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REVIEW ARTICLE

Enhancing Dissolution and Bioavaibility of Purely Water Insoluble Natural Compounds by Solid Dispersion with Hot Melt Extrusion Technique

Sofi Nurmay Stiani[1*], Taofik Rusdiana[1], Anas Subarnas[2]

1. *Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, University Padjadjaran.*
2. *Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, University Padjadjaran KM.21, on street Bandung Sumedang, Hegarmanah, Jatinangor, Sumedang Regency, West Java.*

Corresponding Author Email:** ***Sofia240586@gmail.com

Abstract

The use of herbal remedies is still a trend in the world, especially Indonesia as the second largest country after Brazil is rich in medicinal plants, in addition to having many pharmacological properties also have low side effects. The most common problems with biopharmaceuticals related natural substances are low drug solubility, low biopharmaceutics, stability problems and active substance absorption. Bioavailability is an important factor in achieving the effects of drug therapy. Low bioavailability may occur due to low water solubility, instability in the digestion, and difficulty passing through the membrane. To overcome the problem of bioavaibility of natural material compounds should be made efforts to improve it, one of them with solid dispersion method. The solid dispersion is the dispersion of one or more active ingredients in an inert solid carrier. Technique of Dispersion in the carrier can be by way of hot spin mixing, co-evaporation, co-perception, freeze-drying, spray drying and HME .Techniques that are still rarely used in Indonesia are hot melt extrusion (HME). This study aims to explore characteristics of the chemical properties of natural materials, efforts to increase the bioavailability of natural compounds, and solid dispersion techniques.

Keywords: *Bioavailability, Natural Material, Solid dispersion, hot melts extrusion*

Introduction

Indonesia as a biodiversity country rich in flora and fauna is the basic capital to be able to improve the economic strength of Indonesia in the eyes of the world. One of them by making the flora and fauna into ready-made products and have value.

From the flora that became the strength of Indonesia is the use of herbal medicines are still in great demand by the public because it not only gives a single effect but some pharmacological effects of herbal plants and side effects are minimal.

But the problem arises when the herbal ingredients will be used as a drug / product that is ready to be consumed by patients in terms of bioavaibilitasnya (bioavailability). Bioavailability is a pharmacokinetic parameter of a drug that shows the velocity and duration of the active substance in the blood [1]. Increasing the solubility of herbal medicine is a challenge for scientists in terms of formulation because in the pharmaceutical world the solubility of drugs is very important to be able to give effect. The degree of permeability and the degree of solubility is needed for the absorption of oral drugs in the body and is closely related to the effect [2].

Drugs with low solubility in water will require high doses to achieve effects after oral administration. The solubility of drugs is closely related to bioavailability. Based on Biopharmaceutics Classification System (BCS) the ingredients of the drug are classified into 4 groups as in Table 1 below:

Table 1: Bio pharmaceutics Classification System (BCS) based on FDA 2000 [3]

Class	Permeability	Solubility
I	High	High
II	High	Low
III	Low	High
IV	Low	Low

Most drugs derived from natural substances are problematic in solubility i.e. in BCS entering class II with high permeability, but low solubility, for example the content of

natural ingredients in Celery (Apium graveolens L) as Apigenin belongs to class II [4]. In this review will be discussed BCS class on some natural materials.

