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Original Article

EVALUATION OF ORALLY DISINTEGRATING TABLET OF IBUPROFEN-β-CYCLODEXTRIN INCLUSION COMPLEX

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ABSTRACT

Objective: This study aims to determine the effect of the inclusion complex formation of ibuprofen (IB) with β-cyclodextrin (β-CD) in improving water solubility and taste masking as well as to study the effect of the combined use of super disintegrants in IB-β-CD ODT (Orally disintegrating tablet).

Methods: IB-β-CD inclusion complex was prepared by spray drying technique with a 1:1 molar ratio. ODTs were prepared by the direct compression method using various ratios of Ac-Di-Sol® and Kollidon® CL as super disintegrant. The inclusion complex was characterized using spectroscopy FT-IR (Fourier-transform infrared) and DSC (Differential Scanning Calorimetry). The physical properties and dissolution rate of ODTs were evaluated. Dissolved drug concentration at 60 min (Q_{60}) and Dissolution Efficiency (DE_{60}) was calculated using the dissolution test result.

Results: The unpleasant taste of IB had been successfully masked by IB-β-CD. Formula 1 was observed having 14.5 sec of disintegration, fastest compared to the other formulas. Moreover DE_{60} value of formula I was higher than the other formulas (113.45).

Conclusion: IB-β-CD Inclusion complex prepared by spray drying method (1: 1) increased the water solubility and masked the unpleasant taste compared to IB moreover combination of Ac-Di-Sol® and Kollidon® CL increased ODT dissolution rate.

Keywords: Ibuprofen, Inclusion complexes, β-cyclodextrin, ODT and super disintegrant

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INTRODUCTION

Ibuprofen (IB) is an NSAID (Nonsteroidal Anti-Inflammatory Drug) that belongs to the propionic acid derivative. IB mechanism of action is inhibition of *cyclooxygenase-1* and *cyclooxygenase*-2 isoenzymes by interfering synthesis of prostaglandin from arachidonic acid, whereas prostaglandins are messenger molecules in inflammatory processes [1]. According to the Biopharmaceutics Classification System, IB is a BCS class II drug, which has poor solubility but good permeability properties [2]. Thus, IB absorption is limited by its poor water solubility. This can hamper its oral bioavailability and onset of action. Several approached have been employed to increase IB water solubility and oral bioavailability, such as solid dispersion [3], size reduction [4], copolymer [5], and surfactant [6]. Inclusion complex, especially using cyclodextrin (CD), has been widely used to increase the water solubility of poorly water-soluble drugs as well as enhance bioavailability [7].

CDs are cyclic oligosaccharide which has a hydrophilic outer surface and lipophilic surface in the central cavity. The lipophilic cavity of CD is capable to house lipophilic drugs via a non-covalent bond. Thus, hindering the lipophilic surface of a drug to directly contact with water leaving only CD hydrophilic surface resulting in an increased in water solubility. β-CD is one of the CD family which contains seven-unit of glucose. β-CD has several advantages such as efficient drug loading and complexing mechanism, readily available, and relatively low-cost [8]. Solubility improvement by using inclusion complex with CD has many advantages compared to the other approach, such as improving drug stability, prevent incompatibility during formulation, reduce risk of gastric irritation and odor, as well as taste masking [9].

IB is a widely used analgesic in children and elderly [10, 11]. Children and elderly commonly have swallowing difficulties. This may result in decreased patient compliance and minimize treatment effectiveness [12]. One of the approaches to increase patient acceptance toward orally solid dosage form is an orally disintegrating tablet (ODT). ODT is rapidly dissolved tablet with a small amount of saliva within seconds when placed on the tongue. This is suitable for people with swallowing difficulties. Moreover, ODTs can give rapid onset of action, improve bioavailability due to rapid dissolution and pre-gastric absorption, which reduced the number of drugs that undergo first-pass metabolism [13].

