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Disintegration time of orally dissolving films: various methodologies and *in-vitro/in-vivo* correlation

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Orodispersible films (ODF) have gained a remarkable success in the market, especially in pediatric and geriatric populations. The time required for an ODF to disintegrate is an essential quality and safety feature, thus an appropriate methodology is crucial. The USP disintegration apparatus is not appropriate for ODFs, as the determination of the end point is challenging and may not predict *in-vivo* disintegration time. The aim of the present study was to design and evaluate new disintegration protocols as an attempt to select the best approach that would reflect the *in-vivo* disintegration time in comparison to formerly reported procedures. Novel methods were designed, namely; the frame, the cell, and the agar plate methods, and compared to the previously reported methods; clamp and modified USP disintegration methods. Different ODFs were formulated using various viscosity grades of hydroxypropylmethyl cellulose. The mechanical characteristics of the prepared films were studied using texture analyzer and film folding endurance test. The resultant disintegration time of the films measured by the aforementioned methods were compared and correlated with its *in-vivo* time. Interestingly, the results obtained through the use of the cell method for the low viscosity polymers did not vary significantly from that of their *in-vivo* results ($p>0.05$). Moreover, the disintegration time of all polymeric films determined by the cell method revealed independently on their viscosity the highest correlation with *in-vivo* disintegration time ($R^2 = 0.999$). Such findings indicated the suitability of the cell method in predicting in-vivo disintegration time of low viscosity polymeric films.

1. Introduction

An orodispersible film (ODF) is a drug delivery system that consists of a thin hydrophilic polymer sheet that is intended to disintegrate and release the drug rapidly in the mouth upon contact with the saliva without drinking water or chewing (Preis et al. 2014).

This system has gained much attention among other oral drug delivery systems (Gijare and Deshpande 2018), as it has the ability to fulfill the needs of special populations, including pediatric and geriatric patients, and those having difficulties with swallowing (Slavkova and Breitkreutz 2015; Scarpa et al. 2017) . Their main quality attributes are summarized by their ease of administration, fast disintegration time and accurate dosing by controlling the film size (Choudhary et al. 2012; Irfan et al. 2016).

Disintegration time requirements for orodispersible tablets might be adopted for ODFs, varying between 30 s and 3 min (European Pharmacopeia Commission, Tablets, 2013).

The time taken by an ODF to disintegrate is a critical quality and safety feature; failure of fast disintegration may affect patient compliance or lead to choking (Krause and Breitkreutz 2008). Therefore, it is essential to prove the rapid disintegration of ODFs, by providing a disintegration test that gives a clear determination of end point, with a good correlation with the *in vivo* disintegration behavior. Until now, official guidelines for the determination of the disintegration time of ODFs have not been available (Bhyan et al. 2011). The only statement concerning the assessment of ODF that was mentioned in the European Pharmacopoeia was "disperse rapidly" without specifying the maximum allowed duration for an ODF to disintegrate *in vivo* and its verification under *in-vitro* conditions (European Pharmacopeia Commission, Oromucosal preparations, 2013).

In general, the USP disintegration apparatus is used to determine the disintegration time of ODFs. However, this apparatus which is used initially for solid dosage forms i.e. tablets and capsules is not suitable for ODFs as the detection of the end point is challenging where the polymeric films may stick, tear apart or swell in the sample holder, in addition, there is a high fluctuation in end points depending on the opacity or transparency of the films (Preis et al. 2013).

Many disintegration testing methods for ODFs have been followed in previous studies (Preis et al. 2014; Garsuch and Breitkreutz 2009, 2010; El-Setouhy et al. 2010; Mirsha and Amin 2009, 2011; Sakuda et al. 2010). In the petri dish test, disintegration time is determined by placing the film on a petri dish containing a small volume of water or phosphate buffer (Garsuch and Breitkreutz 2009; El-Setouhy et al. 2010). Another method defined the disintegration time as the time needed for one drop of water or phosphate buffer to tear the film that was previously fixed in a slide frame (Garsuch and Breitkreutz 2009, 2010). Moreover, disintegration tests using a mesh have also been investigated, where a film was placed on a stainless steel mesh with a certain volume of water, then the time required for film disintegration was recorded (Mishra et al. 2009).

In an attempt to mimic the influence of the tongue's movement on the disintegration of the films, a dynamic approach was developed that depended on dipping the film into a volume of purified water at a fixed rate (Sakuda et al. 2010). Other studies applied defined force to the film that is stirred in distilled water once every 10 s (Arya et al. 2010). The last method was operated using an apparatus with defined end point detection, where the film was clamped by a sample holder, and a clip with certain weight was fixed to the bottom of the film. The film was half immersed in water at a rate of 30 times per min at 37±1 °C. Once the ODF started to disintegrate, it could not hold the clip that dropped and the time of the fall was recorded (Preis et al. 2014).

