39th Meeting of National Working Group on Indonesian Medicinal Plant

PROCEEDING

INTERNATIONAL CONFERENCE AND TALK SHOW ON MEDICINAL PLANT

Effective, Safe and Qualified Herbal Medicine for Diabetes Mellitus Treatment

Jakarta, 19th – 21st of October 2010

Organized by :

Agency for the Assessment and Application of Technology (BPPT)
National Working Group on Indonesian Medicinal Plant (POKJANAS TOI)
Association of Indonesian Herbal Medical Doctors (PDHMI)

Supported by :

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INDONESIA

WELCOME MESSAGE

Praise and gratitude towards Allah who has given His Grace so that the International Conference and Talk Show on Medicinal Plant could be conducted in BPPT Jakarta on the 19th – 21st October 2010.

This International Conference and Talk Show on Medicinal Plant which is also the 39th Meeting of National Working Group on Indonesian Medicinal Plant is organized by BPPT in colaboration with the National Working Group on Indonesian Medicinal Plants (POKJANAS TOI), Deutscher Akademischer Austauch Dienst (DAAD) and the Association of Indonesian Herbal Medical Doctors (PDHMI). This Conference is an effort to develop the national herbal medicine industry and as a venue for researchers, policy makers, clinicians, industrialists and observers of the herbal medicine to gather and discuss the issues regarding herbal medicine.

The theme of this Conference is "Effective, Safe and Qualified Herbal Medicine for Diabetes Mellitus Treatment". This theme was chosen because diabetes mellitus is one of diseases that could become a serious threat to public health in the future and currently herbal medicine has not been optimally utilized for the treatment of various diseases, especially diabetes mellitus. This Conference is expected to provide an overview of recent advances in herbal medicine technology, herbal medicine role in the treatment of diabetes, the problems faced by the herbal medicine industry and alternative solutions.

This conference has brought together 88 research papers from researchers of various institutions with a variety of topics, ranging from the cultivation aspects to clinical trials which provide an overview of the research currently conducted by research institution in Indonesia. Through this Conference, it is expected that research institutions with similar interest could collaborate to accelerate research in Indonesian and also as a venue for facilitating collaboration between research institutes, universities and industries.

The committee realizes that there are still many shortcomings that may be less than satisfactory to many parties. Criticisms and suggestions are expected to improve this organization of seminars in the future.

On this occasion the committee expressed the highest appreciation to the guest speakers, papers contributors, participants and sponsors for their cooperation in organizing the International Conference and Talk Show on Medicinal Plant

Jakarta, 19th of October 2010

Organizing Committee
International Conference and Talk Show on Medicinal Plant

The Agency for the Assessment and Application of Technology
BADAN PENGKAJIAN DAN PENERAPAN TEKNOLOGI (BPPT)
BPPT Chairman

His Excellency The Minister of Science and Technology, Mr. Suharna Surapranata

The Director of Deutscher Akademischer Austauch Dienst (DAAD), Indonesia

Chairman of The Association of Indonesian Herbal Medical Doctors (PDHMI)

Distinguished Speakers from China, Malaysia and Republic of Korea

Chairmen of Pharmaceutical Industries,

My colleagues and all participants,

Ladies and Gentlemen,

Assalamu Alaykum wa rahmatullahi wa barakatuh.

Good morning, Selamat Pagi, Salam Sejahtera untuk kita semua.

May God Almighty blesses us in conducting this event

Let us start by expressing our gratefulness to God almighty. His bless and mercy has given us opportunity to be here in the great and special event of **International Conference and Talkshow on Medicinal Plants** which focus on the theme of "Effective, Safe and Qualified Herbal Medicine for Diabetes Mellitus Treatment".

I am delighted to welcome all distinguished guests, invited speakers and participants. To speakers coming from overseas, welcome to Jakarta and welcome to Indonesia. Jakarta is very wet at the moment, due to heavy rain in the last couple of months. I hope this will not discourage you to enjoy your visit to Jakarta.

In this very important moment, allow me to thanks to the committee who has been working verry hard to bring this event into reality. I also would like to express a special thank to the **Assosiation of Indonesian Herbal Medical Doctors** (PDHMI) who has been actively involved and support to this event. And to **Deutscher Akademischer Austauch Dienst (DAAD)** or **German Agency for Academic Exchanges** as a main sponshor, gratitute thanks and most appreciation shall be adressed.

