Innovare Academic Sciences

International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 6, Issue 9, 2014

Original Article

MODEL AND RELEASE PATTERN OF WATER SOLUBLE DRUG FROM NATURAL-POLYMER BASED SUSTAINED RELEASE TABLET DOSAGE FORM

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Received: 11 Jul 2014 Revised and Accepted: 16 Aug 2014

ABSTRACT

Objective: The aim of this research was to investigate and evaluate the drug release characteristics (models and drug release profiles) using natural polymers (pectin, carrageenan and glucomannan) in water soluble drug of sustained release tablet.

Methods: Captopril was used as drug model. Tablet were prepared using wet granulation method. Pectin, carrageenan and glucomannan were used as matrix with various concentration. Physical properties inspections were conducted on granules and tablets. Dissolution test using apparatus II USP model with 50 rpm of speed rotation, 900 ml of HCl 0.1N as medium. The results were analyzed statistically by MANOVA, dependent model and independent model.

Results: The results showed that enhancement of matrix concentrations decreased the fluidity and compact-ability. Drug release of soluble drug using pectin as matrix had not significant different than without matrix.

Conclusion: Tablet using glucomannan and carrageenan as matrix controlled the drug release with initial burst release effect. Weibull models was the best fitting model of release kinetics with the highest coefficient of determination and similarity between predicted and observed data and the release mechanisms were controlled by anomalous transport.

Keywords: Pectin, Carrageenan, Glucomannan, Drug release.

INTRODUCTION

Hydrophilic natural polymer matrix systems are widely used in oral controlled drug delivery because of their flexibility to obtain a desirable drug release profile, cost-effectiveness and broad regulatory acceptance. The ability of the hydrophilic polymer matrices to release an entrapped drug in aqueous medium and to regulate the release of such drug by control of swelling and cross-linking makes them particularly suitable for controlled release applications [1]. Recently many controlled release formulations based on hydrophilic and natural polymer matrices have been developed [2].

Carrageenan is a family of sulfated polysaccharides extracted from red marine algae and that are widely utilized. These polysaccharides are linier polymers consisting of chains of (1→3)-linked β-D-galactose and (1→4)-linked α-D-galactose units which are variously substituted and modified to the 3,6-anhydro derivate, depending on the source and extraction condition [3]. Pharmaceutical applications, carrageenan was used as excipient in emulsions, gels, creams, lotions, eye drops, suppositories, tablets and capsules [4].

Pectin are hydrophilic polysaccharides derived from plant cell walls. They content linier of (1→4) linked α-D-galacturonic acid residue. This uronic acid have carboxyl group, some of which are naturally presented as methyl esters [5]. Pectin gelation characteristics depend of methoxy group. Gelation of high methoxy pectin usually occurs at pH <3.5 and low-methoxy of pectin is gelled with calcium ions [6]. Glucomannan is polysaccharide with high molecular weight consist of D-mannose and D-glucose, can produce firm gel upon contact with water. The firm gel of konjac glucomannan as a potential to control the drug release [7].

Hence, the aim of this research was to investigate and evaluate the drug release characteristics of a captopril sustained release tablet formulation as model drug with high water soluble drug using natural polymer matrices such as carrageenan, pectin and glucomannan.

MATERIALS AND METHODS

Materials

Captopril was purchased from Afine Chemicals Limited (Hangzhou, China), pectin (Cargill, Germany) and magnesium stearate (Peter Greven, Germany) were purchased from Bratachem Chemical (Surakarta, Indonesia), carragenan was purchased from Bogor Agricultural Institute (Bogor, Indonesia), glucomannan was extracted from *Amorphophallus muelleri* (Indonesia), all other chemicals were of pharmaceutical grade. Hydrochloric acid was purcashed from Merck (Darmstadt, Germany) was of analytical grade and demineralized water.