In order to achieve rapid dissolution time, the combination of *super disintegrants* could be used. *Superdisintegrant* is a disintegrant that has been modified to produce a disintegrant that is able to disintegrate rapidly [14]. A Combination of super disintegrant is expected to increase the disintegration rate and dissolution rate of the tablet. *Superdisintegrants* used in this study were Ac-Di-Sol and Kollidon Cl. The formation of IB-β-CD inclusion complex and the incorporation of superdisintegrant mechanism of Ac-Di-Sol and Kollidon Cl are expected to increase solubility, dissolution, and mask the unpleasant taste of IB. Thus, this study aims to determine the effect of the inclusion complex formation of IB with β-CD in improving water solubility and taste masking as well as to study the effect of the combined use of super disintegrants in IB-β-CD ODT (Orally disintegrating tablet).

MATERIALS AND METHODS

Materials

The materials used in this study were ibuprofen, β-cyclodextrin, Ac-Di-Sol®, Kollidon CL, Avicel PH 102, aspartame, magnesium stearate, talc, phosphate buffer pH 7.2, methylene blue, water, methanol p. a., dan ethanol 96%. Distilled water, methanol p.a (pro-analysis), and 96% ethanol. All materials used in this study had a quality for pharmaceutical use *(Pharmaceutical grade)* and analysis (pro analysis).

Apparatus

The apparatus used for this study were tableting machine *(Single Punch* Korsch), hardness tester *(Stokes Mosanto)*, UV/Visible (Hitachi U-2810), analytical balance (Mettler Toledo), disintegration tester (Erweka), friabilator abrasive tester (Erweka type TAP, Germany) dissolution test apparatus (USP type II), spray dryer, FT-IR spectrophotometry and DSC instrument.

Preparation IB-β-CD inclusion complex

IB and β-CD with a mole ratio of 1: 1 were weighted. β-CD was dissolved in distilled water at a temperature of 20-25 °C in a beaker glass, then stirred until a homogeneous mixture was formed. IB, which had been wetted with methanol then it was mixed into β-CD solution with constant stirring until the suspension was formed. The suspension was then spray dried with a temperature of 120 °C. The yield was then weighed to get a solid mass [15–17].

Characterization results of inclusion complexes with FT-IR

2-3 mg of sample was mixed with 400 mg dry KBr then pressed in a *transparent disk* under the pressure of 10000-15000 psi. IR spectra were recorded in the range of 500-4000 cm^{-1} with a resolution of 4 cm^{-1} [18, 19].

Characterization results of inclusion complexes with DSC

A sample of 5 mg was spread over the aluminum pan and heated in a DSC instrument in the nitrogenous room. The heating rate was regulated at 5 °C/min in a temperature range of 25-500 °C [20]. Thermogram was then recorded.

ODT manufacture

ODTs were made by the direct compression method after IB-β-CD inclusion complex had been prepared [21]. Avicel PH 102 was used as a filler binder. Superdisintegrant used were Ac-Di-Sol and Kollidon Cl with various concentrations, magnesium stearate-talk (lubricant), and aspartame as the sweetener agent. The homogeneous mixture of ingredients was compressed with a single punch tableting machine, and the size of the upper and lower punch was set to obtain tablets with 400 mg weight and hardness of 3-5 kg. The composition of each IB ODT formula can be seen in table 1.

Evaluation of physical properties of the tablet

Weight uniformity study was conducted on twenty tablets taken randomly from each formula. The tablets were weighed one by one with an analytical balance. Mean and coefficient of variation (CV) were calculated from weighing results.

The hardness test was done by taking 6 tablets from each formula. The values of the hardness were obtained and then the mean was calculated.

Tablet friability study was done by taking twenty tablets of each formulation and cleaned from dust and weighed. The tablets were then put into friability tester and was ran at 25 rpm for 4 min. Tablets were cleaned from dust and weighed again as final weights, then the friability of the tablet was calculated.

Tablet disintegration and wetting time study

ODT disintegration time test was done by placing a tablet on a 5-cm diameter petri dish containing phosphate buffer pH 7.2 of 20 ml. The disintegration time required by 6 tablets were recorded and then the mean were calculated [22]. The filter paper was folded twice and placed on a petri dish (5 cm diameter) filled with 5 ml of distilled water containing methylene blue. One tablet was then placed gently on the filter paper. The time required to generate a blue color on the entire surface of the tablet was calculated as the wetting time [22].