Ladies and Gentlemen,

I would like to draw your attention that BPPT as a research agency under coordination of the Ministry of Research and Technology, highly supports the development of herbal medicines as one of the BPPT program on health and pharmaceutical sector especially in fulfilling the national self- sufficiency on medicines. Beside Health and medicine, BPPT is conducting other focused program, namely food, energy, ICT, transportation, defence, environment, and manufacturing.

I would like to highlight here that herbal medicine development is strategic choice for developing country like Indonesia where mega biodiversity is one of its comparative advantages. Currently, chemical and semi-chemical drug industries has been dominated by global pharmaceutical industries in developed countries. For this reason, competition in this area is not beneficial for Indonesian pharmaceutical industries where its industrial structure in general, is still very weak and need to be further developed. The choice to promote program on herbal medicine development is the fact that this program has strong national capacity building from upstream to downstream processes by using locally available resources and involving various stakeholders.

Ladies and gentlemen,

This is our main mission to relate the most suitable technology to significantly increase the added value of our bioresources in order to support our national herbal medicine industries. Knowledge and technology would be a foundamental tools in the development of herbal medicine industries which enable to support national economic growth (known as knowledge based economy).

I do realise that to achieve the noble goal is not trouble-free. We need an active participation of all players not only from government institutions as fasilitatory and regulatory bodies, but also from private sectors, academicians as well as researchers to work hand-in-hand toward the best

in the utilization of knowledge and local resources in natural product development.

Ladies and gentlemen,

Since the enthusiasm of back to nature have been gaining popularity and acceptance in recent decade, national herbal medicine industries should become one of the pillars of national economic development. This is also supported by the fact that Indonesia has a second largest biodiversity in the word, with more than 30,000 species of plants. The number of herbal medicine industries keep increasing, numbering to 1,500 companies, big and small corporation. According to Herbal Medicine Entrepreneur Association (**GP Jamu**) data in 2007, not less than 3 million people works on herbal medicine sector from upstream to downstream industries. The market share of herbal medicine has growing significantly, up to 15-20% yearly.

We all hope that herbal medicine will not only fulfil local and national market, but more than that will expand to other countries, as export commodity.

Ladies and gentlemen,

As I have just mentioned before, BPPT, through the **Centre of Pharmaceutical and Medical Technology** - fully supports the herbal medicine development. I hope throughout this great forum, all stakeholders involved in the utilization of medicinal plants will stumble on the best and most suitable ways to develop our biological resources as health products. We would like to utilize our biodiversity as source of natural products to prevent and cure diseases, especially degenerative diseases such as diabetes mellitus, and also to promote our well being. To PDHMI, the **Assosiation of Indonesian Herbal Medical Doctors** we would certainly relay on your share in using herbal medicine as part of formal health services.

At last, we should work closely with all experts and institutions who concern in this area not only from our national side but also from abroad. Therefore, BPPT is continually welcome to all collaborators from national as well as international institutions based on our mutual benefit for each parties involved.

Ladies and gentlemen,

Once again, I would like to thanks to the committee, sponshors, speakers and participants and wishing all a successful symposium.

Finally, by saying "*Bismillahirrohmanirrohim"*, in the name of GOD Almighty, the Most Gracious and the Most Merciful, I have the great pleasure to declare the **International Conference and Talkshow on Medicinal Plants** is officially opened.

Thank you very much for your passion and kind attention,

Wassalamu'alaykum warahmatullahi wabarakatuhu

BPPT Chairman,

Dr. Ir. Marzan Azis Iskandar

CONTENT

ROLE OF NATURAL POLYSACCHARIDES XANTHAN GUM- LOCUST BEAN GUM IN PER-ORAL DRUG DELIVERY SYSTEMS

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ABSTRACT

Xanthan gum is a heteropolysaccaride derived from corn starch and produced by fermentation with the bacteria *Xanthomonas campestris*. Locust bean gum is a natural hydrocolloid obtained from the seed endosperm of the carob tree (*Ceratonia siliqua* L.). The structure of locust bean gum consists of a β-(1→4)-D-mannosa backbone to which D-galactose units are attached α-(1→6). Locust bean gum is a non ionic polysaccaride, which can form gel if it is combined with xanthan gum Locust bean gum is capable of synergistic interactions with xanthan gum.

