Optimization of Polymer and Cross-linker Combination on the Formation of Pectin Film Containing Metformin Hydrochloride

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Abstract: Pectin has been developed as an edible film in drug delivery systems, however pectin has some disadvantages such as rapid drug release, low mechanical strength, and low drug infusion efficiency. The purpose of this study was to optimize the polymer and cross-linker combination on the formation of pectin film containing metformin hydrochloride. The films were prepared using a single or combination of polymer as a matrix and glycerin as a plasticizer. The homogenous mixture of pectin mucilage, alginate mucilage, hydroxyl-propyl methylcellulose (HPMC) mucilage, ethyl-cellulose, glycerin, and metformin hydrochloride was flattened on an object glass (2 cm x 5 cm) and then allowed to dry at room temperature. The all formula were evaluated the capability of forming the membrane or film and elasticity properties. The pectin, alginate, HPMC, and ethyl-cellulose polymer in single or two polymer combination cannot form a film with the addition of metformin hydrochloride. The combination of three polymers of pectin, alginate, and ethyl-cellulose can form a finer, smoother surface, more elastic, rolled and folded membrane/film. The combination of three polymers of pectin, alginate, ethyl-cellulose and the addition of cross-linkers to a combination of pectin, alginate, HPMC provides an optimal film for Drug Delivery System.

1 INTRODUCTION

Pectin is widely used in the pharmaceutical as an ingredient for applications of Drug Delivery System (DDS). Pectin has advantages as a non-toxic nature polymers, low production cost, and high availability (Mishra, 2012). Edible films can be distinguished in three categories based on the raw materials used i.e. hydrocolloids, fats and mixtures of both. The hydrocolloid groups can be prepared from polysaccharides (cellulose, modified cellulose, starch, agar, alginate, pectin, dextrin), proteins (collagen, gelatin, egg white), and also lipids (Omidian and Kinam, 2012).

Drug release from high methoxy pectin has been studied in terms acrylamide grafted pectin was characterized by FTIR, DSC and X-ray diffraction. The polymer was cross-linked with glutaral dehyde and tested for salicylic acid release using a Franz diffusion cell. A grafted hydrogel displayed better film-forming properties than pectin (Sutar, 2008).

Hydrogel membrane based on pectin and polyvinylpyrrolidone have been prepared by physical blending and conventional solution casting methods. The release of salicylic acid was monitored at different aqueous media using a UV Vis spectrophotometer at 294 nm wavelength. The presence of secondary amide, decrease in crystallinity at higher PVP ratio (Mishra, 2008). Amidated pectin complexes with calcium were used in preparation of a multipar-ticulate system with the potential for site-specific colon delivery (Munjeri, 1997).

In the manufacture of edible film from pectin as a drug delivery system, pectin has several disadvantages such as rapid drug release, low mechanical strength, and low drug infusion efficiency. The purpose of this study is the optimize of polymer and cross-linker combination on the formation of pectin film containing metformin hydrochloride.

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2 METHODS

2.1 Materials

Metformin hydrochloride was obtained from Iol Chemicals and Pharmaceuticals Ltd India. Sodium Alginate 500~600 cP was the products of Wako Pure Chemical Industries, Ltd Japan. Pectin was obtained from Cargill Deutschland GmbH Germany, ethyl cellulose was the products of Shanghai Honest Chem Co., Ltd. China, and hydroxypropyl methylcel lulose (HPMC) was the products of Wuhan Senwayer Century Chemical Co., Ltd., China.

2.2 Preparation of Films Containing Metformin Hydrochloride

The films were prepared using the single or combination of polymer as a matrix and glycerin as a plasticizer. The homogenous mixture of mucillage of 4% sodium alginate in water, mucillage of 10% pectin in water, mucillage of 8% HPMC in water, ethylcellulose, glycerin, and metformin hydrochloride (Table 1) was flattened on a object glass (2 cm x 5 cm) and then allowed to dry at room temperature for 48 hours. The films formed were removed carefully, and placed in desiccator.

