Original Article

Drug Release through PEG-Xanthan Gum-Lactose Matrix Comprising Different Amount of Drug

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ABSTRACT

Objective: The purpose of this study is to investigate the effect of xanthan gum and lactose on the physical and release properties of 25-mg and 75-mg indomethacin tablets containing polyethylene glycol (PEG) prepared by mold technique. **Method:** The physical and drug release characteristics of developed matrix tablet were studied. Least square fitting the experimental dissolution data to the mathematical expressions (power law, first order, Higuchi's and zero order) was carried out. **Results:** Because of the more completion dissolution of drug in PEG matrix, the drug release from the lower-drug loading tablet was faster than the higher-drug loading tablet. An addition of xanthan gum could sustain the drug release whereas an addition of lactose diminished the drug dissolution. From curve fitting, most drug release profiles were primarily as Fickian diffusion. **Conclusion:** Amount of indomethacin played an important role on the drug released from PEG matrix consisting xanthan gum and lactose prepared with fusion and mold technique. Xanthan gum and lactose also affected the physical and release characteristics of these investigated indomethacin tablets.

Keywords: Characterization, drug, release, mold tablet, hydroxypropyl methylcellulose, polyethylene glycol

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Introduction

Hydrophilic polymeric matrix systems are widely used to modulate the controlled release of drug substances because of their versatility, effectiveness, and low production cost. Typically, the drug can be incorporated into the polymer matrix in form of particle or molecular dispersion. While the matrix containing a swellable glassy polymer comes into contact with a solvent, a progressive alteration from the glassy to the rubbery state leads to a swelling process. For matrix system, drug is often released by diffusion, because a sort of receding drug boundary comes to exist within the system.[1] The thickness of this hydrate layer determines the diffusion of the drug molecules through the polymer mass into the dissolution fluid. Available hydrophilic polymers include hydroxypropyl methylcellulose (HPMC), hydroxypropylcellulose (HPC), hydroxyethylcellulose (HEC), xanthan gum, sodium alginate, poly (ethylene oxide) and crosslinked homopolymers and copolymers of acrylic acid.

Practically, pharmaceutical tablet is prepared by compression method. Some special tablet such as, orodispersible tablet, could be prepared by freeze drying. Melt extrusion has been recently reported as the procedure to produce the drug matrix system for enhancing or retarding the drug release. The main excipient employed for this system should be molten at

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elevated temperature and could set up as solid matter at room temperature. Polyethylene glycols (PEGs) are widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral and rectal preparations.[2] Polyethylene glycols can also be used to enhance the aqueous solubility characteristics of poorly water-soluble compounds.[3] Particularly, PEG 4000 or 6000 has been employed as a carrier for increasing the dissolution rate of several poorly water–soluble drugs, such as itraconazole[4], diclofenac[5], prednisolone[6] and rofecoxib[6]. All grades of polyethylene glycol are soluble in water and miscible in all proportions with other polyethylene glycol. PEG has potentially been utilized as matrix component prepared with fusion and mold method.

Indomethacin is non-steroidal anti-inflammatory agent with anti-pyretic and analgesic properties. It is a nonselective inhibitor of cyclooxygenase (COX) 1 and 2, enzymes that participate in prostaglandin synthesis from arachidonic acid. It has been used in the symptomatic management of painful and inflammatory conditions. It is used in musculoskeletal and joint disorders including ankylosing spondylitis, osteoarthritis, rheumatoid arthritis and acute gouty arthritis. Usual initial dose by mouth in musculoskeletal and joint disorder is 25 mg two or three times daily with food. To alleviate night pain and morning stiffness, 100 mg may be administered by mouth, or rectally as a suppository. In acute gouty arthritis a suggested dose is 50 mg three times daily and in dysmenorrheal up to 75 mg daily has been suggested. Indomethacin is practically insoluble in water, soluble 1 in 50 of ethanol, 1 in 30 of chloroform, and 1 in 40 to 45 of ether, and soluble in acetone.[7] Because of its low water solubility, therefore indomethacin is used as a model drug in the study.