Table 2: Class BCS on Natural Compounds

S. No	Plant	Marker	Biological Activity	BCS Class	Solution	Reference
1.	Purple sweet potato and purple eggplant, black rice (*Oryza sativa* L.)	Antocyanin	Antioxidant, antiinflammatory, atherosclerosis, reduces risk of stroke and coronary heart, improves eye acuity and improves cognitive behavior	Class III, low toxic effects	Subcritical water extraction techniques	[5][6][7][8]
2.	Cascara sagrada (Coffee Bean)	Cascarosid e A	Stimulant laksatif	Class III	Micronization	[9][10][11]
3.	Garlic (*Allium sativum,* L)	Alliin	Antioxidant, Antiinflammatory	Class III	Supercritical Fluid Extraction	[9][12][13] [14]
		Allicin	Antimicrobial, Antifungi I	Class I	Supercritical Fluid Extraction	[9] [14] [15] [16]
4.	Ginger	6-Gingerol	Analgesic and Anti-inflammatory, inhibits breast cancer / anti-tumor cells, Antioxidant	Class I	[6]-Gingerol-loaded self-microemulsifying drug delivery system ([6]-Gingerol-SMEDDS), Proliposom, Supercritical Fluid Extraction	[9][17][18] [19] [20] [21][14][22]
		8-Gingerol	Imunosupressan, antihipotermi	Kelas I	Solid dispersion, Nano-gingerol	[9][23][24][25]
		10-Gingerol	Antibacterial, anti neuroinflamasi	Class II	Nano-gingerol	[9][26][19] [27] [28]
		6-Shogaol	Antiinflammatory, anti-colon cancer and breast cancer, Antidiabetes	Class I	Chemical modifi-cation (pH change)	[9][29][30][31][32]
		8-Shogaol	Antioxidant	Class II	NA	[9][33]
		10-Shogaol	Antioxidant	Class II	NA	[9][34]
		6-Gingerdione	Antioxidant and antiinflamatory	Class I	NA	[9][35]
		8-Gingerdione	Antioxidant	Class I	NA	[9][36]
3.	Turmeric	Curcumin	Anticancer	Low solubility, low elevation	Formation of Complex Curcumin-β-Cyclo-dextrin Nano-particles In Gel Form, microemulsification, solid dispersion	[37][38][39][40]
4.	Uncaria gambir	Cathecin	Anticancer, Antioxidant	Low solubility	The formation of catechinic crystals with nicoti-namide, complex formation (complex phospho-lipid phospho-lipids)	[37][41][42][43][44]
5.	Celery Herbs (*Apium graveolens* L)	Apigenin	Antikalkuli (in Celery herbs), Antitoxic, Anti-inflammatory, Anticancer	Class II	nanocrystal	[45][46][4] [47]
6.	Capsaicin		nalgesics (dermal path), Anticancer, weight loss, Cardiovascular drugs,	Low solubility	A mixed polymeric system is	[48] [49]

			antihistamines (topical)		created Micelles) polyvinylpyrrolidone (PVP) / sodium cholate / phosph-olipid	
7.	Gingko	Bilobalide	Regeneration of peripheral nerves, Antiiskemia	Class III	Super-critical Fluid Extraction	[9][50][51][52]
		Ginkgolide A	Antiplatelet	Class III	Solid dispersion, nano particles	[9][53][54][55]
		Ginkgolide B	Antiinflammatory pancreas, anti allergic, anti oxidant, neuroprotective, Antiplatelet	Class III	nanoemulsion	[9][56][57][58][53]
		Ginkgolide C	Antiplatelet, Antiadipogenik	Class III	Solid dispersion, nano particles	[9][54][55][59]
		Quercetin-3-O-coumaryl-glycosyl-rhamnosid	Anticancer, antihypertension	Class III	Formation of inclusion complexes with cyclodextrin	[43][37][60]
8.	Ginseng	Ginsenoside Rb1	Anti obesity and antihiperglikemia	Class III	Lipid base formulation	[9][61][62]
		Ginsenoside Rb2	Antidiabetes, Antikolesterol, and lower triglycerides	Class III	Mikroemulsion	[9][63][64][65]
		Ginsenoside Rc	Anti oxidant, anti inflamatory	Class III	NA	[9][66][67]
		Ginsenoside Rd	Imunosupressant, antifungal, acute anti stroke ischemia	Class III	micronization	[9] [68][69][70][71]
		Ginsenoside Re	Antioxidants and antihiperlipidemia	Class III	micronization	[9][72][71]
		Ginsenoside Rf	Antinociceptive and antiinflamatory, anti acne, and hair growers.	Class III	NA	[9][73][74]
		Ginsenoside Rg1	Immunomodulator, anti amnesty and anti aging	Class III	Lipid base formulation	[9][75][76][77]
		Ginsenoside Rg2	improve cerebral and anti-edema circulation	Class IV	NA	[9][78]
9.	Licorice	Glyccyrrhizic Acid	Antiinflamatory	Class IV	ionic liquid-based silica sorbent (cairan ionik)	[9][79][80]
10.	Milk Thistle (Kenikir)	Silybin A	Antioxidant, liver disease therapy	Class III	Formation of Silybin-phosphatidylcholine complex	[9][81][82]
		Silybin B	Antioxidant	Class III	Formation of Silybin-phosphatidylcholine complex	[9] [81][82]
11.	Red Clover	Biochanin A	Antipoliferation and anti-inflammatory	Class IV	encapsulation in mixed micelles containing pluronic F127 and plasdone S630	[9] [83][84]
		Daidzein	Antiinflamatory	Class IV	Solid dispersion	[9][85][86]
		Formononetin	Anticholesterol	Class II	NA	[9][87]
		Genistein	Antiinflamatory	Class IV	Particle size reduction	[9] [85][88]
12.	Senna	Sennoside B	Laksatif	Class III	NA	[9][89]
13.	St.John's Wort	Hyperforin	Antidepresant	Class II	Nano-particles	[9][90][91]
		Hypericin	Antivirus, Antidepressants, Anticancer	Class IV	Nano-particles	[9][92][93]
		Pseudohypericin	Antivirus, Antidepressant	Class IV	NA	[9][94]