Unfortunately, most of the aforementioned methods have subjective unclear end point detection. Moreover, *in-vitro/in-vivo* correlation

of disintegration time was deficient, which leaves no proof for the appropriateness of any of these approaches. The aim of the present study was to design new methods in an attempt to clearly determine the end point and predict the *in-vivo* disintegration time of ODFs compared to formerly reported procedures. Disintegration time of films consisting of hydrophilic polymers of different viscosities (11.25-21 cp, 8-120 cp, 4000 cp and 15000 cp) was investigated by using various approaches and an *in-vitro/in-vivo* comparative study was performed to select the method that confirms best the realistic *in-vivo* situation.

2. Investigations and results

2.1. Mechanical characteristics of orodispersible films

Mechanical characteristics of orodispersible films are important requirements to ensure defect-free films during production, packaging and product release to the market, in addition to its handling by the patient.

The prepared mixtures were able to form uniform elastic films. The properties of the prepared films are summarized in Table 1. The film thickness ranged from 0.083 to 0.108 mm and showed no statistical difference among the different polymeric films (p>0.05), which is mainly attributed to the use of a fixed weight of each polymer during formulation. The prepared films exhibited excellent mechanical properties as the folding endurance of ODFs exceeded 100 folds. Thus, the films are considered flexible due to the absence of visible cracks upon examination under a microscope. As well, the prepared films showed acceptable tensile strength values. The highest tensile strength (TS) was recorded for HPMC K15M films, whereas the lowest value was observed for HPMC E15 films.

Table 1: Mechanical properties of orodispersible films

Formula	Thickness* (mm)	Tensile strength* (N/cm^2)	Folding endurance*
F1	0.088±0.007	1.32±0.33	138±19
F2	0.083±0.005	2.80±0.35	215±35
F3	0.097±0.012	3.45±0.79	>300
F4	0.108±0.011	6.62±1.16	>300

* Mean±SD (n=6)

2.2. Disintegration studies

Film disintegration was assessed by applying five different *in-vitro* methods in phosphate buffer (pH 6.75) as a disintegration medium maintained at 37±1 °C which mimics the saliva (Bala et al. 2014). The disintegration time of the polymeric films measured by the aforementioned tests varied significantly, where the longest disintegration time was recorded for HPMC K100M films, followed by HPMC K4M, HPMC K100LV and HPMC E15 as illustrated in Fig. 1. Furthermore, the disintegration time for the same formulation varied based on the method used, where the recorded average values had the following ascending order; clamp method < cell method < frame method < modified USP method < agar plate method (Fig. 1). A significant difference in the measured end points was obtained by the evaluated *in-vitro* methods, except for the frame and modified USP methods that recorded no significant variation in the disintegration time of HPMC K100LV films as well as HPMC E15 films (p>0.05).

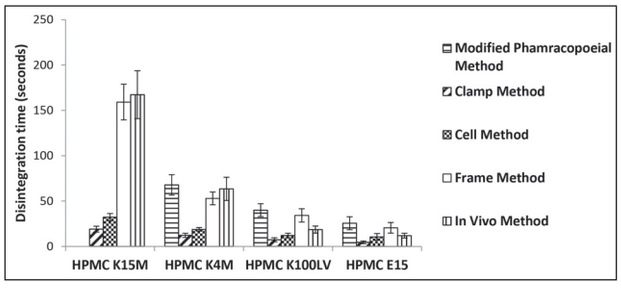

Fig. 1: Disintegration time of orodispersible films assessed using modified Pharmacopeial, clamp, cell, frame and in-vivo methods.

Upon comparing the results of each *in-vitro* method with that of the *in-vivo* results, the frame method proved to be an alternative to the *in-vivo* method for both HPMC K15M and HPMC K4M polymeric films as it showed a non-significant difference in the measured disintegration time of each polymeric film when compared to the *in-vivo* method (p>0.05). On the other hand, the obtained results provide an evidence that the cell method may simulate the *in-vivo* method for both HPMC K100LV and HPMC E15 polymeric films (p>0.05). Moreover, the highest correlation between *in-vitro* and *in-vivo* results of all polymeric films was observed for the cell method (0.999) as shown in Table 2.