Xanthan gum is a heteropolysaccharide with a primary structure consisting of repeated pentasaccharide units formed by two glucose units, two mannose units, and one glucuronic acid unit, in a molar ratio of 2.8:2.0:2.0. Its main chain consists of β-D-glucose units linked at positions 1 and 4. The chemical structure of the main chain is identical to that of cellulose. Trisaccharide side chains contain a D-glucuronic acid unit between two D-mannose units linked at the O-3 position of every other glucose residue in the main chain. Approximately one-half of the terminal D-mannose contains a pyruvic acid residue linked via keto group to the 4 and 6 positions, with an unknown distribution. D-Mannose unit linked to the main chain contains an acetyl group at position O-6. The presence of acetic and pyruvic acids produces an anionic polysaccharide type.[8] Because of its properties in thickening aqueous solutions, as a dispersing agent, and stabilizer of emulsions and suspensions, xanthan gum is used in pharmaceutical formulations, cosmetics, and agricultural products.

The combination of PEG with hydrophilic polymer such as xanthan gum should be used to develop into the system comprising both the drug dissolution enhancement property together with the prolongation of the drug release. The aim of this study was to investigate the effect of xanthan gum and lactose on the physical integrities and release properties of 25-mg and 75-mg indomethacin tablets containing PEG prepared by fusion and mold technique.

Materials and Methods

Materials

Indomethacin (Batch No. 050814, China National Chemical Imp. Exp., China) was used as received. Polyethylene glycol 4000 (lot no. 504907) and polyethylene glycol 400 (lot no. PO76049) were purchased from P.C. Drug Center Co., Ltd., Thailand. Di-sodium hydrogen orthophosphate (lot no. 405300, Ajax Finechem, Australia), hydrochloric acid (lot no. E23W60, J.T. Baker, USA), potassium dihydrogen orthophosphate (lot no. E23W60, Ajax Finechem, Australia), sodium chloride (lot no. AF 407256, Ajax Finechem, Australia), sodium hydroxide (lot no. AF 310204, Ajax Finechem, Australia) were used to prepare the dissolution fluids. Xanthan gum (Xantural 75®) (lot no. 01-100, CP Kelco U.S., Inc. USA.). Lactose (lot no. 080200 A 9249,

Auckland, New Zealand) was passed the 80 mesh sieve before use.

Preparation of Tablet by Mold Technique

Tablets containing 25-mg or 75-mg indomethacin, PEG4000:PEG400 (7:3) and different amount of xanthan gum (0, 5, 10, 15, 20 and 25%w/w) were prepared with the melting and mold technique. The tablet was prepared by melting PEG 4000 on the water bath and mixed with PEG 400, drug and xanthan gum, respectively, and then the mixtures were poured into the stainless steel mold with diameter of 12 mm (Figure 1). The effect of lactose on the physical properties and drug release from matrix tablet was investigated. Tablets of about 0.87 g containing 75-mg of indomethacin, 5% xanthan gum and different amount of lactose (0, 15, 25, 35, 45 and 55%w/w) in 7:3 PEG4000:PEG400 were prepared with the melting and mold technique using the stainless steel mold with diameter of 12 mm. as method described above.

Evaluation of Physical Properties of Prepared Tablet

The hardness of the tablets was determined using a hardness tester (Pharmatest, USA). The tablet thickness and diameter were measured using a thickness tester (Teclock, Japan). A test of drug release was undertaken in 900 mL phosphate buffer pH 6.2 using a dissolution apparatus (Erweka DT 70, Germany) with the basket method at 100 rpm. Samples were collected at specific time intervals and assayed by a UV-Vis spectro-photometer (Perkin-Elmer, Germany) at a wavelength of 323 nm. During the drug release studies, the tablets were observed for physical integrity. Drug release from these tablets was compared to capsule containing only 75-mg indomethacin powder.

Dissolution Profile Fitting

Least square fitting the experimental dissolution data (cumulative drug release > 5% and up to 80%) to the mathematical equations (power law, first order, Higuchi's and zero order) was carried out using a nonlinear computer programme, Scientist for Windows, version 2.1 (MicroMath Scientific Software, Salt Lake City, UT, USA). The coefficient of determination (r^2) was used to indicate the degree of curve fitting. Goodness-of-fit was also evaluated using the Model Selection Criterion (msc)[9], given below.

$$msc = \ln\left\{\frac{\sum_{i=1}^{n} w_i (Y_{obs_i} - \overline{Y}_{obs})^2}{\sum_{i=1}^{n} w_i (Y_{obs_i} - Y_{cal_i})^2}\right\} - \frac{2p}{n}$$

Where Y_{obsi} and Y_{cali} are observed and calculated values of the i-th point, respectively, and w_i is the weight that applies to the i-th point, n is number of points and p is number of parameters.

