

Formulation of a fast-dissolving oral film using gelatin and sodium carboxymethyl cellulose

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Abstract

Background and objective: Orally disintegrating film is a solid dosage form made as an alternative for tablets for pediatric and geriatric patients who have difficulty in swallowing. These formulations are designed to dissolve in the mouth rapidly upon contact with saliva. This study aimed to prepare a thin oro-dispersible film base that can withstand handling in which a drug can be incorporated to provide a new dosage form.

Methods: The solvent casting method was used to prepare the films, in which the ingredients were mixed, dissolved, and cast in a Petri dish. Then, they were left to dry in the oven overnight. Different concentrations of each of the two polymers alone and combined in different ratios were compared using different concentrations of plasticizer.

Results: Successful, transparent films were prepared from gelatin and glycerin. A combination of 70% gelatin and 30% sodium carboxymethyl cellulose with glycerin formed an acceptable film having white color. The film forming capacity of sodium carboxymethyl cellulose alone was not good. All films were tearing and not well formed. All films that contain polyethylene glycol were brittle. Both superdisintegrants reduced the disintegration time for both films, but kyon was more effective than sodium starch glycolate.

Conclusion: A successful oral film was prepared using different types of polymers, which is suitable for incorporating a potent drug to form a new dosage form that is easily portable and does not require water for swallowing.

Keywords: Fast dissolving oral film; Gelatin; Sodium carboxy methyl cellulose; Solvent casting method.

Introduction

The oral drug delivery system is the most common and acceptable route of drug administration because of easy ingestion, patient compliance, and lack of pain. However, the most evident drawback of its difficulty of swallowing, especially for pediatric, geriatric, and nauseous patients causing patient in compliance.¹ To overcome this problem, fast dissolving oral drug delivery systems such as orodispersible tablets and fast dissolving oral strips were developed. This was first developed in the late 1970s.² The orally disintegrating film is a thin film with a thickness of 1-10 mm and an area of 1-20 cm².³ These formulations are

designed to dissolve in the mouth rapidly upon contact with saliva. In these films, the hydrophilic polymer is used as the base for the film. Other excipients are added as required, like plasticizer, colorant, and flavor.⁴ This type of film was originally made as a mouth refreshing, but then pharmacological ingredients were added to produce a new dosage form. The film could dissolve within a few seconds to one minute, releasing the pharmacologically active ingredient with other inactive ingredients, which can mainly be swallowed with saliva to be absorbed in the gastrointestinal tract (GIT).⁵ Typically, an oral film will contain 1-25% w/w of the active drug ingredient.⁵ Different types of

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hydrophilic polymers or a combination of different polymers can be used as a base for the film. The film should be tough enough to withstand handling.⁵ The amount of the polymer should be typically 40-50% w/w of the film.⁴ Examples of polymers used are pullulan, gelatin,⁵ hydroxy propyl methyl cellulose (HPMC), carboxy methyl cellulose (CMC), maltodextrins, and sodium alginate.⁵ In order to improve the mechanical properties of the film, it is necessary to add a suitable type of plasticizer.⁶ It can improve the tensile strength and elongation of the film.⁶ It is required to add 0-20% w/w of plasticizer.⁴ Examples of plasticizer include glycerol, di-butylphthalate, and polyethylene glycols.⁷ All other excipients like fillers, colorants, flavoring, saliva stimulating agents will comprise 0-40% of the film formulation.⁴ Advantages of fast dissolving oral film (FDO) includes ease of swallowing for geriatric and pediatric patients, suitability for patients having difficulty swallowing, no need of water for administration, easily portable, accurate dosing compared to suspensions,⁴ fast onset of action, fast absorption, and improved patient compliance.⁵ However, there are still some limitations for this relatively new dosage form, such as the inability to incorporate high doses of medicine, which should be between 1-30 mg. Some technical manufacturing limitations include difficulty in achieving dose uniformity, film thickness, and expensive packaging.² Many patents have been achieved in this area. WAFERTAB is a patented system for its unique process in preparing the thin film with drug loading; this can be for oral and topical application.³ FOAMBURST is another patented technique granted in 2004 in which capsule is made from foamed film. A film that has a honeycomb structure is made by blowing gas into the film during production. This special honeycomb structured capsule is light and dissolves rapidly, resulting in a melt in the mouth sensation.³ XGel film technology is developed by Bio-progress.³ WOWTAB

