

In contrast, those made of PVP alone were failed to form an acceptable film and the resulted FDF was very fragile and brittle. This may be attributed to the fact that the PVP solution became very viscous and cannot be handled easily. In addition, it is hygroscopic with changeable dissolution profile therefore, PVP is never used alone as a film former [24].

Effect of Plasticizer and Surfactant concentrations

Different formulations (table 1) were utilized to study the effect of plasticizer (glycerol) and surfactant (Tween 80) concentrations on the mechanical strength of MP FDF.

It was found that glycerol as plasticizer gave better mechanical strength when used at low concentration than at higher one (table 2). Therefore, the folding endurance of formula F7 when using 0.35 ml of glycerol was 150 as compared to formula F4, as instance, with folding endurance of 3 when 1 ml of glycerol was used. It is worth mentioning that Sanyang et. al. found that if high levels are used, glycerol may have anti-plasticization effect [25].

Regarding Tween 80 concentration, similar findings were obtained. Better mechanical property was found at low concentration of surfactant. The folding endurance of formula F7 when using 0.15 ml of Tween 80 was 150 in comparison to folding endurance of 3 in formula F4, for example, when using 0.5 ml of tween 80. This may be explained by the fact that the surface-active agent increased

the free volume between chains of the polymer, and by doing so, weaken its integrity [26].

CONCLUSION

The present work revealed that the FDF can be used as suitable alternative for MP oral dosage forms when fast action is desired. The MP FDF showed fast disintegration in the mouth, rapid dissolution and suitable mechanical properties. The formula F7, with a mouth disintegration of 23 second, was selected as the best formula which composed of HPMC as film forming polymer with a minimal amount of surfactant and plasticizer.

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