Table 1: Formula ODT Ibuprofen

Composition	Formula I.	Formula II	Formula III	Formula IV	Formula V
Inclusion complex	322.4	322.4	322.4	322.4	322.4
Ac-Di-Sol	5	7.5	10	12.5	15
Kollidon Cl	15	12.5	10	7.5	5
Avicel pH 102	51.6	51.6	51.6	51.6	51.6
Aspartame	4	4	4	4	4
Mg stearate	0.2	0.2	0.2	0.2	0.2
Talc	1.8	1.8	1.8	1.8	1.8
Total (mg)	400	400	400	400	400

Tablet dissolution study

This test was done by putting ODT into the dissolution medium of 900 ml phosphate buffer pH 7.2 using USP apparatus type II with a rotation speed of 50 rpm with a temperature of 37±0.5 °C. The samples were withdrawn at 1, 3, 5, 10, 15, 20, 30, and 60 min by taking 5.0 ml of the medium (5.0 ml fresh medium was added on each sampling to keep the volume constant). The absorbance was measured at a wavelength of 264 nm and percentage of drug released was calculated [23].

RESULTS AND DISCUSSION

Examination of organoleptic

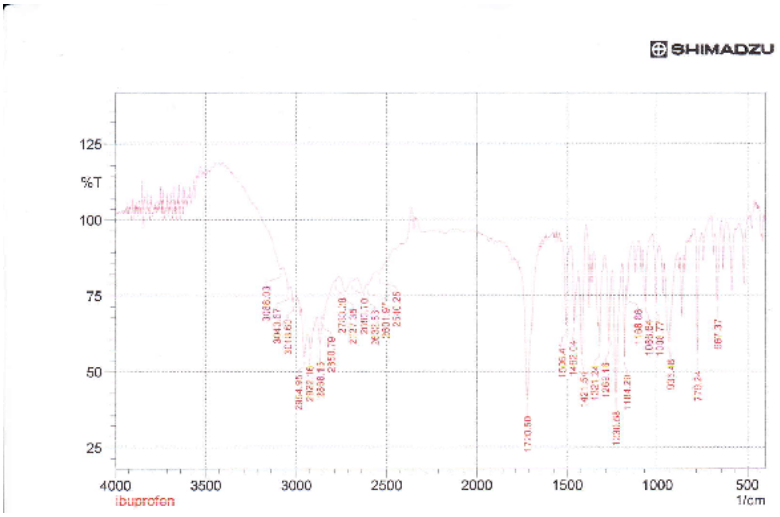
The organoleptic test was conducted to describe the color and taste of pure IB powder and IB-β-CD. Organoleptic test results were shown in table 2. According to table 2 that the spray drying method had undergone an inclusion complex in which inclusion complex results were ranging from tasteless to sweet which successfully masked its original bitter taste. This agrees with several studies that reported that CD inclusion complexes possessed taste-masking properties [24, 25]. Taste masking was the result of entrapment of drug molecule into CD cavity and the presence of sugar molecule in CD, hindered the unpleasant taste [26]. The resulting color was still white since both IB and β-CD were equally white-colored.

Result of characterization of inclusion complex

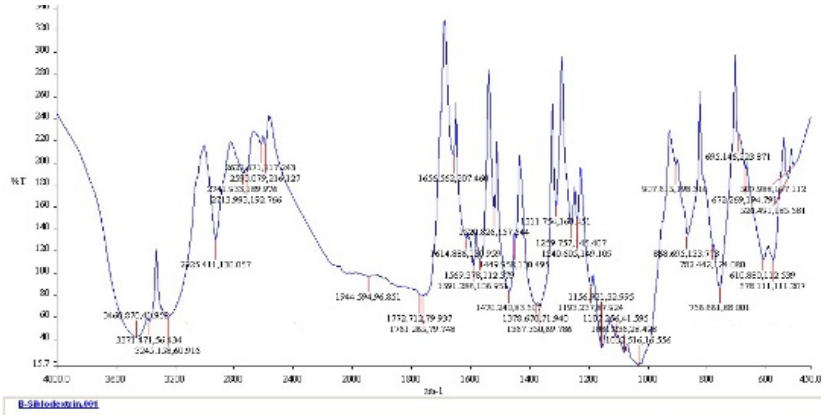
Infrared spectroscopy is a type of spectroscopy that is specific to a molecule that will provide information about the functional groups present in the molecule, selective to isomer because of fingerprint region, quantitative, nondestructive and universal. FT-IR analysis results can be seen in fig. 1.