Table 2: *In-vitro/in-vivo* correlation of disintegration time

Method	Pearson's correlation coefficient
Frame method	0.991 (p<0.01)
Cell method	0.999 (p<0.01)
Clamp method	0.975 (p<0.05)
Modified Pharmacopeial method	0.993 (p=0.074)

3. Discussion

In the present study, novel methods were designed to determine the disintegration time of ODFs, in order to select the optimal approach that would well correlate to the *in-vivo* conditions. Moreover, the use of different viscosity grade polymers aimed to investigate the suitability of the selected method in predicting *in-vivo* disintegration time independent on the building polymer viscosity.

The average disintegration time of the films using various methods recorded the following ascending order: HPMC E15 < HPMC K100LV < HPMC K15M < HPMC K100M. The viscosity grade of the polymers may have played a vital role in retardation of the film disintegration, where films made up with high viscous polymer (HPMC K15M) showed the longest disintegration time. Such finding was furtherly supported by the highest mechanical properties of HPMC K15M films when compared to other polymeric films (Table 1); as previously reported data showed that the high viscosity polymers yield better mechanical properties compared to that of the low viscosity polymers (Mahesh et al. 2010). An analogous pattern was observed in another study where a lower viscosity Methocel® E5 was compared to a higher viscosity Methocel® E15. The films based on the latter polymer had a higher tensile strength and longer disintegration time compared to the former one (Al-Nemrawi et al. 2016).

Concerning the agar plate as a tool to determine the ODF disintegration time, the prepared films were disintegrated in more than 3 min. This can be explained by the relatively small volume of medium and its slow release from agar which retarded its absorption by the films and hence their disintegration. In addition, the end point detection was challenging due to the transparency of the films and the difficulty encountered in distinguishing between swelled and disintegrated ones on the agar surface.

On the contrary, for the formulated films, the clamp method showed the shortest disintegration time. Various factors may have played a role in accelerating the disintegration time of the films; including the relatively large volume of the medium, the vertical movement of the films and the influence of the weight that was attached at the lower end of the films. This assumption was confirmed by Sakuda et al. (2010), where the disintegration time of HPMC films using a similar mechanistic approach, except for the inclusion of weight was 116.3 s that is much higher than that recorded in the present study (4.5-19 s), thereby indicating the significant influence of weight on the disintegration time of the films. Furthermore, the disintegration time measured by the clamp method proved to be significantly lower than that of the cell method (p <0.05), even though an applied weight equivalent to 0.03 N that mimic the minimal force exerted by the

tongue was a common feature of the two methods (Hermes 2012). Unlike the clamp method, the cell method depends on the use of a small volume of disintegration medium and the films are fixed to the PE tube that was kept static during the experiment, which resulted in a longer disintegration time.

During the modified pharmacopeial method, the films were allowed to swell and disintegrate freely within the tubes. Despite the immersion and vertical movement of the tubes, a relatively longer disintegration time was observed when compared to that of the frame method. This may be related to the folding of the free film on itself during the movement of the basket which may have retarded film disintegration (Preis et al. 2013). In addition, it was noticed that parts of the films adhered to the tube wall which may have also affected its disintegration as a result of hindering the adhered film surface from the disintegration medium. Moreover, a difficulty in detecting the end point was faced due to the transparency of the films. On the contrary, the frame method defined the end point clearly. This method unraveled all the drawbacks that were associated with the use of modified pharmacopeial method. Films were fixed in a metallic frame and allowed to oscillate vertically in the medium without being folded on itself or adhered to the tube walls, hence, resulting in a shorter disintegration time. However, no significant discrimination between the disintegration time measured by both methods was observed for the low viscosity polymers, namely, HPMC K100 LV and HPMC E15 ($p>0.05$). Despite the adherence of the films on the wall of the tube and its folding in the modified USP method, the disintegration time of low viscosity polymeric films was not significantly affected by such phenomena, unlike the behavior of high viscosity polymeric films. Interestingly, the results obtained through the use of cell method for the lower viscosity polymers (HPMC K100LV and HPMC E15) did not vary significantly from that of their *in-vivo* disintegration performance ($p<0.05$). Moreover, the disintegration time of the formulated polymeric films determined by the cell method revealed the highest correlation with *in-vivo* disintegration time ($R^2 = 0.999$). To the best of our knowledge, there is no available data in the literature that revealed an *in-vitro/in-vivo* correlation of the disintegration time of orodispersible films. However, a single study has been published demonstrating a high *in-vitro/in-vivo* correlation of orodispersible tablets with a mechanical method that consisted of an additional weight applied to a rotating shaft (Brniak et al. 2015).