Results and Discussion

The Physical Properties of Matrix Tablets

The hardness of tablets increased as the amount of xanthan gum or lactose was increased (Tables 1-4). By comparison, the hardness of tablets containing higher amount of indomethacin was higher than that of tablets containing lower amount of indomethacin. All investigated tablets could be easily removed from the stainless steel mold. The yellowish shade of tablets diminished as the amount of xanthan gum or lactose was increased.

Table 1 Physical integrities of 25-mg indomethacin tablet containing 70:30 PEG4000:PEG400 and different amount of xanthan gum.

Amount of xanthan gum (%)	Physical Properties			
	Weight (g)* (n = 20)	Thickness (mm)* (n = 10)	Diameter (mm)* (n = 10)	Hardness (Newton)* (n = 10)
0	0.8621 ± 0.0138	6.81 ± 0.22	11.96 ± 0.04	12.42 ± 1.08
5	0.8620 ± 0.0091	6.73 ± 0.18	12.05 ± 0.06	12.72 ± 0.62
10	0.8639 ± 0.0119	6.72 ± 0.17	12.04 ± 0.02	13.71 ± 1.33
15	0.8689 ± 0.0082	6.75 ± 0.11	12.03 ± 0.03	15.61 ± 0.97
20	0.8730 ± 0.026	6.80 ± 0.13	12.01 ± 0.03	16.03 ± 1.25
25	0.8781 ± 0.0201	6.76 ± 0.12	12.03 ± 0.05	16.92 ± 1.03

* Presented as mean ± S.D.

Table 2 Physical integrities of 75-mg indomethacin tablet containing 70:30 PEG4000:PEG400 and different amount of xanthan gum.

Amount of xanthan gum (%)	Physical Properties			
	Weight (g)* (n = 20)	Thickness (mm)* (n = 10)	Diameter (mm)* (n = 10)	Hardness (Newton)* (n = 10)
0	0.8551 ± 0.0146	6.73 ± 0.21	11.91 ± 0.03	14.62 ± 1.75
5	0.8709 ± 0.0089	6.82 ± 0.22	12.03 ± 0.02	15.22 ± 1.65
10	0.8685 ± 0.0098	6.73 ± 0.22	12.02 ± 0.03	16.68 ± 1.73
15	0.8739 ± 0.0098	6.65 ± 0.21	12.00 ± 0.02	17.64 ± 1.78
20	0.8810 ± 0.0228	6.82 ± 0.19	12.03 ± 0.02	18.43 ± 1.78
25	0.8762 ± 0.0151	6.72 ± 0.19	12.02 ± 0.02	18.95 ± 1.83

Table 3 Physical integrities of 25-mg indomethacin tablets containing 5%w/w xanthan gum and different amount of lactose in 70:30 PEG4000:PEG400.

Amount of lactose (%)	Physical Properties			
	Weight (g)* (n=20)	Thickness (mm)* (n=10)	Diameter (mm)* n=10)	Hardness (Newton)* (n=10)
15	0.8674 ± 0.0203	6.72 ± 0.12	12.03 ± 0.05	18.62 ± 2.19
25	0.8693 ± 0.0112	6.76 ± 0.11	12.02 ± 0.03	23.21 ± 2.31
35	0.8701 ± 0.0187	6.78 ± 0.29	12.04 ± 0.06	30.41 ± 2.16
45	0.8729 ± 0.0093	6.80 ± 0.20	12.02 ± 0.04	34.46 ± 2.02
55	0.8795 ± 0.0209	6.77 ± 0.18	12.02 ± 0.07	41.80 ± 3.66

* Presented as mean ± S.D.

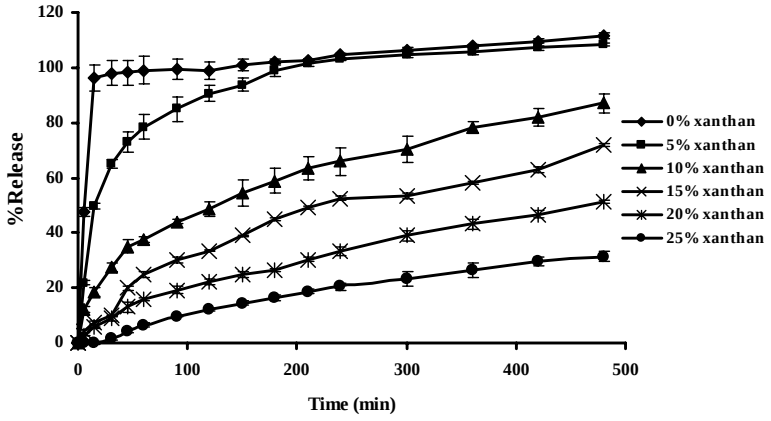
Table 4 Physical integrities of 75-mg indomethacin tablets containing 5%w/w xanthan gum and different amount of lactose in 70:30 PEG4000:PEG400.