tablet refers to "without water tablet," which is developed by Yamanouchi Pharmaceutical Co. Ltd., Japan. This tablet is sufficiently hard before wetting with saliva, but becomes soft and disintegrates or dissolves within 15-20 seconds upon contact with saliva.⁵ Recently many FDO formulations are prepared for different medicines. The fast dissolving oral film of bisoprolol fumarate is prepared using hydroxy propyl methyl cellulose (HPMC) and maltodextrin as film forming polymers and EG 400 as plasticizer, using the solvent casting method.⁸ In this study, an oral fast dissolving film base was prepared using gelatin and sodium carboxy methyl cellulose (SCMC) as film forming polymers and glycerin and polyethylene glycol 400 as plasticizers. This base will be a novel dosage form in which a potent drug that is suitable for oral administration can be incorporated to form a new dosage form. This study aimed to find the best concentration for each polymer including gelatin and SCMC to form a film with acceptable thickness and strength to withstand handling, comparing the film forming capacity of gelatin and SCMC, find the best concentration for each plasticizer including glycerin and polyethylene glycol (PEG 400) that can give enough elasticity to the films with each of the selected polymer, find the best concentration of combined polymers to form a successful film, and reduce the disintegration time of the films by using sodium starch glycolate (SSG) and kyon as super disintegrants and comparing their effectiveness.

Methods

Materials:

The materials used are SCMC, gelatin, glycerin, PEG 400,SSG, kyon, mannitol, sodium saccharin, and citric acid, which are laboratory grade and were provided by the College of Pharmacy of Hawler Medical University. Distilled water was used throughout the experiment.

Method:

Solvent casting method was used for the

preparation of ODF.⁹ Ingredients used for the preparation of the film, including polymer, plasticizer, super disintegrant, sodium saccharin, citric acid, and mannitol, were accurately weighed and mixed with 30 ml of distilled water. The mixture was mixed using a magnetic stirrer and heated to 40°C for one hour. The homogenous viscous solution was poured into a plastic Petri dish and then placed in the oven and left overnight at 40°C to dry.

Calculation for the ingredients:

The polymers were used in three different

concentrations, which are 40, 45, and 50% w/w. Also, three different concentrations were used for the plasticizer, which are 10, 15, and 20% w/w. The other ingredients were used, as shown in Table 1. In general, 36 formulations were prepared using different concentrations of two types of polymers and plasticizers (Table 2). Five more formulas were prepared using combinations of the polymers (Table 3).

Table 1: Concentration of the ingredients in the film formulation.

Compound	%w/w
Polymer	40, 45, 50
Plasticizer	10, 15, 20
Sodium saccharin	5
Citric acid	5
Mannitol	qs.

Table 2: Concentration of the ingredients for the nine basic formulations.

Ingredient	BF1	BF2	BF3	BF4	BF5	BF6	BF7	BF8	BF9
Polymer (HPMC, gelatin)	40%	40%	40%	45%	45%	45%	50%	50%	50%
Plasticizer (glycerin, PEG 400)	10%	15%	20%	10%	15%	20%	10%	15%	20%
Sodium saccharin	5%	5%	5%	5%	5%	5%	5%	5%	5%
Citric acid	5%	5%	5%	5%	5%	5%	5%	5%	5%
Mannitol	qs	qs	qs	qs	qs	qs	qs	qs	qs

Table 3: Concentration for the combination formulas.

Formulas	SCMC % w/w	Gelatin % w/w	Glycerin % w/w	PEG 400 % w/w
F37	25	25		20
F38	25	25	20	
F 39	12.5	37.5		20
F 40	37.5	12.5		20
F 41	12.5	37.5	20	

SSG and kyron, (6%) were added to the successful formulations as superdisintegrants.

Evaluation of oral film

Since oral dissolving films are new dosage forms, no standard evaluation tests are known in the pharmacopeias. Therefore, a set of in vitro evaluation tests was selected from the literature.