This combination can be used for a matrix of a sustained release dosage form based on the ability of the combination of xanthan gum and locust bean gum to form gel. In this research, ibuprofen was used as an active ingredient formulated in control release tablet dosage form.

The results exhibited that the combination of xanthan gum and locust bean gum at a ratio of 1:1 gave the longest in vitro release. Kinetic drug release tend to zero order with dominant mechanism is erosion.

Keywords: xanthan gum, locust bean gum, matrix, sustained release.

INTRODUCTION

Xanthan gum is a heteropolisakarida which has a large molecular weight and produced from the fermentation of carbohydrates by the microorganism *Xanthomonas campestris*. It has a double helical structure of antiparallel bimolekular. Glucan backbone structures protected by the side chains are along the sides, which makes xanthan gum is relatively stable on heating as well as in acid or alkaline conditions. Xanthan gum is easily hydrated in

systems containing water as it can dissolve in cold or hot water (Anonymous, 2005[b]).

Locust bean gum is often also called carob bean gum or a galaktomanan carubin is obtained from the seeds of *Ceratonia siliqua* extraction. Locust bean gum is a galaktomanan, containing chains (1→4) - are associated with β-D-mannopiranosa as the main chain, which in the sixth position associated with α-D-galactose. Locust bean gum is a non-ionic compound so that the ionic strength and pH has no effect on the viscosity, except at extreme pH and high temperature. Locust bean gum partially hydrated in cold water and perfect hydrated when heated (Anonymous, 2005[a]).

Xanthan gum when combined with locust bean gum to form a gel when liquid is in an environment (Baichwal, 2001). This behavior is called synergism. Medicine that is often used so frequently in a day that is can cause the patient to forget to take it and less effectiveness in the treatment. To overcome these events experts designing and developing pharmaceutical dosage forms which can release the drug gradually so that the availability of drugs in the blood can be maintained longer and the drug action can be extended. This dosage form is known as a sustained release dosage form (Ansel, 1989).

Ibuprofen [(±)-2 - (p-isobutilfenil) propionic acid) is a nonsteroidal anti-inflammatory (NSAID) that is often used. Ibuprofen has a short biological half-life of approximately two hours that causes need to be used repeatedly in a day. In the form of tablets are generally used in doses of 200 mg to 800 mg, three to four times daily or 600 mg to 3200 mg per day. This is why ibuprofen is formulated in a dosage suitable for slow release (Kurumaddali et al., 1994, Tehrani and shobeiri, 1995; Shehab and Richards, 1996).

Pembuatan suatu matriks dengan bahan obat berada di dalamnya atau tercampur homogen dengan bahan matriks merupakan salah satu cara yang dapat digunakan untuk membuat sediaan lepas lambat. Bahan pembentuk matriks dapat berupa bahan yang tidak larut dalam air maupun bahan yang larut dalam air dan membentuk gel. Salah satu polimer yang sekarang mulai banyak digunakan untuk matriks sediaan lepas lambat adalah kombinasi dari *xanthan gum* dan *locust bean gum*.

One way to make sustained released preparation use a matrix system. The matrix can be developing with water soluble material and form a gel when liquid is in environment. Combination of xanthan gum and locust bean gum can be consider to be use as matrix sustained release tablet (Anonim, 2005).

According to Higuchi (1963), the release of drug dispersed in a homogeneous solid and inert matrix can be describe following equations (1):

$$Q=[D(2A–Cs)Cs.t]^{½} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (1)$$

The rate of drug release at once (shortly) at time t obtained by differentiate equation (1), and obtained:

$$\frac{dQ}{dt} = \frac{1}{2}\left[\frac{D(2A - Cs)Cs}{t}\right]^{1/2} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (2)$$

In general, A>> Cs, so that equation (1) becomes

$$Q=(2ADCs\,t)^{1/2} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (3)$$

and equation (2) becomes

$$\frac{dQ}{dt} = \left[\frac{ADCs}{2t}\right]^{1/2} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (4)$$

with Q is the amount of drug released after time t per unit area, D is the diffusion coefficient of drug in the matrix, A is the total amount of drug in the matrix per unit volume, and Cs is the solubility of drug in the matrix.