3 EVALUATION

The formulas designed with various combinations of polymers containing metformin hydrochloride (Table 1), the capability of the polymer in each formula to form the membrane/film was observed visually and the elasticity properties was evaluated by rolling or folding the membrane/film.

4 RESULT AND DISCUSSION

4.1 The Film Properties of Single Polymers without Metformin Hydrochloride

The membrane/films of single polymers and combinations without containing metformin hydrochloride were prepared by dissolving the polymers at concentrations which may form a gel. The gel solution is then placed on the mold and dried at room temperature. The gel solutions of the pectin, alginate, HPMC and ethyl cellulose polymers all demonstrate to form a films. The generally obtained films have properties such as plastic, transparent, thin, elastic to be rolled or folded, except for the films of ethyl cellulose showed yellowish white film as shown in Table 2 and Figure 1.

Based on the data in table 2, all of the polymers have the ability to form a good film. Edible film preparations can be distinguished based on the raw materials used namely hydrocolloids, fats and mixtures of both. Edible hydrocolloid group films can be made from polysaccharides such as cellulose, cellulose modification, starch, agar, alginate, pectin, and dextrin (Omidian and Kinam, 2012).

The ability of these polymers to form films and applications as matrices in drug delivery systems has been reported in several studies i.e. combinations of chitosan-alginic films containing antacids as the gastroretentive drug delivery system (Mariadi, 2015), the characterization of pectin/PVP hydrogel membranes containing salicylic acid for drug delivery system (Mishra, 2008), pectin-based biodegradable hydrogels with potential biomedical application as drug delivery system (Sadeghi, 2011), and chitosan-alginate films prepared with chitosan of different molecular weights (Yan, 2001).

Table 1: Formula of films containing metformin hydrochloride

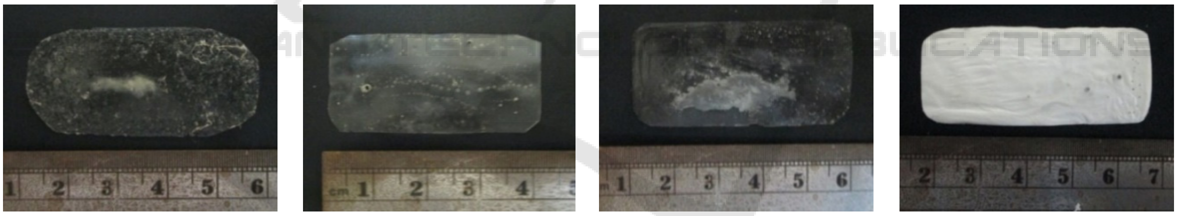
No	Polymers		Polymers Ratio	Metformin hydrochloride	Glycerin
1	Single of polymer without containing metformin hydrochloride	Pectin 10%	-	-	2 drops
		HPMC 8%	-	-	2 drops
		Etil Selulosa 8%	-	-	2 drops
		Alginate 4%	-	-	2 drops
2	Single of polymer containing metformin hydrochloride	Pectin 10%	-	500 mg	4 drops
		HPMC 8%	-	500 mg	4 drops
		Ethyl cellulose 8%	-	500 mg	4 drops
		Sodium Alginate 4%	-	500 mg	4 drops
3	Combination of two polymer containing metformin hydrochloride	Pectin + HPMC	1:1	500 mg	4 drops
		Pectin + Ethyl cellulose	1:1	500 mg	4 drops
		Pectin + Sodium Alginate	1:1	500 mg	4 drops

Table 1: Formula of films containing metformin hydrochloride(cont.)