Amount of lactose (%)	Physical Properties			
	Weight (g)* (n=20)	Thickness (mm)* (n=10)	Diameter (mm)* (n=10)	Hardness (Newton)* (n=10)
15	0.8834 ± 0.0234	6.78 ± 0.19	12.05 ± 0.02	20.30 ± 4.67
25	0.8789 ± 0.0312	6.82 ± 0.31	12.08 ± 0.02	26.40 ± 5.75
35	0.8704 ± 0.0237	6.75 ± 0.25	12.06 ± 0.02	34.50 ± 3.27
45	0.8756 ± 0.0187	6.82 ± 0.26	12.04 ± 0.02	37.70 ± 2.92
55	0.8821 ± 0.0256	6.79 ± 0.21	12.05 ± 0.02	46.70 ± 3.17

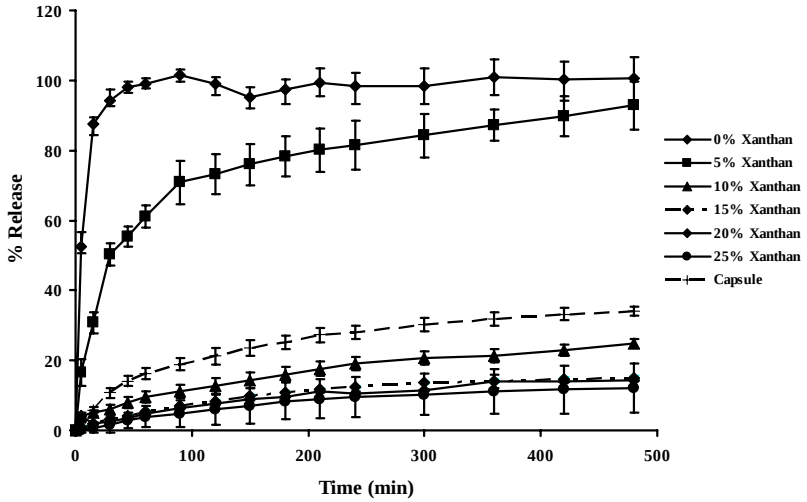
* Presented as mean ± S.D.

In Vitro Drug Release Studies

The dissolution of indomethacin from tablets containing different amounts of xanthan gum is shown in Figure 1. Apparently, the drug release from tablet without an addition of xanthan gum was faster than that containing xanthan gum because the former tablet contained PEG as a carrier for increasing the solubility of indomethacin. Polyethylene glycols (PEGs) are one of the most widely used carriers to prepare solid dispersions due to their low melting point and their ability to provide the hydrophilic environment to enhance the drug solubility.[2] An enhancement of dissolution rate of hydrocortisone and prednisolone has been reported by means of the fusion method, using sorbitol, sucrose, or PEG 6000 as carrier. The carriers were melted at elevated temperature and the drugs were dissolved in molten carriers.[10,11] To confirm this result, drug release form tablet prepared by solid dispersion method was faster than that from capsule containing only indomethacin.



(A)



(B)

Figure Drug release profiles of indomethacin in 25-mg tablet (A) and 75-mg tablet (B) containing different amount of xanthan gum and capsule in phosphate buffer pH 6.2 (n = 3).

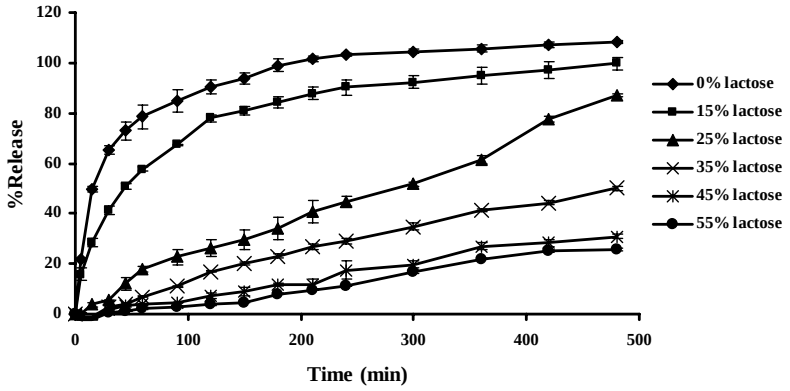
Drug release from tablet containing 5% xanthan gum was faster than that of tablets containing 10%, 15%, 20%, 25% xanthan gum and capsule, respectively. High swelling capacity and gel formation of xanthan gum could retard the release of dissolved drug from the matrix. Relationship between drug release rate and polymer concentration was previously reported by Fu *et al*., (2004).[12] As also described by Ghimire *et al*. (2007)[13], water insoluble drug released from matrix tablets and erosion properties of matrix tablet was found to be dependent upon the polymer concentration; however no direct correlation was found between erosion profile and drug release. Drug release from capsule containing only powder of 75-mg indomethacin was slower than that of all tablets containing xanthan gum because indomethacin powder in capsule is a poorly water-soluble drug (5 µg/mL).[4]