The Following Describes Efforts to Improve Solubility [95]:

- Physical modification by modifying particle size (micronization and nanosuspensi) modification of ordinary crystals such as polymorph, amorphous form and cocristalisation, drug dispersion in carriers such as eutectic mixture, solid dispersion, solid solution and cryogenic techniques.
- Chemical modifications, such as pH change, buffer use, derivatization, complexation, salt formation
- Other techniques such as the Supercritical fluid process, the use of adjuvants (surfactants), stabilizers, Kosolvensi, hydrotrophy, and new excipients.

Micronization

One conventional technique to reduce particle size is micronization. The intrinsic solubility of the drug is often related to the particle size of the drug. By reducing the particle size, the drug surface area increases and drug dissolution also increases. Conventional methods of particle size reduction, such as comminution (particle separation) and spray drying, depend on mechanical pressure to separate the active compound. Micronization is used to increase the dissolution surface area [96].

Nano suspension

Nanosuspension is a nano-sized colloidal dispersion of drug particles stabilized by surfactants [97]. Preparation of nanosuspensi starts from 0.1 µm micronization up to 300 µm then proceeded to nanonization [98]. Nanosuspension can increase the solubility of drugs in water as well as lipid media. Nanosuspensi can be applied as an intravenous, oral, parenteral, ocular, topical and pulmonary preparation and has good results. Making nanosuspensi can be done by reducing the particle size first with Vibrating Ball Mill and ultrasound tools. Decrease in particle size means increased surface area, increased speed of dissolution of active substance.

Solid Dispersion

The solid dispersion is the dispersion of one or more active ingredients in an inert solid carrier. Solid dispersion is one of the techniques in improving the dissolution, absorption and therapeutic effect of a drug. Solid dispersion refers to a solid product consisting of at least two distinct components, having a hydrophilic and hydrophobic matrix. For commonly used hydrophilic compounds are polyvinylpyrrrolidone (PVP), poly ethylene glycol (PEG). Surfactants such as Tween-80 can also be used in dispersion (95). In the research The dispersion system of solid kofein by using polyvinyl pyrrolidone (PVP) K-30 can increase the solubility of kofein compared to the form of physics mixture can be seen from the dissolution test where in the 35th minute at 4: 6% physical mixture it is 63.11% 4: 6% solid dispersion dissolved by 79.34% [47].

Solid Dispersion Technique

Many techniques can be performed on solid dispersion to improve the solubility of drugs that have hydrophobic properties

- Hot spin mixing, new technology in solid dispersion used for the production of amorphous systems. This technology works by combining drugs and carriers into a rapidly spinning hot vessel, allowing the material to melt and then remove the material to the cooling tower. This proved to be an effective platform for dispersed solid production containing testosterone, diegonest and progesterone [99][100].
- Co-evaporation is a solid dispersion technique by dissolving drugs and carriers into organic solvents. After complete dissolution, then evaporation is carried out. The solid mass is like clay, dried and sieved.
- Co-precipitation is a solid dispersion technique used for the simultaneous precipitation of more than one component.
- Freeze-drying, is freeze drying by removing the water content of the frozen product without going through the liquid phase first.
- spray drying is a drying process by exposing liquid particles (in droplets) to hot-gas bursts with temperatures higher than droplet temperatures or the process of converting liquids into solid products, used in food, pharmaceutical, chemical and nanotechnology industries.