No	Polymers		Polymers Ratio	Metformin hydrochloride	Glycerin
4	Combination of three polymers containing metformin hydrochloride	Pectin + Sodium Alginate + Ethyl cellulose	1:1:1	500 mg	4 drops
		Pectin + Sodium Algintae + HPMC	1:1:1	500 mg	4 drops
		Pectin + Ethyl cellulose + HPMC	1:1:1	500 mg	4 drops
5	Combination of two and three polymers with the addition of Crosslinker ($CaCl_2$) containing Metformin hydrochloride	Pectin + Alginate + $CaCl_2$ 1% + metformin HCl	1:1	500 mg	4 drops
		Pectin + Alginate + $CaCl_2$ 2% + metformin HCl	1:1	500 mg	4 drops
		Pectin+ Alginate + $CaCl_2$ 3% + metformin HCl	1:1	500 mg	4 drops
		Pectin + Alginate + Ethyl cellulose + $CaCl_2$ 1% + Metformin HCl	1:1:1	500 mg	4 drops
		Pectin + Alginate + HPMC + $CaCl_2$ 1% + Metformin HCl	1:1:1	500 mg	4 drops

Table 2: The properties of single polymer membrane/film

No	Polymer	Thickness of the membrane/film (mm)	Properties of Film
1	Pectin 10%	0.27±0.05	Transparent film: thin, elastic and roll able/foldable
2	HPMC 8%	0.14±0.01	Transparent film: thin, elastic and roll able/foldable
3	Ethyl Cellulose 8%	0.34±0.02	Yellowish white film: thin, elastic and roll able/foldable
4	Alginat 4 %	0.75±0.17	Transparent film: thin, elastic and roll able/foldable



Pectin HPMC Alginate Ethylcellulose

Figure 1: The Films of pectin, alginate, HPMC and ethyl cellulose polymer

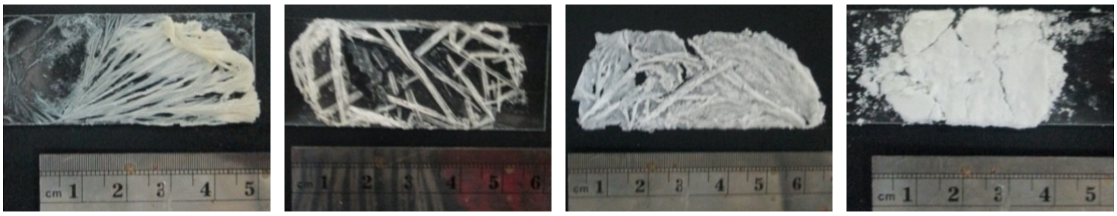
4.2 The Membrane Properties of Single Polymer Contains Metformin Hydrochloride

The gel solution of the pectin, alginate, HPMC and ethylcellulose polymers added with metformin HCl respectively, indicates that this mixture can not form the membrane/ film, but produces crystalline particles of metformine HCl-coated polymer as shown in Table 3 and Figure 2.

From the obtained data, the membrane/film can not be formed suspected that it is related to the water-soluble nature of metformin HCl, so that when mixed with the polymer gel solution dissolves between the gel and metformin HCl. The gel solution breaks into liquid and dilute, this is because the dissolved metformin HCl can break the crosslinks in the polymer chains of the gel. The breaking of crosslinks of the gel preparations of these polymers results in the loss of the gel properties, so that when the mixture is dried it can not form membrane /films. In physical gels, the nature of the crosslinking process is physical. This is normally achieved via utilizing physical processes such as association, aggregation, crystal lization, complexation, and hydrogen bonding. While physical hydrogels are reversible due

Table 3: The membrane properties of single polymer contains metformin hydrochloride

No	Polymer	The resulting film membrane	
		The result	Properties of membrane
1	Pectin 10% + Metformin HCl	Could not formed films	Produce irregular crystals
2	HPMC 8% + Metformin HCl	Could not formed films	Produce rod-shaped crystals
3	Alginate 4% + Metformin HCl	Could not formed films	Produce irregular crystals
4	Ethyl cellulose 10% + Metformin HCl	Could not formed films	Produce powder