- 1- Visual inspection: the films were inspected visually for their homogeneity, transparency, flexibility, peel ability, and surface texture.¹⁰
- 2- Thickness uniformity of the films: this was done by using a digital compass (Vernier caliper). The thickness of the film is an indication of the content uniformity.
- 3- Folding endurance: this is determined by folding the strip at the same place back and forth repeatedly fifty times. The number of times the film is folded without breaking is determined as the folding endurance of the film.⁶
- 4- In vitro disintegration time: modified disintegration time test was used. In a small sized beaker containing 10 ml of

distilled water at 37°C, a piece of 2 cm² film was carefully put in the center. The film was observed and the time measured when the film starts to disintegrate.¹⁰ This was repeated four times.

Statistical analysis

All experiments were performed in triplicates, and values were expressed as mean ± standard deviations. Statistical significance was assessed using one-way analysis of variance (ANOVA) and student t-tests, as appropriate. Values with *P* < 0.05 indicate that the difference is statistically significant.

Results

A total of 41 films were prepared with different concentrations of polymer and plasticizer to find successful films. From all the formulated films, only two were successful, F 36 and F 41. The results for the formation and appearance of films are listed in Table 4.

Table 4: Results for the properties of the prepared films.

Formulas (polymer + plasticizer)	Film appearance	Peelability and brittleness
F1 (SCMC 40% + PEG 10%)	Film formed, white in color and rough surface	Sticky cannot be removed
F2 (SCMC 40% + PEG 15%)	Film formed with white color and rough surface	Peelable, but brittle
F3 (SCMC 40% + PEG 20%)	Film formed with white color and rough surface	Sticky and brittle
F4 (SCMC 45% + PEG 10%)	Film formed with white color and rough surface	Sticky, and brittle
F5 (SCMC 45% + PEG 15%)	Film formed with white color and rough surface	Peelable and a little brittle
F6 (SCMC 45% + PEG 20%)	Film formed with white color and rough surface	Sticky and brittle
F7 (SCMC 50% + PEG 10%)	Film formed with white color and rough surface	Sticky and brittle
F8 (SCMC 50% + PEG 15%)	Film formed with white color and rough surface	Very sticky
F9 (SCMC 50% + PEG 20%)	Film formed with white color and rough surface	Easily peelable but very brittle
F10 (SCMC 40% + glycerin 10%)	Film not well formed, with white color and rough surface	Sticky
F11 (SCMC 40% + glycerin 15%)	Film not well formed, with white color and rough surface	Sticky
F12 (SCMC 40% + glycerin 20%)	Film not well formed, with white color and rough surface	Sticky
F13 (SCMC 45% + glycerin 10%)	Film not well formed, with white color and rough surface	Sticky

