Thai Journal of Pharmaceutical Sciences (TJPS)

5th International Conference on Pharmaceuticals, Nutraceuticals and Cosmetic Science (IPNaCS 2017)

Effect of Plasticizers on Physicochemical and Mechanical Properties of Hydroxypropyl methylcellulose (HPMC) Film Using Simplex Lattice Mixture Design

Pakorn Kraisit [1*], Sureewan Duangjit[2]

[1] Division of Pharmaceutical sciences, Faculty of Pharmacy, Thammasat University, Pathumthani 12120 Thailand.
[2] Division of Pharmaceutical Chemistry and Technology, Faculty of Pharmaceutical Sciences, Ubon Ratchathani University, Ubon Ratchathani 34190 Thailand.

* Corresponding author: Tel. +66(0)25644444; Fax. +66(0)25643156; E-mail address: pakorn54@tu.ac.th

Keywords: Hydroxypropyl methylcellulose (HPMC), Simplex Lattice Mixture Design, Film, Plasticizer

Introduction

Hydroxypropyl methylcellulose (HPMC) is a cellulose-derived polymer that has been widely used in the preparation of many dosage forms for drug delivery systems because of its flexibility, ease of use, biodegradability, biocompatibility, and excellent film-forming ability.(1) Films are a popular type of dosage form for many routes of drug administration due to their small size, softness, flexibility, and increased patient compliance. In addition, films give more accurate drug dosing when compared with gel, liquid, and ointment dosage forms.(2) However, most cellulose-derived polymers form films that crack and become brittle upon handling and storage.(3) Plasticizers have been extensively used to increase flexibility and reduce brittleness by improving the physical and mechanical properties of films.(3, 4) Polyols such as glycerol and polyethylene glycol (PEG) are generally used as plasticizers during the film-forming process.(5) They can reduce intermolecular forces and improve the mobility of polymer chains leading to increased flexibility and workability of polymer films.(6, 7) Each type of plasticizer has different properties depending on the molecular structure, size, shape, number of oxygen atoms, and ability to bind water.(3) Trial and error methodology has been used by many researchers to investigate the effects of various plasticizer types on the comprehensive characteristics of their films. The traditional method is quite time consuming, unpredictable, expensive and laborious.(1, 8) Design of experiment (DOE) is a type of statistical optimization method used to study large numbers of independent and dependent variables using the fewest number of experiment runs.(9) The DOE method can efficiently resolve problems that arise from traditional methods and provide a method for characterizing formulations and processes.(1) Response surface methodology (RSM) is a favorite method for characterization and optimization of several pharmaceutical researches such as drug delivery optimization, drug dosing etc.(8, 9) RSM is used to analyze variables when interaction effects of variables are complex.(9)

The purpose of this study was to examine the effects of various types of plasticizers (PEG 200, PEG 400, and glycerol) on the physicochemical and mechanical properties of HPMC films using a simplex lattice mixture design approach. The characteristics of HPMC films such as contact angle, surface free energy, dispersive force, polar force, tensile strength, and % elongation were used as the response (dependent variables).

Methods

Preparation of HPMC films

HPMC (K15M) films were prepared using the solvent casting technique.(1) Briefly, HPMC solution (1.0% w/v) was prepared by dissolving HPMC powder in distilled water with constant stirring until a clear solution was obtained. Then, 2 g of a mixture of the studied plasticizers (PEG 200, PEG 400, and glycerol) was added to the HPMC solution at different ratios correlating to each treatment (Table 1) and mixed until the mixture was homogeneous. The mixture solution was poured onto a glass plate and dried at 50°C for 10 h in a hot air oven. Dried films were peeled off and kept in a vacuum desiccator prior to use in experiments.

Experimental Design and Statistical analysis

A simplex lattice mixture design was used to determine the effects of PEG 200 (X_1), PEG 400 (X_2), and glycerol (X_3) mixtures on the physicochemical properties of the HPMC films. The upper and lower limits of percentage of each plasticizer were set as follows:

$$0 \le X_1 \le 100\ (\%) \quad (1)$$
$$0 \le X_2 \le 100\ (\%) \quad (2)$$
$$0 \le X_3 \le 100\ (\%) \quad (3)$$
$$X_1 + X_2 + X_3 = 100\ (\%) \quad (4)$$

Consequently, the components of the plasticizers of HPMC films were studied by changing their amount concurrently, and the total amount of the three components was adjusted to 100%, as described in Equations (1) – (4).