Pectin + Metformin HCl | HPMC + Metformin HCl | Alginate + Metformin HCl | Ethylcellulose + Metformin HCl

Figure 2: Single polymer (pectin, alginate, HPMC and ethyl cellulose) can not form a film membranes with Metformin HCl

to the conformational changes. Hydrogels are also classified as hydrogels responsive to changes in terms of their interaction with the surrounding environment, i.e., responses to the changes in pH, temperature, and the composition of the surrounding liquid. Depending on its structure, hydrogel can respond to environmental changes by changing its size or shape (Omidian and Kinam, 2012).

4.3 The Memran/Film Properties of Pectin (two polymer combination) That Contain Metformin HCl

The membrane/film properties of pectin (two polymer combination) that contain metformin HCl shows the same results as a single polymer that can not form a film, as in the Table 4 and Figure 3.

Table 4: The film membrane properties of polymer (two polymer combination) containing Metformin HCl

No	Polymer	The result
1	Pectin + HPMC + Metformin HCl	Could not formed films
2	Pectin + Ethylcellulose + Metformin HCl	Could not formed films
3	Pectin + Alginate + Metformin HCl	Could not formed films

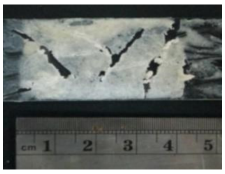
4.4. The Membrane/Film Properties of Pectin (three polymer combination) Containing Metformin HCl

The properties of the pectin membranes/films (three polymer combination) containing metformin HCl can be seen in Table 5 and Figure 4, that the combination of three polymers gives different results, some formulas may form membranes/films and some other can not. It will be dependent on combination of the polymer from the formula.

The combination of pectin, alginate and ethylcellulose polymer can form membran/film, but combination with ethylcellulose powder provides better membrane/film than mucilago ethyl cellulose, which is obtained more smooth and flat surface membrane, elastic, easily rolled and folded. It is assumed that the ethyl cellulose powder as a hydrophobic polymer covers/coats the metformin HCl so it is not disturb the stability of the gel solution of the hydrophilic pectin and alginate polymers and capable to form a membrane/film.

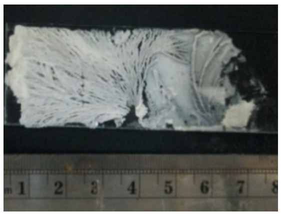
Table 5: The membrane film of polymer (three polymer combination) that contain metformin HCl

No	Polymer	Thickness (mm)	Properties of film
1	Pectin + Alginate + mucillage of ethyl cellulose + Metformin HCl	0.96±0.02	Retrieved membranes/films with a rough surface containing metformin HCl, uneven, and perforated crystals
2	Pectin + Alginate + powder of ethyl cellulose + Metformin HCl	0.71±0.04	Retrieved membranes /films with a smoother and flat surface, elastic, easily rolled and folded
3	Pectin + Alginate + HPMC + Metformin HCl	-	Could not formed films
4	Pectin + HPMC + Ethyl cellulose + Metformin HCl	-	Could not formed films



Pectin + HPMC
+ Metformin HCl

Pectin + Ethylcellulose
+ Metformin HCl



Pectin + Alginate +
Metformin HCl

Figure 3: Polymers of pectin, alginate, HPMC and ethyl cellulose (two polymers combination) can not form film membranes with Metformin HCl

Pectin + Alginate
+ mucillage of Ethyl
cellulose + Metformin HCl

Pectin + Alginate
+ powder of Ethyl cellulose
+MetforminHCl

Pectin + Alginate
+ HPMC + Metformin HCl

Pectin + HPMC
+ Ethylcellulose
+ Metformin HCl

Figure 4: Polymers of pectin, alginate, HPMC and ethyl cellulose (three polymer combination) containing Metformin HCl: only a combination of pectin + alginate and powder of Ethyl cellulose are capable of forming a good film.