F14 (SCMC 45% + glycerin 15%)	Film not well formed, with white color and rough surface	Sticky
F15 (SCMC 45% + glycerin 20%)	Film not well formed, with white color and rough surface	Sticky
F16 (SCMC 50% + glycerin 10%)	Film not well formed, with white color and rough surface	Sticky
F17 (SCMC 50% + glycerin 15%)	Film not well formed, with white color and rough surface	Sticky
F18 (SCMC 50% + glycerin 20%)	Film not well formed, with white color and rough surface	Sticky but brittle
F19 (gelatin 40% + PEG 10%)	Film not well formed, with white color and rough surface	Sticky but brittle
F20 (gelatin 40% + PEG 15%)	transparent with smooth surface film formed	Sticky and brittle
F21 (gelatin 40% + PEG 20%)	Transparent, smooth and broken film is formed	Sticky and brittle
F22 (gelatin 45% + PEG 10%)	Transparent, smooth and broken film is formed	Sticky and brittle
F23 (gelatin 45% + PEG 15%)	Transparent, smooth and broken film is formed	Sticky and brittle
F24 (gelatin 45% + PEG 20%)	Transparent, smooth and broken film is formed	Sticky and brittle
F25 (gelatin 50% + PEG 10%)	Transparent, smooth and broken film is formed	Sticky and brittle
F26 (gelatin 50% + PEG 15%)	transparent with smooth surface film formed	Peelable and brittle
F27 (gelatin 50% + PEG 20%)	Transparent, smooth and broken film is formed	Peelable and brittle
F28 (gelatin 40% + glycerin 10%)	A yellowish transparent film with smooth surface is formed	Sticky and brittle
F29 (gelatin 40% + glycerin 15%)	A transparent with smooth surface film is formed	Sticky and brittle
F30 (gelatin 40% + glycerin 20%)	A transparent with smooth surface film is formed	Sticky and brittle
F31 (gelatin 45% + glycerin 10%)	A transparent with smooth surface film is formed	Sticky and brittle
F32 (gelatin 45% + glycerin 15%)	A whitish with smooth surface film is formed	Sticky and brittle
F33 (gelatin 45% + glycerin 20%)	A transparent with smooth surface film is formed	Sticky and brittle
F34 (gelatin 50% + glycerin 10%)	A transparent with smooth surface film is formed	Sticky and brittle
F35 (gelatin 50% + glycerin 15%)	A transparent with smooth surface film is formed	Sticky and brittle
F36 (gelatin 50% + glycerin 20%)	A transparent with smooth surface film is formed	Peelable and not brittle
F37 combination polymer (SCMC 25% + gelatin 25%) + PEG 20%	A yellowish, opaque film with smooth surface is formed	Easily peelable but brittle
F38 combination polymer (SCMC 25% + gelatin 25%) + glycerin 20%	A yellowish, opaque film with smooth surface is formed	Sticky
F39 combination polymer (SCMC 12.5% + gelatin 37.5%) + PEG 20%	A yellowish, opaque film with smooth surface is formed	Sticky
F40 combination polymer (SCMC 37.5% + gelatin 12.5%)+PEG 20%	A whitish transparent with rough surface film is formed	Sticky
F41 combination polymer (SCMC 12.5% + gelatin 37.5%) + glycerin 20%	A whitish transparent with rough surface film is formed	Peelable, not brittle, soft and flexible

Figure 1 below shows the photos for some of the films prepared. For the two successful films, further evaluation tests were done, like thickness and folding endurance. Thickness was measured using

Vernier caliper at ten different places of the film, and the mean and standard deviation were calculated. The results are shown in Table 5.

Table 5: Thickness and folding endurance of the two successful films. Results given as mean ± SD

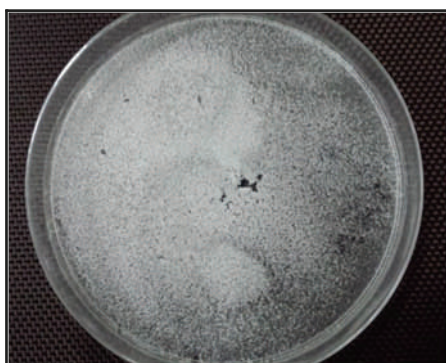
Test	F36	F41	P value (α=0.05)
Thickness	0.14 ± 0.010	0.29 ± 0.050	0.007
Folding endurance	51±1.52	38 ± 4.966	0.012



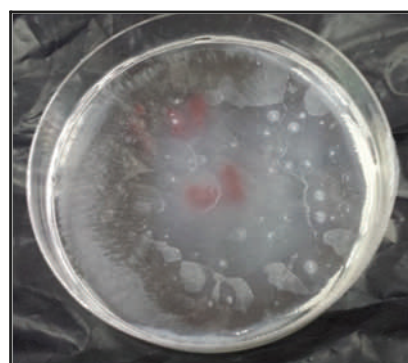
Film containing gelatin 50% and glycerin 20% (F 36)



Film containing a combination of gelatin and SCMC (F 41)



Film containing SCMC and glycerin



Film containing gelatin and PEG 400

Figure 1: Photos of the formulated films.

Disintegration time results

Two different super disintegrants were tested in an attempt to reduce the disintegration time of the films, which included SSG and kyron. The results are shown below in Table 6. The results shown in Figure 2 compare the efficacy of SSG

and kyron in reducing the disintegration time of the film containing gelatin 50% as polymer (F36). In Figure 3, the efficacy of the same super disintegrants in reducing the disintegration time of the film is shown when used with formula 41 in the same concentration.