Table 2: Powdered ibuprofen organoleptic test results and inclusion complex results

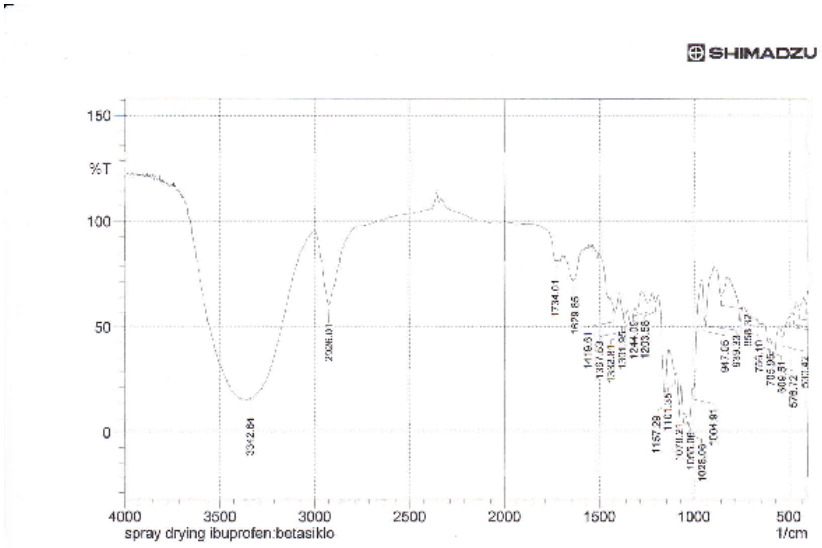
Organoleptic parameters	IB	IB-β-CD	
		Physical mix	*Spray drying*
Color	White	White	White
Flavors	Bitter	A bit bitter	No taste



(a)



(b)



(c)

Fig. 1: Test results *Fourier-transform infrared (FTIR) spectroscopy* (a) Ibuprofen, (b) β-cyclodextrin, (c) Results of inclusion complex

Based on the fig. 1. IB appeared at a peak around 1720.50 cm^{-1}(carbonyl stretching of iso propionic acid group) and 2954.95 $cm^{-1}$and 1066.64 cm^{-1} regions. While on spectra of inclusion complex results showed no visible peaks like the pure ibuprofen, an only peak which was similar to that β-CD, peak which was widened peak at 3342.64 and 2926.01 cm^{-1} regions. This proved that IB had been incorporated into the β-CD cavity.

Analysis with DSC can provide information about the change of material properties to heat with enthalpy as parameter measured.

Character determination with DSC in IB, β-CD, and IB-β-CD with spray drying method presented in table 2.

The thermogram of IB shown endothermic peak of 77.21 °C, whereas on the result of the inclusion complex the endothermic peak was not visible. The thermogram of inclusion complexes shown an endothermal peak of 125, 96 °C, where this peak was also visible on the β-CD thermogram.

Thus, proved IB had successfully entered the β-CD cavity.

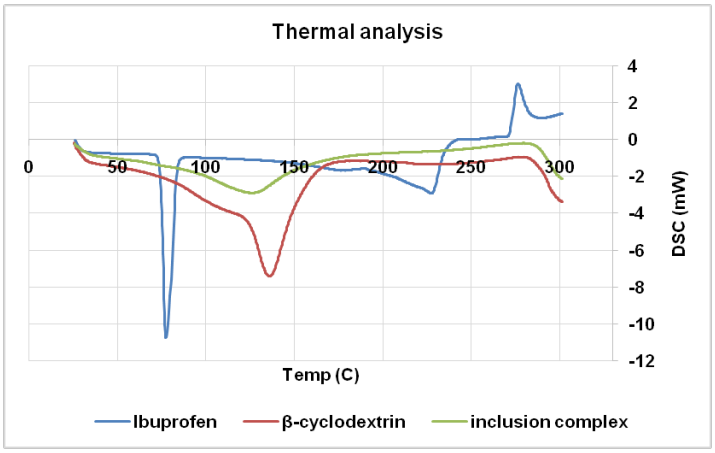


Fig. 2: Test results differential scanning calorimetry (DSC) (a) Ibuprofen, (b) β-cyclodextrin, (c) Results of inclusion complexes