Type of matrix diffusion and development in general do not follow the Fickian diffusion mechanism. The simple equation that can describe the behavior of drug release from hydrophilic matrix systems are:

$$\frac{Mt}{M\infty} = kt^n \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (5)$$

Mt / M ~ is the fraction of drug release in time t, k is a constant and n is the exponential diffusion which indicatives of the mechanism of drug release (Wise, 2000).

METHODS

Materials

Ibuprofen (USP., BP., Hubei Biocause Helan Pharmaceutical CO., LTD.), *Xanthan gum* (degussa Texturant Systems, France), *Locust bean gum* (degussa Texturant Systems, France), Avicel® PH 101 (Asahi Kasei Chemcal Corp., Tokyo, Japan), Polivinilpirolidon K-30 (ISP Technologies Inc., Wayne, New Jersey), Magnesium stearat (Peter Greven CV, Nederland), talk (Haichen, China), Natrium hidroksida (pa, Merck), Kalium dihidrogen fosfat (pa, Merck).

Equipments

Single punch tabletting machine (Type TDP, Shanghai, China), analytical balance (Sartorius), hardness tester (Schleuniger Hardness Tester, tipe 6D-30, Germany), friabilation tester (Erweka, type TA-3, Germany), dissolution tester (Erweka, type DT70, Germany), fluid bed dryer (Glatt, Germany), spectrophotometer UV-VIS (Hitachi, type U-1100, Japan).

Tablet Manufacturing Method

Ibuprofen tablets made from a variety of formulas. The difference formula based on different combinations of the matrix. Combination matrix used is xanthan gum and locust bean gum. The concentration used for each combination were: xanthan gum, locust bean gum = 1: ½: 1:1, 1:1 ½. Composition formula ibuprofen tablets can be seen in Table I.

Table I. Composition (mg per tablet) of Sustained Release Tablet Ibuprofen (600 mg)

Ingredients	Amount (mg/tablet)		
	Formula I	Formula II	Formula III
Ibuprofen	400	400	400
Xanthan Gum	12.5	12.5	12.5
Locust Bean Gum	6.25	12.5	18.75
Avicel® PH 101	91.25	85	78.75
PVP K-30	30	30	30
Mg Stearat	6	6	6
Talk	54	54	54
Weight of one tablet	600	600	600

Formula I : Xanthan gum : Locust bean gum = 1 : ½
Formula II : Xanthan gum : Locust bean gum = 1 : 1
Formula III : Xanthan gum : Locust bean gum = 1 : 1½

The combination of matrix and Avicel ® PH 101 is mixed until homogeneous and added water to form granules, then sifted with a sieve mesh 16. The granules are dried using a fluid bed dryer at 55 ° C for 30 minutes. Sifted dry granules by sieve mesh 18.Dried granules are mixed with ibuprofen and added to a solution of polyvinylpyrrolidone to form the mass of granules, and sieved with a sieve mesh 16. The granules are dried by fluid bed dryer at a temperature of 55 ° C for 30 minutes, then sieved with a sieve mesh 20. Added magnesium stearate and talk, then mixed and homogeneous granules were observed physical properties. Then 600 mg of the prepared granules was compressed using single punch tablet machine with the same hardness was 17-18 Kp.

Characterization of Granules and Tablets

The flow characteristics, bulk and tapped density of granules were measured to verify the improvement in physical characteristics of granules for tabletting. Physical properties of tablets include tablet weight uniformity, tablet hardness, tablet friability and the disintegration time of tablet, other than that conducted the assay of ibuprofen tablets.

Drug Release Testing

The dissolution test was carried out using a dissolution apparatus II method USP over a 6-h period. The dissolution media was phosphate buffer pH 7.2. The temperature of medium and the rotation speed of the paddle were maintained at 37 °C (±0.5 °C) and 100 r/min, respectively. Six tablets were used for each test. Samples (at 5 mL) were withdrawn and replaced with 5 mL fresh phosphate buffer according to following time scheme: 30, 60, 90, 120, 180, 240, 300, and 360 min. The samples were filtered using 0.45 µm Milipore filter. The filtered sample was measured spectrophotometrically at 265 nm to determine the amount of released drug.

RESULTS AND DISCUSSION

Table II shows that bulk density has a smaller value than the value of tapped density and has a significant difference between bulk density and tapped density. This indicates that these granules have large void between particles. From the data of Carrs's index indicated that all formulas have a good flow properties because of Carr's index gained less than 20% and Hausner ratio values less than 1.25. Thus a mixture of granular flow is expected to be free flowing and to give homogeneity of content of ibuprofen in tablets.