In the present study, a high *in-vitro/in-vivo* correlation was observed for the cell method, which could be attributed to the small volume of the disintegration medium and the minimal force applied by the attached weight that simulate the volume of saliva secreted in the mouth (Navazesh and Kumar 2008) and mimic the force applied by the tongue (Hermes 2012).

From the above findings, it can be concluded that the cell method could predict *in-vivo* disintegration time of orodispersible films ($R^2=0.999$, $p<0.01$), where the characteristics of this method is quite similar to the *in-vivo* condition vis-à-vis the fluid volume and the applied force. Furthermore, the insignificant difference in the results obtained by the cell and *in-vivo* methods for the low viscosity polymeric films indicated the suitability of the method as a simulator to *in-vivo* method for ODFs. Based on the above outcomes, the cell apparatus is considered as a promising broad spectrum methodology for assessing the disintegration time of polymeric ODFs. Accordingly, further investigations are required by testing film formulations of various polymeric types and a wider range of viscosity grades to prove its potential use as an *in-vivo* substitute.

4. Experimental

4.1. Materials

Hydroxypropylmethyl cellulose K15M (HPMC K15M, viscosity 15000 cp), Hydroxypropylmethyl cellulose K100 LV (HPMC K100LV, viscosity 8-120 cp), Hydroxypropylmethyl cellulose E15 (HPMC E15, viscosity 11.25-21 cp), Hydroxypropylmethyl cellulose K4M (HPMC K4M, viscosity 4000 cp), Polyethylene glycol 400 (PEG 400) and agar were purchased from Sigma-Aldrich. All other chemicals and materials used were of analytical grade.

4.2. Preparation of orodispersible films

The films were prepared by the solvent casting method. Two percent aqueous solutions of different viscosity grades of hydroxypropyl methyl cellulose polymer were dissolved in an aqueous medium containing 5 % polyethylene glycol as a plasticizer, namely, HPMC E15, K100LV, K4M and K15M, which were encoded as F1, F2, F3 and F4, respectively. The prepared solutions were allowed to stand overnight to get rid of air bubbles. Subsequently 10 ml of each solution was casted in agar plate (64 cm^2) and dried in oven at 40 °C for 12 h. Afterwards, the dried film was cut into pieces of 4 cm^2, wrapped in aluminum foil and stored in an air tight container at room temperature (25±1 ºC) for further studies.

4.3. Mechanical characterization of orodispersible films

4.3.1. Determination of film thickness

The thickness of the films was measured using a micrometer (DIN-863/II, China). The measurement was performed on five different points of each film and the average thickness of six samples was then calculated (Prabhushankar et al. 2010)

4.3.2. Tensile strength determination

The tensile strength of the films was measured as an average of six determinations using a texture analyzer (Mark-10, ESM 303, USA). Samples were clamped vertically, leaving 1 cm apart from each clamp. The films were then pulled at a rate of 100 mm/min with a contact force of 0.05 N and the tensile strength was defined as the maximum load required to rupture the film, calculated using the following equation (Mishra et al. 2011):

$$\text{Tensile strength} = \frac{\text{load at rupture}}{\text{film thickness} \times \text{film width}}$$

4.3.3. Film folding endurance

The folding endurance of the films was determined by repeatedly folding one film at the same place as described by Liew et al. (2012). The recorded number of folds made before the appearance of cracks represents the folding endurance value. The average of six determinations was calculated for each formulation.

4.4. In-vitro disintegration time

Different methods were used to measure the disintegration time of ODFs. The experiment was repeated six times for each method, and the average values were determined.

4.4.1. Modified pharmacopoeial method

The disintegration test was performed using the pharmacopeial disintegration apparatus. Six films were placed separately into the tubes of the USP apparatus that was allowed to move up and down in the disintegration medium (phosphate buffer, pH 6.75 at 37±1 ºC) at a rate of 30 times per min until complete disintegration (The United States Pharmacopeial Convention 2009).

4.4.2. Clamp method

The test system was adapted from Preis et al. (2014) with some modifications. It consisted of a holder to clamp in the film and another clamp equipped with additional weight which is attached to the lower part of the film. The added weight served to attain a total of 3 g. The attached film was allowed to be partially immersed (50 %) in the disintegration medium (phosphate buffer, pH 6.75 at 37 ± 1 °C) at 30 times per min.