The viscosity of xanthan solutions strongly increases with increasing concentration of the polymer. The behavior is attributable to the intermolecular interaction or entanglement, increasing the effective macromolecule dimensions and molecular weight. The presence of salts in solution influences the xanthan viscosity.[14,15] The drug release from capsule was only about 20% drug release at 8 hours. Therefore, this solid dispersion system could enhance the release of indomethacin when compared with that from 75-mg indomethacin capsule. Xanthan gum played the important role by rapid hydration after contact to dissolution fluid and subsequently to form gel around the tablet and the dissolved drug molecules gradually diffused from the tablet through the developed gel layer into the dissolution fluid. Therefore the dissolved drug molecules inducing with carrier could prolong release by an addition of xanthan gum in the matrix system.[16]

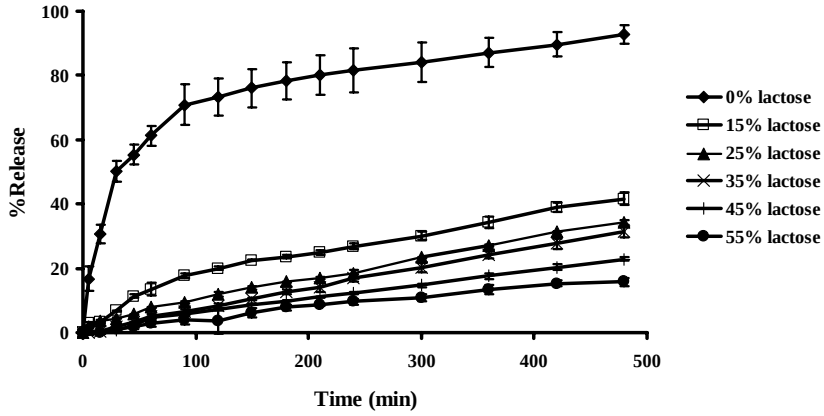
The drug dissolution from tablet containing lower drug loading (25-mg) was faster than that of tablet containing higher drug loading (75-mg) as shown in Figures 1 and 2. This indicated that the more freely soluble drug from the first case owing to its higher amount of carrier to induce the drug dissolution and the dissolved drug could diffuse through the polymeric gel layer according to the concentration gradient more easily than the later system. After addition of different amount of lactose into xanthan gum matrix, the percentage of drug release was lower as presented in Figure 2. The drug release decrement for tablet containing the increment amount of lactose was due to a diminishment of drug carrier amount. Similar result has been mentioned previously for utilization a ram extruder to prepare directly a fast release dosage form of carbamazepine with uniform shape and density, comprising polyethylene glycol 4000 (PEG) as a low melting binder which an addition of lactose in this system reduced the dissolution rate.

Analysis of the drug release data

To analyze the in vitro release data, the curve fitting of drug dissolution profiles to various kinetic models was carried out to describe the release kinetics. Large value of the coefficient of determination (r^2) or model selection criteria (MSC) indicated a superiority of the dissolution profile fitting to mathematical equations. Kinetics of drug release from the developed matrices was analyzed using the power law expression. This equation (an empirical equation) gained popularity for analysis of release data.[17] The n value from power law is the diffusional exponent which characterizes the transport mechanism of the drug. The transport mechanisms are classified based on the value that n assumes. For a cylinder, the drug transport mechanism is by Fickian diffusion when n = 0.45. If $0.45 < n < 0.89$, it indicates anomalous (non-Fickian) transport. For values of n = 0.89, case II or zero order release kinetics is indicated. Case II relates to polymer relaxation, while non-Fickian release is described by two mechanisms; the coupling of drug diffusion and polymer relaxation.[17,18]



(A)



(B)

Figure 2 Drug release profiles of indomethacin in 25-mg tablet (A) and 75-mg tablet (B) containing 5% xanthan gum and different amount of lactose in phosphate buffer pH 6.2 (n = 3).