The characteristics of HPMC films such as contact angle (Y_1), surface free energy (Y_2), dispersive force (Y_3), polar force (Y_4), tensile strength (Y_5) and % elongation (Y_6) were used as the response (dependent variables). The responses of all model formulations were evaluated by Design-Expert® Software (version 9; Stat-Ease, Inc., U.S.A.). In total, 14 experiments with 10 ratios of plasticizers (Table 1) were designed by the software and were run in random order. Each experiment was performed in triplicate measurements (n = 3).

Wettability and surface free energy measurements

Contact angle measurements were used to study the wettability of HPMC films by using the sessile drop technique (FTA 1000, First Ten Angstroms, USA). Wu harmonic equation (Equations 5 & 6) was used to calculate the surface free energy, which was determined based on measurements of the contact angle of three distinct standard liquids i.e., distilled water, formamide, and ethylene glycol at 25°C.

$$\gamma_S = \gamma_S^d + \gamma_S^p \quad (5)$$

$$(1+\cos\theta)\gamma_S = [4\left(\frac{\gamma_S^d\,\gamma_L^d}{\gamma_S^d} + \gamma_L^d\right) + 4\left(\frac{\gamma_S^p\,\gamma_L^p}{\gamma_S^p} + \gamma_L^p\right) \quad (6)$$

where γ_S is total surface free energy, γ_S^p , γ_S^d are polar and dispersive forces of the blend films, respectively. γ_L^p, γ_L^d are polar and dispersive forces of standard liquids, respectively. θ is the contact angle between the blend film and the standard liquid.

Mechanical properties

A texture analyzer (TA.XT.plus Texture Analyzer, Stable Micro Systems, UK) was employed to determine the mechanical properties of HPMC films. HPMC films were cut into 3.5 cm $\times$ 0.6 cm rectangles. The blend films were held between two grips stretched at a speed of 0.1 mm/s until the point of tensile failure and force-displacement curves were recorded through a 50 N loaded cell. Maximum force and maximum displacement of the films were measured, and then converted to tensile strength and elongation at breakage. The parameters were calculated using the following equations:

$$\text{Tensile strength} = F/A \quad (7)$$

where F is maximum force for film failure and A is the cross-sectional area of the film.

$$\text{Elongation (\%)} = \frac{\Delta L}{L} \times 100 \quad (8)$$

where ΔL is the increase in the length at breakage of the film and L is the initial film length.

Table 1 A simplex lattice mixture design of plasticizer components in HPMC films

Mixtures	X_1	X_2	X_3	PEG 200 (%)	PEG 400 (%)	Glycerol (%)
1	0	0	2	0	0	100
2	0	0	2	0	0	100
3	0	1	1	0	50	50
4	0	2	0	0	100	0
5	0	2	0	0	100	0
6	0.33	0.33	1.33	16.6	16.6	66.6
7	0.33	1.33	0.33	16.6	66.6	16.6
8	0.66	0.66	0.66	33.3	33.3	33.3
9	1	0	1	50	0	50
10	1	1	0	50	50	0
11	1	1	0	50	50	0
12	1.33	0.33	0.33	66.6	16.6	16.6
13	2	0	0	100	0	0
14	2	0	0	100	0	0

Results and discussion

The response surface of HPMC films demonstrating the effect of different types and amounts of plasticizers on each response factor are shown in Fig. 1. The contact angle of HPMC film ranged from 47.4 to 69.2, as shown in Fig. 1A. The addition of PEG 400 to HPMC films displayed the smallest contact angle, indicating that the wettability of this film was increased compared to HPMC films containing PEG 200 or glycerol. This result could be explained by the potential molecular structure and number of –OH groups displayed on the structure of each plasticizer.[3, 5] The molecular structure of PEG 400 shows considerably increased numbers of –OH groups than PEG 200 and glycerol, exhibiting a more hydrophilic surface on the HPMC film compared to the other plasticizers in the films.[3] Surface free energy and polar force varied from 37.5 to 52.7 mJ/m^2 and 21.2 and 40.5 mJ/m^2, as shown in Fig. 1B and Fig. 1D, respectively. These responses confirmed the effect of PEG 400 on wettability behavior in HPMC films such that increases in PEG 400 led to increases in surface free energy and polar forces of the film, implying that films containing PEG 400 have increased wettability on the surface compared to HPMC films using PEG 200 and glycerol as plasticizers in the films. However, the different types of plasticizers did not significantly affect the dispersive force of HPMC surface films, as shown in Fig. 1C. Tensile strength and % elongation are widely used for determining the mechanical properties of films. They ranged from 4.4 to 13.2 MPa and 79.1 to 101.9, as shown in Fig. 1E and Fig. 1F, respectively. The addition of glycerol in HPMC films resulted in higher tensile strength compared with the other plasticizers, but the results were not statistically significant. Percent elongation of HPMC films using PEG 200 as the plasticizer was increased compared to films containing the other plasticizers. These results correlate with another finding that medium molecular weight plasticizers, containing oxygen atoms that are able to interact with the HPMC matrix, are preferable.[10] It is well known that plasticizers change the functional properties of polymer films by decreasing intermolecular forces and increasing the mobility of polymer chains, leading to increased flexibility and extensibility.[11]