  The principle of spray drying is simply used by spraying liquid into the hot gas stream, evaporating and drying droplets in the distribution and separating and collecting

solid particles from the gas stream. The process is very fast and the gas-product contact is very short. The gas temperature drops rapidly due to intensive evaporative cooling while the droplet temperature remains low and heat-sensitive products can be processed. Movement of droplets and particles following the gas stream in the dryer [101],

- HME (Hot Melt Extrussion) [102]

In the pharmaceutical industry melt extrusion has been used with various purposes, namely:

- Increase the dissolution rate of the drug formed by disperses solid or solid solution.
- Control and modify drug release
- Covering the bitter taste of the active ingredient. The bioavailability of the oral preparations is dependent on the solubility and permeability of the drug.

HME (Hot Melt Extrusion) is commonly used in plastics, rubber, and food industries. Currently widely used in various applications namely solid dispersion, microencapsulation, targeted drug delivery, flavor closure, film preparations, implants, continuous release, nanotechnology, and floating drug delivery [103].

HME (Heat Melt Extraction) is the processing of polymeric materials for the mixing process of molecular polymer and / or polymer and active ingredients. In pharmaceutical manufacturing, HME for dispersion of active substances in the matrix at the molecular level, or solid form .In the HME process, APIs and excipients are fed into the extruder, all components are cut, heated, polished, combined and dispersed, and ultimately by dies. With things to be taken into account are the melting of the extruder die, the pressure on the die, and the torque [104].

Materials Used for Preparation in HME (Hot Melt Extrusion)

- Polymers the selection of the right polymer as a matrix to form a stable solid solution is a crucial factor in HME. Polymers with high solubilization capacity are particularly suitable because they can dissolve large quantities of the drug. The polymer for HME should exhibit thermoplastic characteristics and must be thermally stable at the proper exchanger temperature.

  In developing the HME drug system, glass transitions and melting temperatures are important factors. The extractability of the polymer is primarily determined by Tg or Tm and viscosity melting (melt viscosity) [104].

- API (Active Pharmaceutical Ingredient) Less than 10% of new drug candidates show good solubility and high permeability, and 30-40% of the drugs appearing on the World Health Organization's Essential Drug List are reported to be less soluble in water or lipophilic. HME disperses the drug in a matrix at the molecular level by forming a solid solution [104].
- Plasticizer, such as triacetin, citrate ester, vitamin E TPGS (D-alpha tocopherol polyethylene glycol 1000 succinate) surfactant and low molecular weight polyethylene glycol.

Characteristics of the Materials used in HME [103]

- The materials must meet the same level of purity and safety as used in traditional dosage forms.
- The materials should be easily damaged inside the extruder and solidify on exit.
- The materials must be thermostable and maintain acceptable physical and chemical stability during the HME process and thereafter during long-term storage. The temperature stability of a single compound is a prerequisite for the process by using this HME, for a short process it does not rule out the possible thermo labile compounds to be used.
- The desired in vitro release and in vivo performance should be achieved by the final dosage form.

Based on Kolter and Karl [105] research entitled Suitability of Plasticized Polymers for Hot Melt Extrusion, Kollidon® VA 64, kollidon 12 PF and Soluplus® showed the best and most suitable polymers for HME (*Hot Melt Extrusion*). The polymer may be combined with a naturally occurring active substance such as the extract as it has been proven in the study [54] that with the HME (Hot Melt Extrusion) solid dispersion of ginkgo biloba extracts can increase dissolution rate and bioavailability.