The r^2 from curve fitting to power law equation was in a range of 0.9771 to 0.9989 and msc was in a range of 2.78 to 6.23 (Tables 5, 7, 9 and 11). From curve fitting, the most of drug release from 25-mg and 75-mg indomethacin tablets containing different amount of xanthan gum were fitted well with Higuchi's model since r^2 and msc from their curve fitting were higher than first-order model and zero order curve fitting. The n value of the most release profile fitting was also close to 0.45 which indicated the Fickian drug release behavior (Table 6, 8, 10, 12). Near zero-order release was achieved for the drug release from 75-mg indomethacin tablets containing high amount of lactose (Table 12) hence they exhibited a Case-II transport.[19] These results were in agreement with the ones published that established correlation among the swelling, erosion and drug release in hydrophilic matrices elaborated from natural gums as xanthan, karaia and locust bean gum.[20] However, it could not specify the tendency of release kinetic of drug release from tablets containing 25-mg indomethacin tablet containing lactose. This different release mechanism might be due to the limitation of drug

solubilization in different amount of carrier as mentioned previously. ND means "not determined" for cumulative drug release which was less than 5% or more than 90% and that data points were not substantial enough to be determined by curve fitting. Practically, all the kinetic models, other than the zero order, fitted well at early time periods. Therefore, modeling analysis was carried out by fitting the dissolution data until the time 90% of the drug released.

Table 5 Comparison of degree of goodness-of-fit from curve fitting of drug dissolution from 25-mg indomethacin tablet containing different amount of xanthan gum in 70:30 PEG4000:PEG400 system in phosphate buffer pH 6.2 to different release models.

Amount of xanthan gum (%)	Power law		First order		Higuchi's		Zero order	
	r^2	msc	r^2	msc	r^2	msc	r^2	msc
0	ND	ND	ND	ND	ND	ND	ND	ND
5	ND	ND	ND	ND	ND	ND	ND	ND
10	0.9965	5.18	0.9774	3.48	0.9857	3.94	0.9163	2.17
15	0.9898	4.04	0.9570	2.78	0.9772	3.42	0.9060	2.00
20	0.9973	5.45	0.9956	5.11	0.9904	4.34	0.9845	3.86
25	0.9974	5.32	0.9921	4.44	0.9953	4.95	0.9857	3.85

ND = not determined.

Table 6 Estimate parameter from curve fitting of drug dissolution from 25-mg indomethacin tablet containing different amount of xanthan gum in 70:30 PEG4000:PEG400 system in phosphate buffer pH 6.2 to power law expression.

Amount of xanthan gum (%)	k ± sd*10^{-1}	tl ± sd (min)	n ± sd
0	ND	ND	ND
5	ND	ND	ND
10	0.7053 ± 0.0525	1.78 ± 1.15	0.41 ± 0.01
15	0.6058 ± 0.0085	26.28 ± 2.18	0.39 ± 0.03
20	0.1040 ± 0.0202	-7.38 ± 7.53	0.63 ± 0.03
25	0.0895 ± 0.0236	27.65 ± 12.97	0.58 ± 0.04

ND = not determined.

Table 7 Comparison of degree of goodness-of-fit from curve fitting of drug dissolution from 75-mg indomethacin tablet containing different amount of xanthan gum in 70:30 PEG4000:PEG400 system in phosphate buffer pH 6.2 to different release models.

Amount of xanthan gum (%)	Power law		First order		Higuchi's		Zero order	
	r^2	msc	r^2	msc	r^2	msc	r^2	msc
0	ND	ND	ND	ND	ND	ND	ND	ND
5	0.9985	5.95	0.8996	1.90	0.8560	1.54	0.7572	1.02
10	0.9944	4.73	0.9519	2.73	0.9896	4.26	0.9391	2.49
15	0.9816	3.45	0.8806	1.76	0.9449	2.54	0.8762	1.73
20	0.9955	5.46	0.8987	1.85	0.9597	2.81	0.9276	2.23
25	0.9913	4.98	0.8935	1.80	0.9562	2.68	0.9166	2.04

ND = not determined.

Table 8 Estimate parameter from curve fitting of drug dissolution from 75-mg indomethacin tablet containing different amount of xanthan gum in 70:30 PEG4000:PEG400 system in phosphate buffer pH 6.2 to power law expression.