Table II. Physical Properties of Granules

Formula	*Bulk density* (g/mL)	*Tapped density* (g/mL)	Carr's Index (percent)	Hausner Ratio
I	0.34	0.38	12	1.12
II	0.35	0.39	11	1.11
III	0.32	0.36	12	1.13

Percent friability of all formulas to meet the requirements of less than 0.8% showing resistance to the effects of tablet manufacturing process. Physical strength of the exterior of the tablet in the fight against mechanical shock is what determines the size of the fragility.

Table III. Physical Properties of Tablet

Formula	Tablet Hardness (Kp)	Tablet Friability (percent)	Disintegration Time (min)	Content Uniformity (percent)	cv of Content Uniformity (percent)
I	17.7	0.1	117	94.8	0.41
II	18.1	0.1	170	85.9	2.87
III	17.5	0.2	150	96.0	0.78

The disintegration time of all formulas using a matrix formula in which a combination of xanthan gum and locust bean gum is affected by formulation. With the same relative hardness tablet disintegration time obtained varies. The longest disintegration time of the formula II, this is probably due to the ratio of xanthan gum and locust bean gum = 1:1 causing the internal structure of the tablet will have a smaller porosity which causes the water will be difficult to penetrate and increase the disintegration time of tablets.

Table III shows that the content of ibuprofen in tablets of each formula has a cv of less than 5%, this means that contentof ibuprofen in each tablet in each formula is uniform.This content uniformity data illustrate that tabletting process goes well and produces tablets with active substances which approached the ideal levels.

Dissolution profiles was obtained by plotting the percent drug released *vs.* time as shown in Figs.1. The profile of drug released showed that the formula III has the percent of drug release of the most high despite the destruction of much longer time when compared with formula I. This is because formula III shows the mikrogranular while the formula I are makrogranular. While the profile of drug release on the formula II shows the release of the longest when compared with other formulas.

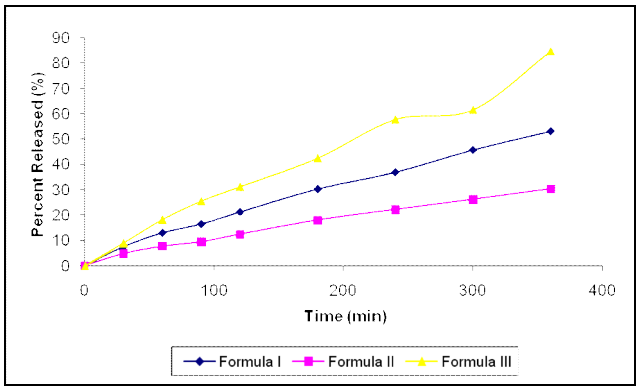

Figure 1. Release profile of ibuprofen sustained release tablet

Table IV. Mathematical Modeling and Drug Release Kinetics of Ibuprofen Sustained Release Tablet

Formula	Zero Order		Higuchi	First Order	Exponential Diffusion (n)
	k (mg/min)	r	r	r	
I	0.5190	0.9991	0.9922	0.9975	0.873
II	0.2679	0.9980	0.9933	0.9993	0.603
III	0.8130	0.9919	0.9830	0.9447	0.570

Table IV shows that both diffusion and erosion mechanisms applicable to the release of ibuprofen from matrix xanthan gum-locust bean gum in medium phosphate buffer pH 7.2, with the dominant mechanism is erosion. Characteristics of drug release, represented by the value of n. All formulas have the value of n greater than 0.45 and smaller than 0.89 means that the release characteristics of ibuprofen following the anomalous diffusion transport mechanism, where the rate of diffusion and polymer relaxation are comparable. N value above also indicates that the controlled drug release more than one process.

CONCLUSION

Xanthan gum in combination with locust bean gum can be used as a slow release matrix tablet of ibuprofen with the kinetics of drug release tends to zero order and the dominant mechanism is erosion. The mechanism of drug transport that occurs is anomalous diffusion, which states that the controlled drug release more than one process. Levels of locust bean gum is used in combination matrix may affect the rate of dissolution, where the ratio of 1:1 between Xanthan gum and locust bean gum provides drug release profile of the longest with the lowest dissolution rate compared to other formulas.

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