

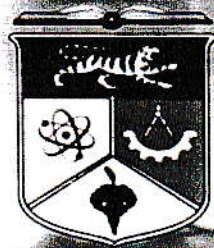
Proceeding

The First International Seminar on Science and Technology

OSTEG 2000

*The Challenge of Sciences in a Global
Warming Era: Issues and Opportunities
for a Better Life*

SCIENCE FOR A BETTER
LIFE



UNIVERSITI KEBANGSAAN MALAYSIA



UNIVERSITI MALAYSIA TERENGGANU

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**at Kahar Muzakkir Auditorium Universitas Islam Indonesia
Jogjakarta, Indonesia**

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The Effect of Polyvinylpyrrolidone (PVP) to The *in Vitro* Intestinal Absorption of Pentagamavunon-0 (PGV-0) on Rats

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Abstract

PGV-0 is a synthetic compound which is modified compound from curcumin. This compound would be expected to be a new drug, since this substance has a potent inflammatory effect with a very low toxicity. However, this substance has poor biopharmaceutic properties, it means that this compound is practically insoluble in water. It has been reported, that the solubility of PGV-0 was increased by presence of PVP. So the aims of this study was to know the effect of PVP to the *in vitro* intestinal absorption of PGV-0 on rats. It was evident that the PGV-0 absorption was increased significantly by PVP addition, but there was not any effect on the lag time of the *in vitro* intestinal absorption.

Key words : PGV-0, PVP, *in vitro* absorption

Introduction

A number of active compounds of drgs are poorly soluble in the aqueous fluid of gastrointestinal tract. Consequently, the *in vivo* dissolution rate of these compounds are low, and the gastrointestinal absorption tend to be incomplete.

Pentagamavunon-0 (PGV-0) is a curcumin derivate, a synthetic compound that would be expected to be a new drug. This substance has potent anti-inflammatory effect with a very low toxicity. However, this compound is practically insoluble in water, so the gastrointestinal absorption will be limited by dissolution. By improving its solubility would be increased its dissolution rate and the bioavailability as well. The correlation between the solubility of substance and its dissolution rate follows the Fick's first law equation as follows (Martin, *et al.*, 1993)

$$dC/dt = D A/V h \times (C_s - C_b) \quad (1)$$

where, dC/dt = the dissolution rate; A = surface area; V = volume of dissolution medium; h = the thickness of the diffusion layer, C_s = solubility and C_b = the concentration of diffusant or the concentration of diffusant at time, t .

Wahyuningsih (2004) had proved that the solubility of PGV-0 was increased with presence of polyvinylpyrrolidone (PVP). This substance is pharmacologically inactive and non-

toxic. In industrial pharmacy. PVP is used as the the formulation expience, for instant can be used as the fastner at tablet formulation (Anonim, 1986). Some opinions consider that crustal growth will be hindered by PVP, and it can be used as adjuvant at the preparing the solid dispersion of the poor solubility of drug, it means to increase it dissolution behavior (Chiuou and Riegelman, 1971; Akbuga *et al.*, 1988).

The main point of this study was to know, the effect of PVP to the *in vitro* intestinal absorption of PGV-0, and the effect to the lag time at its diffusion process. The everted small intestinal sac technique was used at this study, and carried out with the modification of Crane and Wilson apparatus (Bates and Gibaldi, 1970).

The mass transfer through the intestine membrane relating to the lag time follows the equation (Martin *et al.*, 1993):

$$M = D A K C_d / h (t - t_L) \quad (2)$$

Where, M = the amount of diffusant has be transferred at the time t ; D = the diffusivity in intestinal membrane, A = the area of the membrane; K = the partition coefficient between membrane and aqueous medium in the intestine; C_d = the concentration of the diffusant; h = the membrane thickness; and t_L = lag time, and

$$t_L = h^2/6D \quad (3)$$

Methodology

The main material applied to this study was pentagamavunon-0 (2,5-bis{4'-hydroxy-3-methoxybenzylidene} cyclopentanone), obtained from MOLNAS Faculty of Pharmacy, Gadjah Mada University. The other chemicals were: PVP 25 p.a. (E Merck), albumin p.a. (E Merck), Sodium chloride p.a. (E Merck), and the other chemical were pharmaceutical grade, and the test animals were male rats (Wistar)

The male rats were fasted for a period of 20 to 24 hours. Water was allowed *ad libitum*. The animals were killed by anesthetized with ether. The abdominal region were exposed by mean of a midline incision. The entire small intestine were excised, and the rats was sacrificed, if necessary. The lumen were flushed immediately with cold normal saline (physiologic sodium chloride solution), and the distal portion (10 to 15 cm from the pylorus) is cut and discarded to prevent inclusion of the entrance of the bile duct in the test segment. The next step was to evert the entire small intestine with a smooth glass (Bates and Gibaldi, 1970).