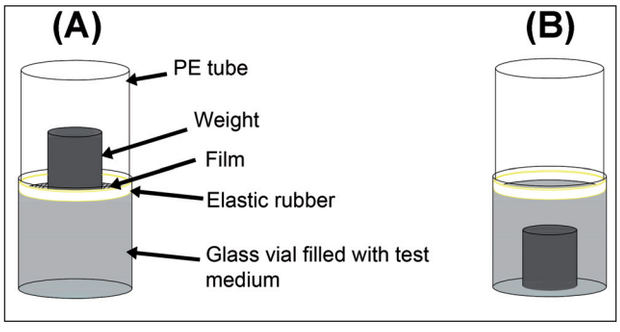

Fig. 2: Diagrammatic illustration of cell assembly for the determination of the disintegration time of orodispersible films. Starting point (A) and end point (B).

4.4.3. Cell method

The cell method apparatus consisted of two parts as shown in Fig. 2; the first part is composed of a small volume glass vial, whereas the second is a 5 cm polyethylene (PE) tube that fits the vial opening (key and lock) and a three grams weight. The film was fixed on the circumference of the PE tube, then the weight was inserted in order to be laid on the surface of the attached film. Consequently, the equipped PE tube

was fitted in the glass vial that was filled with phosphate buffer (pH 6.75) to barely contact the disintegration medium. Upon contact with the disintegration medium which represents the zero time, the film swelled and disintegrated and was unable to hold the weight that eventually disrupted the film and dropped at the bottom of the vial. The time elapsed between the film contact with the disintegration medium and the fall of the weight was measured.

4.4.4. Frame method

The design of the test system was inspired by compendial disintegration apparatus as shown in Fig. 3, where a holder equipped with a metallic frame was used to hold the film edges. The film was allowed to reciprocate vertically into 500 ml phosphate buffer (pH 6.75) at 37±1 °C at a rate of 30 times per minute. With time, a hole within the metallic frame is formed which increased in area upon disintegration. Once the film was completely disintegrated, an empty frame was considered as the experiment end point.

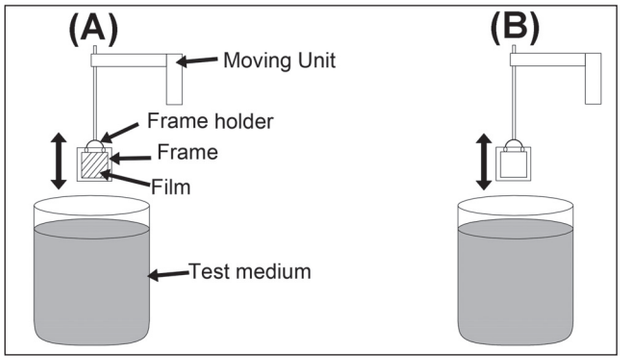

Fig. 3: Diagrammatic illustration of frame assembly for the determination of the disintegration time of orodispersible films. Starting point (A) and end point (B).

4.4.5. Agar plate method

An agar plate was prepared using 50 ml of 2 % agar solution in phosphate buffer at pH 6.75 according to Saxena et al. (2011). The agar plate was partially immersed in a water bath at 37±1 °C, and the film was placed on its surface. The disintegration time was defined as the time interval between placing the film on the agar surface until its complete disintegration.

4.5. In-vivo determination of ODF disintegration time

The *in-vivo* disintegration time of ODFs under investigation was assessed on six healthy volunteers of both genders. The study protocol was approved by the institutional review board (IRB) committee, Beirut Arab University, Lebanon (No. 2018H-0054-P-R-0251). Prior to the study, the volunteers were informed about the purpose and nature of the study. The volunteers participated in a four-period, double-blind study after providing a written informed consent. Participants were requested to place the film on the tongue and move it against the hard palate of the mouth, then allow it to disintegrate with gentle movement of the tongue (Kakutani et al. 2010). Complete disintegration of the films was denoted by the absence of its sensory detection by the tongue, which was confirmed by the investigator observation of its disappearance. Subsequently, volunteers were asked to rinse their mouth with a glass of water. In each phase of the study, one ODF formulation was given to the six volunteers. Another ODF formulation was given to the volunteers the next day. The same procedure was repeated up to 4 days to complete the evaluation of the formulations studied.

4.6. Statistical analysis

Results were expressed as mean±S.D. The level of statistical significance was assessed by ANOVA (one way analysis of variance) using SPSS 20 (SPSS Inc., Chicago, USA) followed by tuckey's test. Results with a *p*-value of less than 0.05 were considered statistically significant. Moreover, Pearson's correlation coefficients of *in-vitro*/*in-vivo* results were computed for each tested method.

Conflicts of interest: None reported.

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