Table 3: The advantages and disadvantages of Hot Melt Extrussion [103]

No	Advantages of HME	Disadvantages of HME
1.	Continuous process	Processing thermolable compounds
2.	High Troughput	Limited number of heat stable polymer
3.	Solvent free technique	Requires raw materials with high flow properties
4.	Increases solubility and bioavailability of poorly water-soluble drugs	Requires high energy supply
5.	No downstream processing required	
6.	Wide application in pharmaceutical industry	
7.	Useful for low compressibility index active pharmaceutical ingredients (APIs)	
8.	Comparatively thermodynamically stable	
9.	Exposure to oxygen in extrusion channel is limited	

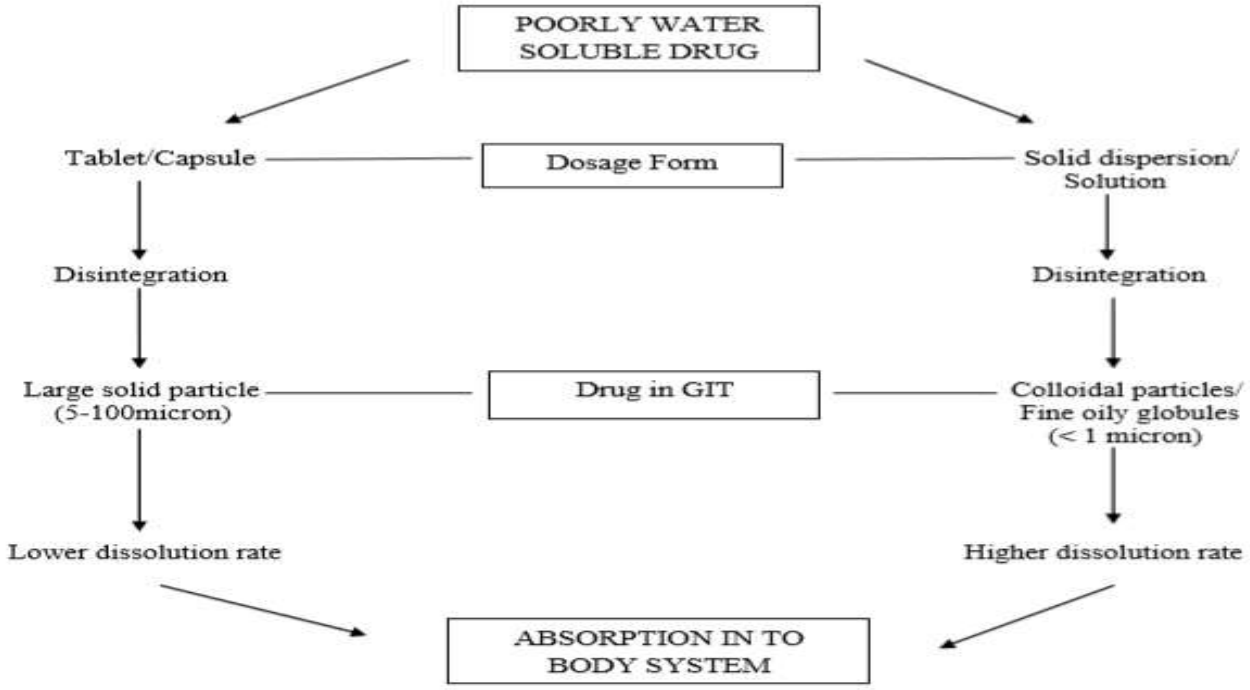

Figure 1:Bioavailability Improvement Scheme with Solid Dispersion compared with conventional tablets [106].

Advantages of Solid Dispersion

- Can reduce particle size: Preparation of solid dispersion results in particles by shrinking the particle size so that surface area is increased and dissolution rate increases. The end result is an increase in bioavailability [106].
- Can increase wettability: Wettability is improved during the production of solid dispersion. It has been suggested that the presentation of particles to the dissolution medium as a separate entity can physically reduce aggregation. In addition, many carriers used for solid dispersion may have wetting properties; then increased wetting may cause reduced agglomeration and increased surface area [106].
- Can increase drug porosity: Particles in solid dispersion are found to have higher porosity levels. Increased porosity also depends on carrier properties; for example, a solid dispersion containing a linear polymer produces larger and more porous particles than those containing reticular polymers thereby, resulting in a higher degree of dissolution. Increased porosity of solid dispersion particles also speeds up the drug release profile [106].
- Can lower the crystal structure of the drug to amorphous form. Drugs in an amorphous state: Soluble crystalline water solubility drugs, when in an amorphous state tend to have higher solubility. The drug in the amorphous state shows a higher drug release because no energy is needed to break the crystal lattice during the dissolution process. In solid dispersion, drugs are presented as a saturated solution after the dissolution of the system, and it is speculated that, if the drug settles, it is a metastatic polymorphic form with a higher solubility than the most stable crystal form [106].