Methods

Tablet formulation

Captopril a water-soluble drug was used as drug model. A 20% (50 mg) captopril was used of each tablet, using 1% magnesium stearate as lubricant and lactose as filler to adjust the weight of tablets (250 mg). Amount of matrices were added according to Table 1.

Table 1: Composition of formula

Matrices	Formulas									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Pectin	-	50	100	150	-	-	-	-	-	-
Carrageenan	-	-	-	-	50	100	150	-	-	-
Glucomannan	-	-	-	-	-	-	-	50	100	150

Preparation of captopril tablet

Tablets were formulated according to Table 1. Wet granulation method was employed for formulation. All of the components in formula except lubricant (1% magnesium stearate) were mixed in the mixer for 16 minutes 25 rpm followed by addition demineralized water to the blend until elastic mass of wet granules was achieved. Mass of wet granules were passed through 16 mesh sieve. Wet granules were dried in oven at temperature 40°C for 6 hours. The dried granules were passed through 18 mesh sieve and" within were and mixed with magnesium stearate in mixer for 4 minutes 25 rpm. The granules were characterized by particle size distribution test with analytical sieving, moisture content, bulk density and tapped density. The mass of tablets were characterized by fluidity and compact-ability, the compact-ability was conducted with the deepness of upper punch of 5.3 mm and the lower punch of 8.15 mm.

The tablet compression process used single punch tablet machine model TDP-1 Shanghai, China. The weight of tablets were arranged 250 mg and the hardness were controlled 10-12 kg and were tested using Gouming YD-1 hardness tester.

Drug release

The drug releases were determined using Electrolab TDT-08L dissolution tester type apparatus II (paddle method), 900 ml of HCl 0.1N as dissolution medium maintained at 37±0.5°C at 50 rpm for 6 hours. Aliquots of 10 ml were withdrawn at 15, 30, 45, 60, 90, 120, 180, 240, 300 and 360 minutes with replacement of 10 ml of the fresh media. All the samples were analyzed directly at 202.4 nm (λ_{max} of captopril) using an UV-Vis Hitachi U-2900 spectro photometer.

Drug release kinetics

Drug release kinetics is assumed to reflect different release mechanism of controlled release matrix system.

Therefore six kinetic models were applied to analyze the drug release data to find the best fitting equation. These models are zero-order release, first-order release, Hixson-Crowell, Weibull, Higuchi release and Korsmeyer-Peppas. The release mechanism based on the exponential diffusion value (*n*) of Korsmeyer-Peppas equation. The best fitting equation based on coefficient of determination (R^2), AIC (Akaike's Information Criterion) and RMSE (root mean square error).

Statistical analysis

The drug release (dissolution efficiency 360 minutes (DE_{360}), cumulative drug release at 60 minutes (Q_{60}) and mean dissolution time (MDT)) were analyzed statistically by MANOVA level of 95% ($p = 0.05$), if significant different followed by t-LSD test. The drug releases were computed by free open source software KinetDS® [8].

RESULTS AND DISCUSSION

Physical properties of mass tablet was shown in Table 2. Granules using pectin and carrageenan showed that enhancement of matrix concentrations increased the fluidity. Granules using glucomannan as matrix, enhancement of matrix concentration reduced fluidity, the fluidity was shown by flow time and angle of repose. Enhancement of matrix concentrations reduced the compact-ability. The fluidity was directly affected by moisture content, bulk density and tapped density. Decreasing the compact-ability were affected of elastic deformation of the matrices. Free flowing of granules not less than 10 second for 100 gram granules [9]. The particle distribution size was shown by the amount of fines in each formula less than 10% and the particle size normally distributed. Good flow-ability will produce uniform dosage form with constant filling granules in the compression room. Compact-ability was shown by the tablet hardness after compaction, higher of compact-ability the mass of tablet will easily be compressed and formed compact mass with low pressure.