Evaluation of physical properties of IB ODTs

The result of the uniformity test of all formula weights showed that CV value was less than 5%. The resulting ODTs hardness was at the accepted range, where good ODT has a range of 3-5 kg hardness. Friability test results indicate a value of less than 1%, which fulfilled the requirement. The wetting time of the ODT formulas showed that formula I had the fastest time compared to other formulas. The disintegration test of all formulas showed that all the tablets disintegrated within less than one minute. Formula 1 showed the most rapid disintegration time and corresponded to the wetting time, where the highest proportion of Kollidon Cl would aid the process of water entry into the tablet, easily expanding tablets without rapid gel formation. Thus, the tablets would disintegrate rapidly. The highly porous structure of Kollidon CL would accelerate the disintegration rate, as water would rapidly enter the tablet and increase the wetting rate [27]. The result of physical properties evaluation can be seen in table 3.

Dissolution test results

The dissolution profile of the five ODT formulas, where in the first 3 min the amount of nifedipine released was more than 50%. This happened because the combination of two superdisintegrants made the tablets disintegrate and dissolve rapidly. The three aforementioned formulas had more than 80% dissolved percentage in 60th minute. Formula 1 had the highest solubility compared to other formulas. Improvement in dissolution time potentially improved drug oral bioavailability since the rate-limiting step of the absorption of IB was dissolution time [28].

Table 3: Parameter of ODT physical characteristics

Formula	Uniformity of weights (CV %)	Hardness (kg/cm $^{2)*}$	Friability (%)*	Disintegration time (sec)*	Wetting time (sec)*
1	0.35	4.19±0.20	0.05±0.01	14.50±0.46	7.30±0.36
2	0.33	3.81±0.14	0.07±0.01	18.72±0.55	8.09±0.30
3	0.25	3.72±0.13	0.07±0.01	20.78±0.66	9.46±0.29
4	0.28	3.76±0.13	0.13±0.02	27.74±0.62	13.47±0.59
5	0.31	3.69±0.09	0.14±0.01	28.72±0.77	18.76±0.42

*The data are written the average value and the SD value of each formula

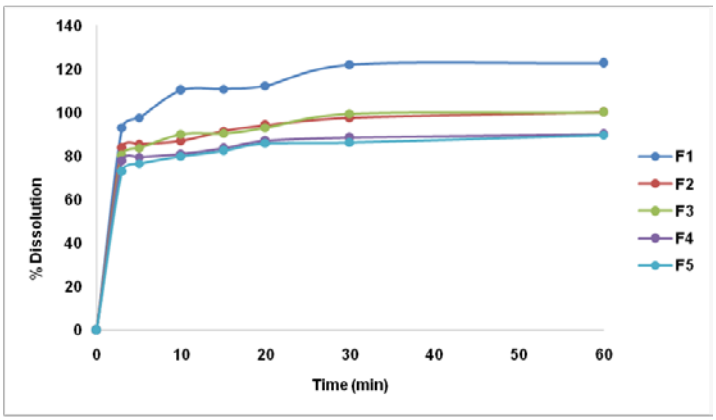


Fig. 3: Dissolution profile of Ibuprofen ODT

Table 4: Values DE60

Formula	DE60
	113.45
	92.75
III	93.16
I.	84.46
II	83.06

Table 4, showed that the DE_{60} value of formula I was greater than the other formulas. Differences in the composition of super disintegrant in every formula gave distinction in dissolution test results (DE_{60}). Where the increase in the number of Ac-Di-Sol in each formula gave distinctive dissolution results. Ac-Di-Sol increases water penetration through porous surface into the tablet [29], resulting in rapid dissolution time.

CONCLUSION

The formation of IB-β-CD inclusion complex using spray drying method (1: 1) can increase solubility and mask bitter taste compared to IB alone. Moreover, combination of super disintegrant Ac-Di-Sol and Kollidon Cl can increase ODT dissolution rate.

AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

There is no conflict of interest from this works.

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