Table 6: Results for the disintegration time for the two successful formulas using sodium starch glycolate and kyron.

Sample	Disintegration time (sec)		P value ($\alpha=0.05$)
	Added 6% SSG	6% kyron	
F 36	27 ± 5.706137	16 ± 2.861381	0.040
F 41	46 ± 5.356071	16 ± 1.469694	0.007

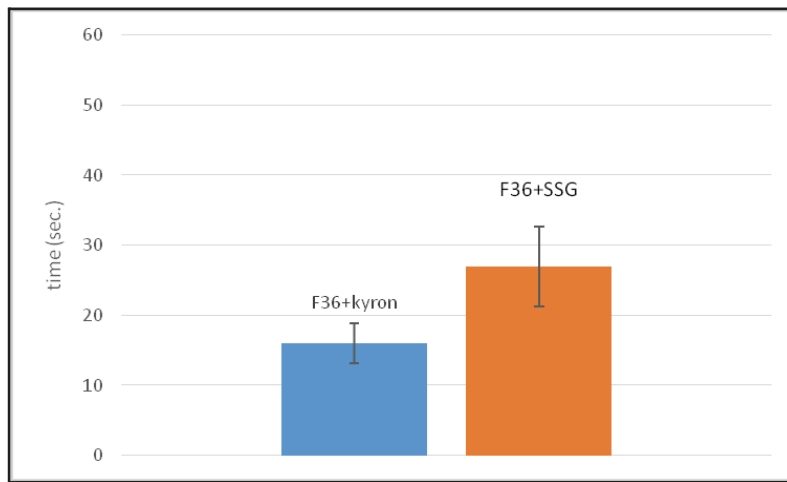


Figure 2: Comparing the disintegration time of the films made with gelatin (F36) containing SSG and kyron.

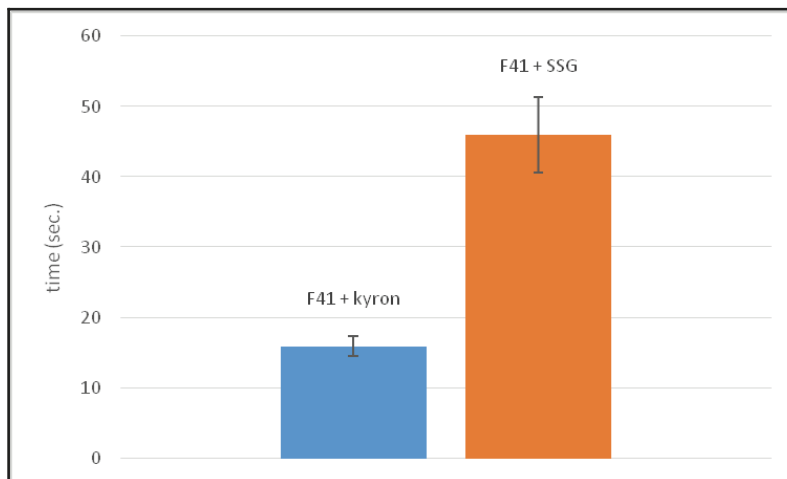


Figure 3: Comparing the disintegration time of the film made with a combination of the polymers SCMC and gelatin (F41) using SSG and kyron.