Table 2: Physical properties of granules (mean ± SD)

Formulas	Bulk density (g/ml)	Tapped density (g/ml)	Moisture content (%)	Flow time (second)	Compact-ability (kg)	Angle of repose (°)
F1	0.629±0.01	0.731±0.01	0.50±0.00	5.08±0.38	1.28±0.16	24.90±0.81
F2	0.624±0.01	0.714±0.00	2.33±0.29	5.24±0.50	3.71±0.28	23.10±1.22
F3	0.655±0.01	0.744±0.01	3.16±0.29	4.26±0.48	2.73±0.30	23.02±1.45
F4	0.560±0.01	0.653±0.01	3.33±0.29	4.96±0.34	1.58±0.13	25.61±0.47
F5	0.482±0.00	0.537±0.01	3.63±0.32	6.24±0.13	1.38±0.34	27.56±0.35
F6	0.476±0.00	0.548±0.00	4.47±0.06	6.60±0.23	1.21±0.41	28.44±0.92
F7	0.533±0.00	0.600±0.01	5.30±0.26	5.76±0.17	0.96±0.04	27.97±0.86
F8	0.514±0.01	0.615±0.01	1.60±0.61	5.50±0.28	4.40±0.90	25.72±0.44
F9	0.500±0.00	0.566±0.01	1.87±0.81	6.27±0.22	2.22±0.43	27.03±0.75
F10	0.500±0.00	0.590±0.00	2.97±0.95	6.91±0.19	1.47±0.17	29.50±1.15

Table 3: Physical properties of captopril tablets (mean ± SD)

Formulas	Hardness (kg)	Drug content (%)	DE_{360} (%)	MDT (minutes)	Q_{60} (%)
F1	4.52±0.28	96.29±2.85	90.64±3.42	16.99±1.48	89.77±6.37
F2	12.17±0.79	102.83±4.22	84.00±2.18	54.59±4.15	75.26±3.60
F3	11.12±1.06	99.91±5.37	86.08±1.44	43.32±8.86	82.50±2.97
F4	10.14±0.61	97.28±4.09	87.53±2.96	43.27±7.89	83.79±6.00
F5	10.74±0.42	111.71±1.68	55.68±2.34	123.95±3.61	34.59±0.34
F6	10.48±0.79	110.18±2.04	57.60±2.00	117.30±3.00	34.31±0.35
F7	10.86±0.98	107.68±2.55	60.03±0.81	110.41±9.39	43.79±2.72
F8	12.08±0.64	105.27±3.02	63.14±3.79	84.85±4.55	37.09±0.83
F9	10.54±0.67	101.99±3.72	73.40±1.81	63.53±12.01	55.21±8.63
F10	9.28±0.50	99.57±2.68	79.22±3.94	44.43±3.06	74.92±3.69

Uniformity of dosage form was determined by the drug content of captopril tablets. Uniformity of dosage form as required in Indonesian Pharmacopeia IV, otherwise the drug content not less than 85% and not more than 115% with the relative standard deviation not more than 6% [10].

The controlled hardness of tablet was expected the hardness not affected the drug release from dosage form.

Fig. 1 showed that the drug release from natural polymers based sustained release captopril tablets. Drug release using pectin,

carrageenan and glucomannan as matrices, enhancement of matrix concentrations increased drug release was shown by DE_{360}, decreasing MDT and increasing Q_{60}.

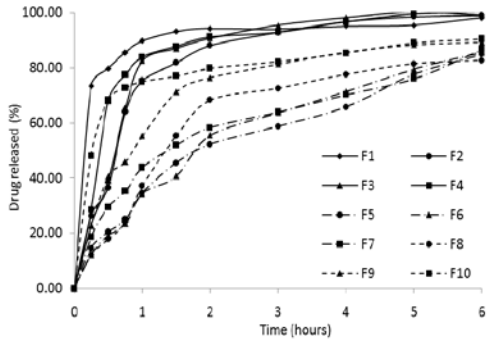

Fig. 1: Drug release of captopril natural-polymers based sustained release tablet