- To increase solubility in water from drugs whose solubility is poor in water [107].
- To mask the taste of the drug substance [107].
- To prepare a fast disintegration oral tablet [107].
- To obtain a homogeneous distribution of small quantities of drugs in a solid state (105).
- To stabilize unstable drugs [107].
- To remove a liquid or gas compound [107].
- To formulate the main dose of quick release in the form of a slow release preparation [107].
- To formulate a dose of Sustained release or a prolong release regimen of dissolved drugs using a carrier of poor or insoluble solubility [107].

Solid Dispersion Mechanism in Increasing Solubility [108]

A number of methodologies can be adapted to increase the solubility of poor drugs in water and further to improve their bioavailability.

Reduce Particle Size

When solid dispersion is exposed to aqueous media, the carrier dissolves and releases the drug as fine colloidal particles. Improved surface results resulted in higher dissolution rates of poor water soluble drugs.

The Drug is Amorphous

Poor water-soluble crystalline crystals in an amorphous state tend to have higher solubility. This is because no energy is needed to break the crystal lattice in an amorphous state during dissolution.

Particles with High Porosity

Particles in solid dispersion are found to have high porosity. Increased porosity of solid dispersion particles speeds up the drug release profile. The increase in porosity depends on the carrier properties, that is, the yield of the linear polymer in the larger and more porous particles than the reticular particles.

Particles with Increased Wettability

The strong contribution to increased drug solubility associated with increased wettability of the drug has been verified in solid dispersion. Carriers with surface activity, i.e., cholic acid and bile salts can significantly improve the wettability properties of drug yields in enhancing dissolution profiles.

Disadvantages of Solid Dispersion [106]

- Solid dispersion is not widely used in commercial products because it is possible that during processing (mechanical pressure) or storage (temperature and moisture pressure) the amorphous form can crystallize.
- The effect of moisture on the storage stability of amorphous drugs is also of significant concern, as it can improve drug mobility and increase drug crystallization.
- Most of the polymers used in solid dispersion can absorb moisture, which can result in phase separation, crystal growth or conversion from amorphous to crystal state or from metastable crystal form to more stable structure during storage. This can lead to decreased solubility and dissolution rate. Therefore, the full potential exploitation of amorphous solids requires stabilization in solid state, and during in vivo performance.
- The scale is bad for manufacturing purposes.
- Great preparation methods and expensive.
- Reproducibility of physicochemical characteristics.
- Difficulty in incorporating into dosage formulations.
- Improved manufacturing process.
- The stability of the drug and its carrier.

Classification of Solid Dispersions

The drug data is dispersed molecularly in amorphous form (Cluster) or in crystal particles by melt method or solvent method. Therefore, based on the molecular arrangement, different types of solid dispersion can be distinguished as in Table 4 [106].

Table 4: Type of Solid Dispersion [106]

No.	Solid dispersion type	Matrix *	Drug **	Remarks No.	Phases
1.	Eutectics	C	C	First type of solid dispersion prepared	2
2.	Amorphous precipitations in crystalline matrix	C	A	Rarely encountered	2
3.	Solid solutions	-	-	-	-
i	Continuous solid solutions	C	M	Miscible at all composition, never	1

				prepared	
ii	Discontinuous solid solutions	C	M	Partially miscible, 2 phases even though drug is molecularly dispersed	2
iii	Substitutional solid solutions	C	M	Molecular diameter of drug (solute) differs less than 15% from the matrix (solvent) diameter. In that case the drug and matrix are substitutional. Can be continuous or dis-continuous. When discontinuous: 2 phases even though drug is molecularly dispersed.	1 or 2
4.	Interstitial solid solutions	C	M	Drug (solute) molecular diameter less than 59% of matrix (solvent) diameter. Usually limited miscibility, discontinuous Example: Drug in helical interstitial spaces of PEG.	2
5.	Glass suspension	A	C	Particle size of dispersed phase dependent on cooling/ evaporation rate. Obtained after crystallization of drug in amorphous matrix	2
6.	Glass suspension	A	A	Particle size of dispersed phase dependent on cooling/ evaporation rate. Many solid dispersions are of this type	2
7.	Glass solution	A	M	Requires miscibility OR solid solubility, complex formation upon fast cooling OR evaporation during preparation, many (recent) examples especially with PVP	1