Discussion

In the preparation of the films, a mild increase in temperature (40°C) was used during mixing in order to increase the solubility of gelatin because it is insoluble in cold water.¹¹ Different concentrations of SCMC and gelatin as polymer and glycerin and PEG 400 as plasticizer were tested to prepare the films as shown in Table 4. All films using SCMC and PEG 400 were brittle and sticky to the petri dish except for films containing 15% PEG and 40% and 45% of SCMC, which were peelable. Those two films were unacceptable because of their high tendency to brittleness. Furthermore, PEG 400 was not suitable with SCMC to form an orodispersible film while it could be preferable to use with other polymers like HPMC E15.¹ Films containing SCMC and glycerin with all the concentrations were brittle and sticky; also, films were not formed. This means that the film forming capacity of polymers can be affected by the plasticizer. Moreover, glycerin is not a suitable plasticizer to be used with SCMC for producing desirable films. The plasticizer has to be compatible with the polymer to improve the mechanical strength of the polymer. Incorporation of an inappropriate amount of plasticizer may lead to the formation of cracked film⁹ as seen in this formula. Films containing gelatin as film forming polymer in all three concentrations and PEG 20% were all rejected. Therefore, most of the films were broken and sticky. However, when the gelatin and PEG concentration increased, the films were not sticky but still brittle. Thus, the desired film cannot be formed from gelatin and PEG 400 as a film forming polymers. Therefore, a suitable plasticizer had to be selected to improve the mechanical properties of the film.⁶ Films formed from gelatin and glycerin as a polymer were unacceptable because they were very sticky and could not be removed from the Petri dish. However, the film formed from 50% gelatin and 20% glycerin (F36) was accepted since the film was easily peelable, transparent with a smooth

and un brittle surface. Thus, super disintegrant was added to this formula and was further tested. In order to determine further effects of polymer, a combination of the two polymers were tried. All of the combined formulations were produced from 50% polymer and 20% plasticizer, similar to the desirable film concentrations. Moreover, the film prepared from equal ratios of the polymers and PEG as plasticizer was not sticky but unacceptable because the produced film had a higher tendency for brittleness. Furthermore, PEG was replaced with glycerin while the produced film was unacceptable because it was very sticky. Further studies were done in which a combination including 70% of SCMC polymer and 30% of gelatin. However, the films formed were very sticky and unacceptable for further investigations. While the films produced with opposite concentrations, i.e., 70% gelatin and 30% SCMC and PEG 400 used as a plasticizer, the formed films were sticky to the Petri dish. However, when glycerin was used as a plasticizer (F41), the films were easily peelable from the Petri dish without any degree of brittleness. Furthermore, the evaluation tests were done for the two successful films. Folding endurance was performed to find the mechanical stability of the films. When the films folded in the same place back and forth for fifty times, F36 was still intact, and no sign of braking was apparent. Thus, it was considered acceptable.⁶ However, F41 had a folding endurance of 38, which shows low mechanical stability of the film (Table 4). Furthermore, the films were quite thin, with a thickness of 0.14 mm and 0.24 mm for formula 36 and 41, respectively (Table 5). To reduce the disintegration time of the films, super disintegrants were added. In this study, two super disintegrants were tested, which are SSG and kyron, with a concentration of 6%. With formula 36, Kyron has significantly reduced the disintegration time than SSG ($P < 0.05$) to be only 16 seconds compared to 27 seconds, as shown in Table 6 and

Figure 2. Similarly, in formula 41 kyron has provided a significantly lower disintegration time being only 16 seconds compared to SSG, which provided a disintegration time of 46 seconds ($P < 0.05$), as shown in Table 6 and Figure 3. Nonetheless, both of them have provided acceptable disintegration. Therefore, kyron is a suitable super disintegrant to be used with both films, while SSG was preferred with films made with gelatin alone but was not acceptable with films containing SCMC. This variance may be due to difference in their mechanism of action as Kyron acts by swelling and capillary action¹² while SSG works by rapid water uptake.¹³

Conclusion

The orally disintegrating film is an emerging oral dosage form, which is elegant, easily portable, and does not require water for swallowing. Gelatin with glycerin can produce a successful film base, which can be used as a new dosage form if a suitable active pharmaceutical ingredient is incorporated. However, when SCMC was used with glycerin, suitable films were not formed. This means that the film forming capacity of SCMC was disrupted when mixed with glycerin. PEG 400, when used with either gelatin and SCMC could not produce a successful film, which was not suitable with either form of polymers, but could be suitable with other types of polymer. The combination of the two polymers has produced an acceptable film when used with glycerin. However, the folding endurance was less than required, which could be due to the incompatibility of SCMC with glycerin. Both types of super disintegrants have significantly reduced the disintegration time of the films; nonetheless, kyron was better in reducing the disintegration time for both films.

Competing interests

The authors declare no competing interests.

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