Different concentrations ($p<0.05$) and different matrices ($p<0.05$) provided the different of DE_{360}, MDT and Q_{60}. Formula using pectin as matrix not significant different than the tablet without matrix ($p>0.05$) in DE_{360}, MDT and Q_{60}. Captopril as water soluble drug, low compact-ability of pectin affected the interparticle bonding, thus the particle disintegration rapidly upon contact with medium and matrix act as gel forming layer with water-uptake pass through the porous of tablet, and the amount of absorbed water increased with enhancement of matrix concentrations. Enhancement of matrix concentration increased the swelling ability then followed by erosion and the drug released from matrix. Lactose acted as channeling agent and form porous matrix thus increasing the drug release rate [11]. Previous work showed that glucomannan controlled the slightly soluble drug (metronidazole) slowly for 12 hours [12].

Desirable drug release profiles indicating the drug release lower than drug release tablet without matrix with lower DE_{360} and Q_{60}, and longer mean dissolution time (MDT) than tablet without matrix. Tablet using carrageenan and glucomannan showed the slower release than tablet without matrix.

Table 4: Models and kinetics release captopril natural polymer based sustained release tablet

Model	Statistics	F5	F6	F7	F8	F9	F10
Zero-order	R^2	0.943	0.929	0.907	0.796	0.746	0.677
	RMSE	5.50	6.65	6.28	11.87	11.06	6.64
	AIC	61.13	64.92	63.79	76.50	75.10	64.89
First-order	R^2	0.803	0.780	0.756	0.665	0.612	0.578
	RMSE	10.83	13.84	9.63	19.47	14.31	7.03
	AIC	74.67	79.59	72.33	86.40	80.24	66.03
Higuchi	R^2	0.978	0.945	0.929	0.877	0.653	0.534
	RMSE	3.39	5.79	5.50	9.23	12.95	29.41
	AIC	51.47	62.16	61.12	71.15	78.25	94.65
Hixson-Crowell	R^2	0.859	0.840	0.814	0.714	0.661	0.611
	RMSE	8.30	10.36	8.11	15.64	12.81	6.87
	AIC	69.36	73.79	68.89	82.02	78.04	65.57
Weibull	R^2	0.986	0.992	0.987	0.961	0.972	0.931
	β	0.786	0.872	0.641	0.868	0.681	0.343
	RMSE	2.61	2.01	2.32	5.36	3.23	3.20
	AIC	46.19	40.96	43.90	60.62	50.47	50.29
Korsmeyer-Peppas	R^2	0.985	0.983	0.976	0.934	0.913	0.847
	n	0.563	0.628	0.451	0.649	0.406	0.393
	RMSE	2.66	3.45	2.76	8.14	6.38	4.06
	AIC	46.61	51.77	47.33	68.95	64.07	55.03

k = drug release constant rate, β = shape parameter of Weibull equation.

Some kinetic release models were applied to describe the drug release from tablet were zero-order release, first-order release, Higuchi model's, Weibull model's, Hixson-Crowell equation and Korsmeyer-Peppas equation. Mechanism of drug release based on the exponential diffusion coefficient of Korsmeyer-Peppas equation, fick diffusion (n = 0.45), anomalous transport ($0.45<n<0.89$), case II transport (n = 0.89) and *super case II transport* (n>0.89) [13].

Mechanism of captopril release from tablet was controlled by anomalous transport showed by exponential diffusion value within 0.45 to 0.89. F7 and F9 the drug release were controlled by fick diffusion with initial burst release [14]. The kinetic release to describe the drug release based on the goodness of fit there are the highest of determination coefficient, the lowest of RMSE and the lowest of AIC, the selected model have similarity between observed and predicted model [15].

Weibull model was the best fitting to describe kinetic releases. The model has function between log-log from plot time with –ln fraction of cumulative drug left. Based on β of Weibull model's (β<1) indicating that the initial burst release with higher slope in the initial time followed drug release exponentially [16]. Initial burst release effect indicating the high soluble of drug with the matrix uncontrolled drug release in the initial time [17].