The corresponding residual plot between run number and internally studentized residuals of each response was used to check the reliability of these results, as shown in Fig. 2. In the entirely randomized run, the vertical spread of the internally studentized residuals was in line from bottom-to-top, suggesting that all data points lay within the limits of a 95% confidence interval.[1]

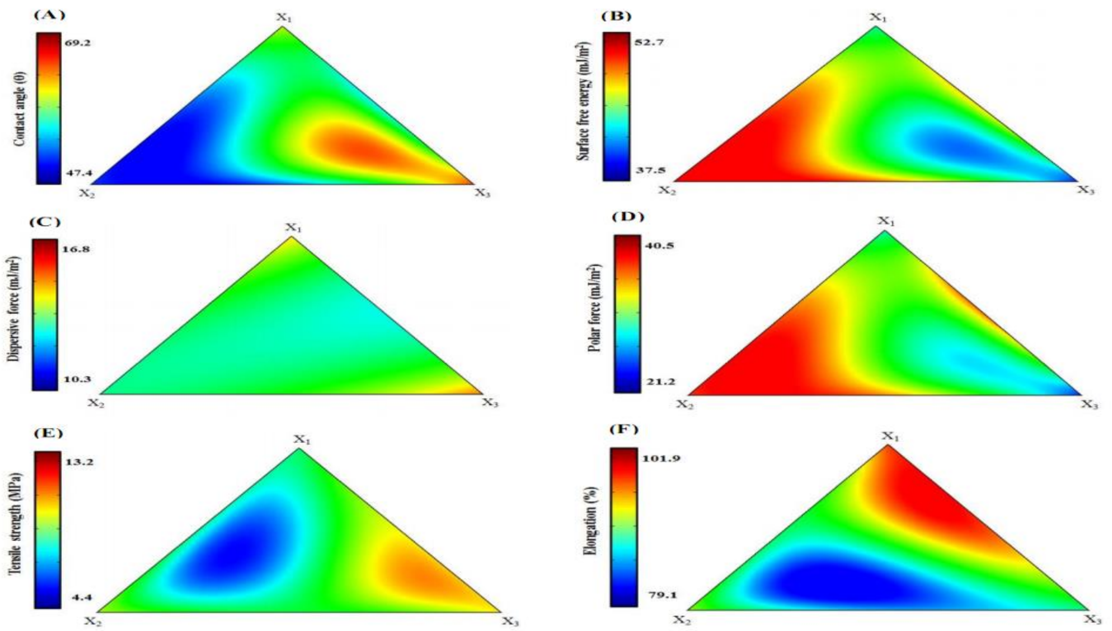

Figure 1 The response surface of HPMC films demonstrating the effect of various amounts and types of plasticizers on contact angle (A), surface free energy (B), dispersive force (C), polar force (D), tensile strength (E) and % elongation (F).

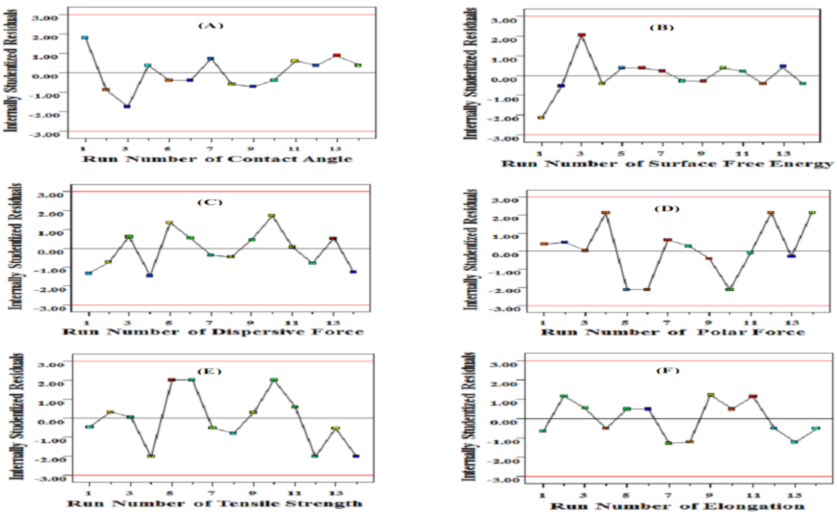

Figure 2 The corresponding residual plot between run number and internally studentized residuals for various responses of contact angle (A), surface free energy (B), dispersive force (C), polar force (D), tensile strength (E) and % elongation (F).