The distal end of 7 cm jejunum segment was tied, and the proximal end attached to the *cannula*. The segment was suspended in a predetermined volume (75 ml) of mucosal solution which containing of saturated PGV-0 as mucosal solution at $37^0 \pm 0,5^0$ C. The *cannula* was adjusted to immerse the sac completely. A small volume (1.4 ml) of drug-free physiologic sodium chloride solution was then placed the serosal compartment. The mucosal solution was continually gassed with carbogen 100 bubbles per minutes (Bates and Gibaldi, 1970).

For determining the rate of PGV-0 transfer across the intestine, the entire volume of *serosal* solution was removed from the sac at each time interval, then the concentration of PGV-0 was assayed spectrophotometrically. A fresh physiologic sodium chloride solution was finally added to the sac, to serve as the *serosal* fluid for next-time period. At conclusion of the experiment, the gut may be assayed for accumulated PGV-0.

Results and Dicussions

The first step of this study was making orientation by using varying concentrations of PGV-0 and PVP solution as the *mucosal* solution and the normal saline as the *serosal* solution. After 75 minutes incubation, the concentration of PGV-0 which had been transferred to the *serosal* solution

was assayed spectrophotometrically. The results were undetectable PGV-0, because the concentration of PGV-0 were very low.

The absence of *in vitro* absorption in this trial was may be because of the difference the serosal solution used in this trial witch physiological solution. In the body, drugs are distributed through out the body by blood. Albumin is the main component of blood protein which bind most of the drug, while the other protein have less role in drug binding (Shargel *et al.*, 2005). So the next step was a trial for the orientation by adding albumin to the *serosal* solution.

From that trial, absorption was finally detected when *serosal* solution contained albumin. Based on that, for the next trial were used mucosal solution consisted of 5 mg % PGV-0 in physiologic sodium chloride with 2 % PVP. For the *serosal* solution, were used 1 % albumin in the physiologic sodium chloride and the concentration of PGV-0 were assayed after 90, 180 and 270 minutes incubation.

In this *in vitro* absorption trial, would be observed the influence of PVP to the amount of PGV-0 transported through jejunum or ileum. In this study, saturated solution of PGV-0 in physiologic sodium chloride solutions with and without PVP were used as mucosal solution. The pertinent value for the jejunum trial were given in Table I.

Table I. The amount of cumulative of PGV-0 which is transported through jejunum from saturated solution PGV-0 and mixture PGV-0 - PVP from mucosal solution to serosal solution *in vitro*.

No.	The amount of cumulative of PGV-0 which is transported in jejunum					
	90 (Minute)		180 (Minute)		270 (Minute)	
	PGV-0 solution	PGV-0 – PVP solution	PGV-0 solution	PGV-0 – PVP solution	PGV-0 solution	PGV-0 – PVP solution
1	0,0003*	0,0034*	0,0029*	0,0144	0,0029*	0,0144
2	0,0004*	0,0018*	0,0028*	0,0148	0,0028*	0,0148
3	0,0005*	0,0014*	0,0033*	0,0214	0,0033*	0,0214
4	0,0005*	0,0027*	0,0039*	0,0236	0,0039*	0,0236
5	0,0005*	0,0035*	0,0027*	0,0168	0,0027*	0,0168
Mean	0,0005	0,0027	0,0031	0,0182	0,0031	0,0182

Description : * = calculation result of extrapolation

For analyze the effect of PVP to the amount of PGV-0 transported through jejunum, was done by Paired t-test in SPSS with $P < 0,05$. It means that PVP could increase transported PGV-0 through jejunum. This data support the estimation that PVP could increase PGV-0 absorption by increasing PGV-0 solubility.

From table I, the linear regression was made. The amount of transported PGV-0 was used as time function to calculate the lag time. From each linear equation, can be calculated the intersection according to the x-axis to determine the lag time value, as seen to the table II.

Table II. The lag time PGV-0 at jejunum by using mukosal solution without PVP and also with PVP.