4.5 The Membrane/Film Properties of Pectin (three polymer combination) with the Addition of $CaCl_2$ Containing Metformin HCl

Interestingly, the addition of crosslinkers ($CaCl_2$) to a combination of polymers containing metformin HCl is a combination of the polymer pectin, alginate and HPMC in the previous data can not form membrane/film, but the addition of $CaCl_2$ showed different results, it is capable to form a thin films, elastic, easily rolled and folded, as shown in Table 6 and Figure 5. It can be explained that one of the properties of sodium alginate is having the ability to form a gel by addition of a calcium salts and caused by the occurrence of chelating between the L-guluronic of alginate chains with calcium ions. This gel is a cross link network composed of the calcium alginate forming egg box conformation (Morris,, 1978).

5 CONCLUSIONS

A single and combination of the polymers containing metformin hydrochloride could not formed films. The combination of pektin, alginat, and ethylcellulose pectin and the addition of crosslinker ($CaCl_2$) in pectin alginate and HPMC polymer combination capable to form an optimum membrane/film and potential for drug delivery system.

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Table 6: The membrane/film of pectin (three polymer combination) with the addition of $CaCl_2$ containing Metformin HCl

No	Polymer	Thickness (mm)	Properties of film
1	Pectin + Alginate + $CaCl_2$ 1% + metformin HCl	-	Could not formed films
2	Pectin+ Alginate + $CaCl_2$ 2% + metformin HCl	-	Could not formed films
3	Pectin+ Alginate + $CaCl_2$ 3% metformin HC	-	Could not formed films
4	Pectin + Alginate + Ethyl cellulose + CaCl2 1 % Metformin HCl	1.32 ±0.03	Retrieved thin, rigid, non-rolled and folded film membranes.
5	Pectin+Alginate + HPMC+ $CaCl_2$ 1% + Metformin HCl	0.87±0.03	Retrieved thin, elastic, transparent, irregularly shaped, easily rolled or folded film membranes.

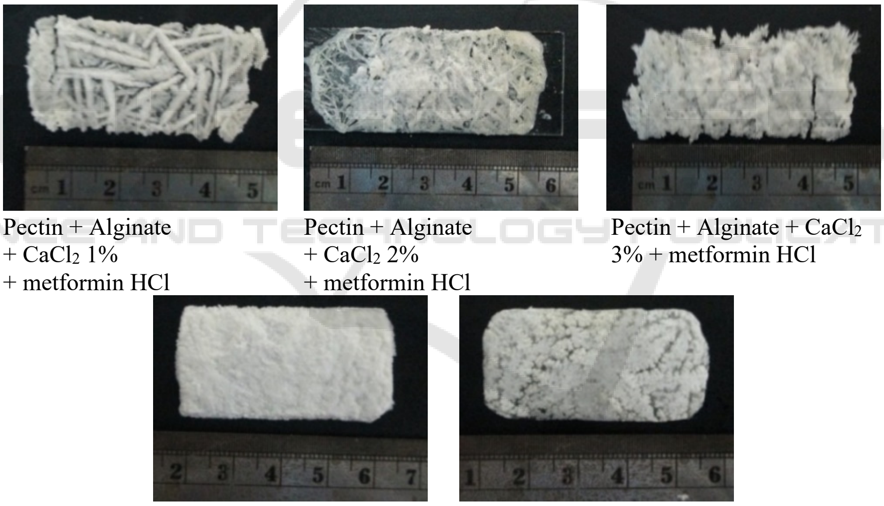

Figure 5: Pectin Membrane Film (three polymers combination) with addition ($CaCl_2$) Containing Metformin HCl: combination of pectin + alginate + powder of Ethyl cellulose and combination of pectin + alginate + HPMC capable to form a film membrane.

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