* A: matrix in the amorphous state, C: matrix in the crystalline state ** A: drug dispersed as amorphous clusters in the matrix, C: drug dispersed as crystalline particles in the matrix, M: drug molecularly dispersed throughout the matrix

Table 5:Polymers / Matrices used in solid dispersion [109]

Tipe Polimer	Polimer
Polimer sintetik	Polyvinylpyrrolidone (povidone)
	Polyethylene glycols
	Polymethacrylates
Polimer berbasis produk Alami (cellulose derivatives, starch derivatives)	Hydroxypropylmethylcellulose
	Ethylcellulose
	Hydroxypropylcellulose
	Cyclodextrines

Cryogenic Technique

This technique is the process of forming nano particles of porous structures and increasing the solubility of drugs performed under low temperature conditions.

Salt Formation

Drugs that have acidic or alkaline properties if changed in salt form will increase solubility and their rate of dissolution, such as the salt form Sodium ibuprofen has a higher drug release than the profen mothers so as to provide faster drug action [110].

PH Setting

The drug can be increased solubility in water by the pH setting. The solubility of the acid and the weak base will decrease as the pH increases while the weak acid will increase its solubility by increasing the Ph. The pH adjustment will affect the solubility of a drug such as a change in pH from pH 6.2 to 1.5 and 12.5 causes an increase in solubility ofloxacin about ten times [111]

Surfactant Addition

The addition of surfactants, especially non-ionic surfactants, will increase the solubility of the drug.

Hydrotropic

Is a solubilization process, in which the addition of a large amount of second solute, will result in increased solubility of the first solute in water. The hydrotropic agent is an ionic organic salt, comprising an alkali metal salt of various organic acids. Additives or salts that increase solubility in a given solvent are said to be "soluble salts" of the solute and salts which decrease the solubility of the "soluble salt" of the solute. Hydrotrophy indicates increased solubility in water due to the presence of a large number of additives [95].

Supercritical Fluid Process / Fluid Supercritis

Supercritical fluid methods are mostly used with carbon dioxide (CO2), which is used as a solvent for drugs and matrices or as an anti-solvent. When supercritical CO2 is used as a

solvent, the matrix and drug are dissolved and sprayed through the nozzle, into an expansion vessel with lower pressure and particles soon to form. This technique does not require the use of organic solvents and since CO2 is considered environmentally friendly, this technique is called 'solvent free'.

This technique is known as Rapid Expansion of Supercritical Solution (RESS). However, the application of this technique is very limited, since the solubility in CO2 of most pharmaceutical compounds is very low (<0.01% by weight) and decreases with increasing polarity [107].

Co-crystals

The crystalline is a crystalline complex in which two or more neutral molecules are in the stoichiometric ratio [112]. A cocristal study was conducted between indomethacin-saccarin and had the result that the co crystal was not hygroscopic and the rate of dissolution was faster than that of gamma indomethacin [113].

Conclusion

Most secondary metabolites contained in natural materials fall into class II is low solubility, high permeability and class III that is high solubility and low permeability in BCS (Biopharmacetics Classification System) So the problems that are often encountered when formulating natural materials is a challenge to increase the solubility of active substances in order to achieve the therapeutic effect of a natural compound. One solution with solid dispersion method that has many advantages such as can increase solubility, and mask the unpleasant taste of natural compounds.

Techniques that are still rarely used in Indonesia in terms of solid dispersion applications are with HME (Hot Melting Extrussion) which can cover the deficiencies in solid dispersion. Solid dispersion method HME (*Hot Melting Extrusion*) application can increase dissolution rate and bioavaibility of active substances derived from natural materials.

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