CONCLUSION

Natural polymer-based matrix tablets of water soluble drug (captopril) were prepared using pectin, carrageenan and glucomannan. Formulas with glucomannan and carrageenan as matrix controlled the drug release with initial burst release effect.

CONFLICT OF INTERESTS

Declared None

ACKNOWLEDGMENT

The research was supported by *Hibah Madya Desentralisasi DIKTI* 2013 from The Ministry of Education Council Republic of Indonesia.

REFERENCES

1. Nokhodchi A, Raja S, Patel P, Asare-Addo K. The role of oral controlled release matrix tablets in drug delivery system. J BioImpacts 2012;2(4):175-87.
2. Shah SNH, Asghar S, Choudhry MA, Akash MSH, Rehman N, Baksh S. Formulation and evaluation of natural gum-based sustained release matrix tablet of flurbiprofen using response surface methodology. J Drug Dev and Ind Pharm 2009;35(12):1470-8.

3. Jana S, Gandhi A, Sen KK, Basu SK. Natural polymer and their application in drug delivery and biomedical field. J Pharm Sci Tech 2011;1(1):16-27.
4. Singh KK. Carragenan. In: Rowe RC, Sheskey PJ, Quinn ME, editors. Handbooks of Pharmaceutical Exipients. London: Pharmaceutical Press; 2009. p. 122.
5. Sungthongjeen S, Srimornsak P, Pitaksuteepong T, Somsiri A. Effect of degree of esterification of pectin and calcium amount on drug release from pectin-based matrix tablets. AAPS Pharm Sci Tech 2004;5(1):1-8.
6. Cook W, Quinn ME, Sheskey PJ. Pectin. In: Rowe RC, Sheskey PJ, Quinn ME, editors. Handbooks of Pharmaceutical Exipients. London: Pharmaceutical Press; 2009. p. 478.
7. Wang K, Fan J, Liu Y, He Z. Konjac glucomannan and xanthan gum as compression coat for colonic drug delivery: experimental and theoretical evaluations. J Front Chem Eng China 2010;4(1):102-8.
8. Mendyk A, Jachowicz R, Fijorek K, Dorozynski P, Kulinowski P, Polak S. KinetDS: an open source software for dissolution test data analysis. J Dissolution Technology 2012;19(1):6-11.
9. Fudholi A. Methodology Formulation in Direct Compression. J Medika 1983;7(9):586-93.
10. Indonesian Pharmacopoeia. The Indonesian Pharmacopoeia Commission. 4th ed. Jakarta: Ministry of Health Republic of Indonesia; 1995. p. 999-1002.
11. Rajabi-Siahboomi A, Levina M. The influence of excipients on drug release from hydroxypropyl mehylcellulose matrices. J Pharm Sci 2004;98:2746-54.
12. Yuan L, Yulin D. *In vitro* evaluation of Konjac glucomannan as novel excipients for floating systems. J Controlled Release 2011;152:33-6.
13. Colombo I, Lapasin R, Grassi G, Grassi M. Understanding Drug Release and Absorption Mecanisms: A Physical and Mathematical Approach. New York: Taylor & Francis Group; 2007. p. 388-411.
14. Costa P, Lobo JMS. Review: modeling and comparison of dissolution profile. Eur J Pharm Sci 2001;13:123-33.
15. Motulsky HJ, Christopoulos A. Fitting Model to Biological Data Using Linear and Nonlinear Regression: A Practical Guide to Curve Fitting. San Diego: Graph Pad; 2003. p. 53-4,134-43.
16. Yuksel N, Kanik AE, Baykara T. Comparison of in vitro dissolution profiles by ANOVA-based, model-dependent and independent methods. Int J Pharm 2000;209:57-67.
17. Huang X, Brazel CS. On the importance and mechanism of brust release in matrix–controlled drug delivery systems. J Controlled Release 2001;73:121-36.