No.	Lag time PGV-0 at jejunum without PVP (minute)	Lag time PGV-0 at jejunum with PVP (minute)
1	69,67	51,22
2	58,33	70,91
3	62,14	72,89
4	68,75	70,67
5	57,14	55,70
	$\bar{X} = 63,21$ SD = 5,18	$\bar{X} = 64,28$ SD = 8,98

Paired t-test analysis between lag time PGV-0 in jejunum not using and using PVP shows meaningless difference ($P > 0.5$), which mean, that PVP addition did not change the PGV-0 lag time in jejunum. It may be because of the fact that , even PVP can increase the absorption of PGV-0 by complex formation PVP-PGV-0, but the free PGV-0 the only capable to pass the membrane.

The amount of transported PGV-0 through ileum, using saturated solution of PGV-0 in the physiologic sodium chloride, with or without PVP as the mucosal solution, can be seen in table III.

Analog the effect of PVP to the in vitro absorption of PGV-0 through jejunum, the effect through ileum given the same result. Using Paired analysis t-test shows that PVP could improve the absorption of PGV-0 through ileum significantly ($P < 0.05$), and PVP was not influent to the lag time at the ileum absorption process of PGV-0 ($P > 0.05$), as seen to the table IV.

Table III. The amount of cumulative of PGV-0 which is transported through ileum from saturated solution PGV-0 and of mixture PGV-0 - PVP from mucosal solution to serosal solution *in vitro*.

No.	The amount of cumulative of PGV-0 which is transported in ileum					
	90(minute)		180(minute)		270(minute)	
	PGV-0 solution	PGV-0 - PVP solution	PGV-0 solution	PGV-0 - PVP solution	PGV-0 solution	PGV-0 - PVP solution
1	0,0003*	0,0011*	0,0010*	0,0056	0,0029*	0,0144
2	0,0003*	0,0021*	0,0011*	0,0063	0,0028*	0,0148
3	0,0004*	0,0024*	0,0011*	0,0095	0,0033*	0,0214
4	0,0005*	0,0030*	0,0013*	0,0114	0,0039*	0,0236
5	0,0004*	0,0017*	0,0009*	0,0074	0,0027*	0,0168
Mean	0,0004	0,0021	0,0011	0,0080	0,0031	0,0182

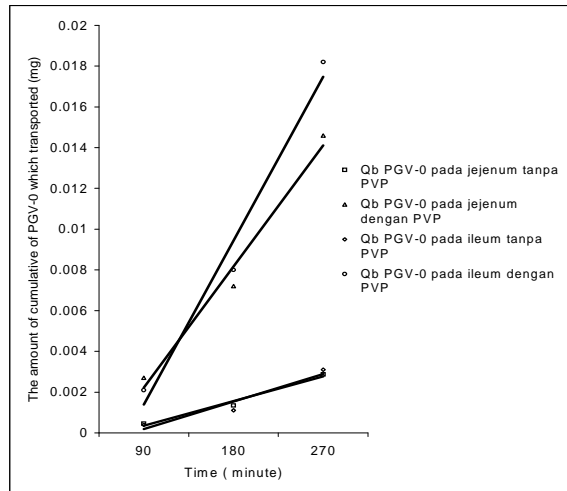
Description : * = Calculation result of extrapolation

Tables IV. The lag time PGV-0 at ileum by using mucosal solution without PVP and also with PVP.

No.	Lag time PGV-0 at ileum without PVP (minute)	Lag time PGV-0 at ileum with PVP (minute)
1	85,71	85,14
2	78,57	70,42
3	81,25	66,67
4	78,95	71,82
5	73,85	77,38
	$\bar{X} = 78,70 \pm$ SD = 4,14	$\bar{X} = 74,80 \pm$ SD = 5,98

The PGV-0 lag time in jejunum and ileum were both more than 15 minutes. This such drug material usually generates absorption problem through the biomembrane. From slope curve at the figure 1, seen that the absorption rate of PGV-0 through jejunum was faster than through ileum.

Fig 1. The amounts of cumulative of PGV-0 which is transported at jejunum and ileum applies mucosal solution without PVP and with PVP



Conclusion

1. In this *in vitro* absorption trials, PVP could be enhancer in the absorption of PGV-0 significantly ($P < 0.05$) either through jejunum or ileum at male rats.
2. The lag time of PGV-0 transport through jejunum or ileum, PVP did not any effect ($P > 0.05$).

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