Amount of xanthan gum (%)	k ± sd*10^{-1}	tl ± sd (min)	n ± sd
0	ND	ND	ND
5	0.0098 ± 0.0011	64.39 ± 4.23	0.51 ± 0.02
10	0.0187 ± 0.0025	14.64 ± 4.70	0.42 ± 0.02
15	0.0225 ± 0.0041	46.32 ± 7.05	0.32 ± 0.03
20	0.0238 ± 0.0072	28.21 ± 9.38	0.43 ± 0.05
25	0.0162 ± 0.0091	15.94 ± 62.13	0.44 ± 0.11

ND = not determined.

Table 9 Comparison of degree of goodness-of-fit from curve fitting of drug dissolution from 25-mg indomethacin tablet, 5% xanthan gum containing different amount of lactose in 70:30 PEG4000:PEG400 system in phosphate buffer pH 6.2 to different release models.

Amount of lactose (%)	Power law		First order		Higuchi's		Zero order	
	r^2	msc	r^2	msc	r^2	msc	r^2	msc
0	0.9977	5.07	0.9475	2.28	0.8922	1.56	0.7878	0.88
15	0.9964	4.88	0.9903	4.13	0.9869	3.84	0.9172	1.99
25	0.9892	3.98	0.9559	2.76	0.9289	2.28	0.9877	4.03
35	0.9974	5.34	0.9959	5.11	0.9901	4.21	0.9872	3.96
45	0.9771	2.92	0.9738	3.07	0.9751	3.12	0.9671	2.84
55	0.9772	2.78	0.9655	2.70	0.9771	3.11	0.9558	2.45

Table 10 Estimate parameter from curve fitting of drug dissolution from 25-mg indomethacin tablet, 5% xanthan gum containing different amount of lactose in 70:30 PEG4000:PEG400 system in phosphate buffer pH 6.2 to power law expression.

Amount of lactose (%)	k ± sd*10^{-1}	tl ± sd (min)	n ± sd
0	2.9082 ± 0.1673	4.68 ± 0.13	0.24 ± 0.01
15	1.0766 ± 0.1071	2.52 ± 0.92	0.41 ± 0.02
25	0.0032 ± 0.0057	-96.17 ± 63.62	1.24 ± 0.26
35	1.0314 ± 0.0256	45.85 ± 9.91	0.64 ± 0.04
45	0.0982 ± 0.1209	116.40 ± 52.77	0.59 ± 0.20
55	0.1370 ± 0.1402	170.58 ± 36.35	0.52 ± 0.17

Table 11 Comparison of degree of goodness-of-fit from curve fitting of drug dissolution from 75-mg indomethacin tablet, 5% xanthan gum containing different amount of lactose in 70:30 PEG4000:PEG400 system in phosphate buffer pH 6.2 to different release models.

Amount of lactose (%)	Power law		First order		Higuchi's		Zero order	
	r^2	msc	r^2	msc	r^2	msc	r^2	msc
0	0.9985	3.10	0.8996	1.90	0.8560	1.54	0.7572	1.02
15	0.9898	4.13	0.9577	3.10	0.9597	3.26	0.9667	3.10
25	0.9969	5.27	0.9956	5.12	0.9549	2.77	0.9965	5.33
35	0.9989	6.23	0.9976	5.65	0.9301	2.30	0.9988	6.37
45	0.9959	5.27	0.9981	5.87	0.9641	2.93	0.9991	6.64
55	0.9897	3.83	0.9030	1.83	0.9886	3.97	0.9890	4.52

Table 12 Estimate parameter from curve fitting of drug dissolution from 75-mg indomethacin tablet, 5% xanthan gum containing different amount of lactose in 70:30 PEG4000:PEG400 system in phosphate buffer pH 6.2 to power law expression.

Amount of lactose (%)	k ± sd*10^{-1}	tl ± sd (min)	n ± sd
0	0.0098 ± 0.0011	64.39 ± 4.23	0.51 ± 0.02
15	0.0167 ± 0.0042	9.22 ± 8.78	0.52 ± 0.04
25	0.0011 ± 0.0005	-37.21 ± 18.46	0.92 ± 0.07
35	0.0008 ± 0.0002	-8.46 ± 10.99	0.97 ± 0.05
45	0.0032 ± 0.0012	55.32 ± 10.12	0.91 ± 0.05
55	0.0050 ± 0.0038	70.33 ± 39.05	0.58 ± 0.12

Conclusion

The fusion and mold technique was used to develop the indomethacin tablet in PEG matrix. Amount of poorly water-soluble drug such as, indomethacin, played an important role on the drug released from PEG matrix containing xanthan gum and lactose. Because of the more completion dissolution of drug in PEG matrix, the drug release from the lower-drug loading tablet was faster than the higher-drug loading tablet. An addition of xanthan gum could sustain the drug release whereas an addition of lactose diminished the drug dissolution.