Conclusion

The simplex lattice design is a type of RSM design that is used to investigate the effects of various types of plasticizers on the physicochemical and mechanical properties of HPMC. The addition of PEG 400 to HPMC films showed the smallest contact angle, indicating that the wettability of this film was increased compared with the other films. The response surface of surface free energy and polar force confirmed these results demonstrating that increases in PEG 400 led to increases in film wettability. Percent elongation of HPMC films using PEG 200 as a plasticizer was increased compared with films containing the other plasticizers. This finding could be explained by the molecular weight and number of oxygen atoms on the plasticizer surface that were able to interact with the HPMC matrix. It is well known that plasticizers change the functional properties of polymer films by decreasing intermolecular forces and increasing the mobility of polymer chains, leading to increased flexibility and extensibility. Therefore, data on the effects of different plasticizers on wettability and mechanical properties of HPMC films could be beneficial for further development of polymer films applied for use in many routes of drug administration.

Acknowledgements

The authors sincerely thank the financial support provided by Thammasat University under the TU Research Scholar, Contract No. TP 2/68/2556. In addition, the authors gratefully thank Rama Production Company for kindly giving HPMC samples. Grateful thanks also go to Faculty of Pharmacy, Silpakorn University for supporting facilities and equipment.

References

1. Kraisit P, Limmatvapirat S, Nunthanid J, Sriamornsak P, Luangtana-Anan M. Preparation and Characterization of Hydroxypropyl Methylcellulose/Polycarbophil Mucoadhesive Blend Films Using a Mixture Design Approach. Chemical and Pharmaceutical Bulletin. 2017;65(3):284-94.
2. Giovino C, Ayensu I, Tetteh J, Boateng JS. Development and characterisation of chitosan films impregnated with insulin loaded PEG-b-PLA nanoparticles (NPs): A potential approach for buccal delivery of macromolecules. International Journal of Pharmaceutics. 2012;428(1–2):143-51.
3. Antoniou J, Liu F, Majeed H, Qazi HJ, Zhong F. Physicochemical and thermomechanical characterization of tara gum edible films: Effect of polyols as plasticizers. Carbohydrate Polymers. 2014;111:359-65.
4. Ding C, Zhang M, Li G. Preparation and characterization of collagen/hydroxypropyl methylcellulose (HPMC) blend film. Carbohydrate Polymers. 2015;119:194-201.
5. Bajdik J, Fehér M, Pintye-Hódi K. Effect of plasticizer on surface of free films prepared from aqueous solutions of salts of cationic polymers with different plasticizers. Applied Surface Science. 2007;253(17):7303-8.
6. Jouki M, Khazaei N, Ghasemlou M, HadiNezhad M. Effect of glycerol concentration on edible film production from cress seed carbohydrate gum. Carbohydrate Polymers. 2013;96(1):39-46.
7. Laboulfie F, Hémati M, Lamure A, Diguet S. Effect of the plasticizer on permeability, mechanical resistance and thermal behaviour of composite coating films. Powder Technology. 2013;238:14-9.
8. Sood S, Jain K, Gowthamarajan K. Optimization of curcumin nanoemulsion for intranasal delivery using design of experiment and its toxicity assessment. Colloids and Surfaces B: Biointerfaces. 2014;113:330-7.
9. Rahman Z, Zidan AS, Khan MA. Non-destructive methods of characterization of risperidone solid lipid nanoparticles. European Journal of Pharmaceutics and Biopharmaceutics. 2010;76(1):127-37.
10. Jost V, Langowski H-C. Effect of different plasticisers on the mechanical and barrier properties of extruded cast PHBV films. European Polymer Journal. 2015;68:302-12.
11. Dick M, Costa TMH, Gomaa A, Subirade M, Rios AdO, Flôres SH. Edible film production from chia seed mucilage: Effect of glycerol concentration on its physicochemical and mechanical properties. Carbohydrate Polymers. 2015;130:198-205.