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References

1. Conti S, Magia L, Segalea L. *et al*. Matrices containing NaCMC and HPMC 1. Dissolution performance characterization. *Int J Pharm* 2007;333:136-142.
2. Trapani G, Franco M, Latrofa A. *et al*. Physicochemical characterization and *in vivo* properties of Zolpidem in solid dispersions with polyethylene glycol 4000 and 6000. *Int J Pharm* 1999;184:121-130.
3. Urbanetz NA. Stabilization of solid dispersions of nimodipine and polyethylene glycol 2000. *Eur J Pharm Sci* 2006;28:67-76.
4. Wang X, Armasa HN, Blaton H *et al*. Phase characterization of indomethacin in binary solid

dispersions with PVP VA64 or Myrj 52. *Int J Pharm* 2007;123:163-169.

5. Fini A, Moyano JR, Gines JM, Perez-Martinez JI, Rabasco AM. Diclofenac salts, II: solid dispersions in PEG6000 and Gelucire 50/13. *Eur J Pharm Biopharm* 2005;60:99-111.
6. Leonardi D, Barrera MG, Lamas MC, Salomon CJ. Development of prednisolone: polyethylene glycol 6000 fast-release tablets from solid dispersions: solid-state characterization, dissolution behavior, and formulation parameters. *AAPS PharmSciTech* 2007;8(4) Article 108 (http://www.aapspharmscitech.org).
7. Ahuja N, Katare OP, Singh B. Studies on dissolution enhancement and mathematical modeling of drug release of a poorly water-soluble drug using water-soluble carriers. *Eur J Pharm Biopharm* 2007;65:26-38.
8. Kennedy JF, Bradshaw IJ. Production, properties and applications of xanthan. *Program Industrial Microbiol* 1984;19:319-371.
9. MicroMath *Scientist Handbook Rev.* 7EEF, MicroMath, Salt Lake City, 1995: pp.467.10.
10. Allen LV, Levinson RS, Martono DD. Dissolution rates of hydrocortisone and prednisolone utilizing sugar solid dispersion systems in tablet form. *J Pharm Sci* 1978;67:979-981.
11. Zerrouk N, Chemtob C, Arnaud P. *et al*. *In vitro* and *in vivo* evaluation of carbamazepine-PEG 6000 solid dispersions. *Int J Pharm* 2001;225:49-62.
12. Fu XC, Wang GP, Liang WQ, Chow MS. Prediction of drug release from HPMC matrices: effect of physicochemical properties of drug and polymer concentration. *J Control Rel* 2004;95:209-216.
13. Ghimire M, McInnes F, Mullen A, Stevens H. *In-vitro* erosion and dissolution of HPMC tablet containing indomethacin. *The AAPS J* 2007;9:54.
14. Kang KS, Pettit DJ. Xanthan, gellan, wellan, and rhamsan. In: Whistler RL, BeMiller JN, (eds). *Industrial gums,* New York, Academic Press, 1993. pp. 341-398.
15. Smith JH, Pace GW. Recovery of microbial polysaccharides. *J Chem Tech Biotech 1982;*32:119-129.
16. Perissutti B, Newton JM, Podczeck F. *et al*. Preparation of extruded carbamazepine and PEG 4000 as a potential rapid release dosage form. *Eur J Pharm Biopharm* 2002;53:125–132.
17. Talukdar MM, Van den Mooter G, Augustijns P, Tjandra-Maga T. *In vivo* evaluation of xanthan gum as a potential excipient for oral controlled-release matrix tablet formulation. *Int J Pharm* 1998;169:105-113.
18. Durig T, Fassihi R. Guar-based monolithic matrix systems: effect of ionizable and non-ionizable substances and excipients on gel dynamics and release kinetics. *J Control Rel* 2002;80:45-56.
19. Vendruscolo CW, Andreazza IF, Ganter JL, Ferrero C. Xanthan and galactomannan (from *M. scabrella*) matrix tablets for oral controlled delivery of theophylline. *Int J Pharm* 2005;296:1-11.
20. Sujja-areevath J, Munday DL, Cox PJ, Khan KA. Relationship between swelling, erosion and drug release in hydrophillic natural gum mini-matrix formulations. *Eur J Pharm Sci* 1998;6(3):207-217.