Review Article

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Solid Dispersion Technology for Improving the Solubility of Antiviral Drugs

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ABSTRACT

Most drugs, including antiviral drugs, show low solubility in water, which affects dissolution, bioavailability, and therapeutic effectiveness. Therefore, many antiviral drugs are given in very large doses. One of the efforts to overcome these problems is the application of solid dispersions in which polymers and surfactants can trap drug molecules that are in the amorphous phase. Drugs in a hydrophilic carrier will increase wettability, water absorption capacity, and porosity of particles, so that the drug is released better. This review article will discuss the development of technology in solid-state, how solid dispersion overcomes the lack of solubility and the rate of dissolution of antiviral drugs, and solid dispersion preparation techniques. We also discuss some examples of successful applications of solid dispersion methods to antiviral drugs that have been circulating on the market. Overall, this review article offers information of innovation in the development of antiviral drugs to provide more solid dispersion antiviral drug products.

Keyword: *antiviral drugs; poorly aqueous solubility; solid dispersion technology*

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INTRODUCTION

Viral infections have a significant impact on global health which causes millions of deaths every year (Lembo et al., 2018). For example, the corona virus infection that is currently happening which spread so fast that we need an appropriate and effective antiviral drug. The development of antiviral drugs in recent years has continued to increase. In 1990 only 5 drugs were licensed as antiviral drugs, meanwhile now there are over 40 antiviral drugs are on the market, including anti-human immunodeficiency virus (anti-HIV) and herpes simplex virus (HSV) drugs (Lembo and Cavalli, 2010). Many antiviral drugs products in the market are given by oral route. However, most of these antiviral drugs have poor solubility and low permeability. This is a very crucial obstacle to be considered because it will affect the bioavailability and effectiveness of the therapy. Based on the Biopharmaceutical Classification System (BCS) system, drugs that have poor solubility, high permeability, are included in class II (low solubility, high permeability), while other problematic BCS classes are III (high solubility, low permeability), and IV (low solubility, low permeability) (Amidon et al., 1995). Some antiviral drugs that have poor solubility are including ritonavir (0.4 mg/mL) (Dengale et al., 2015), zidovudine (10 mg/mL) (Yoshida et al., 2015), and telaprevine (0.0355 mg / mL) (Xiong et al., 2019), while antiviral drugs with low permeability are including acyclovir ($1.59\ 10^{-6}$ cm/s) (Ates et al., 2016; Nart et al., 2015), zidovudine ($0.05\ 10^{-4}$ cm/s) (Quevedo and Briñón, 2009), and saquinavir ($0.746\ 10^{-6}$ cm/s) (Kuo and Kuo, 2008). Based on this, it is necessary to develop a method to improve the solubility of antiviral drugs.

Some methods that have been developed to improve the solubility of drug including changing crystal habits (salt formation, metastable crystals, and co-crystals), amorphization, reduction in particle size (nanoparticles and micronization), or interactions between molecules, such as the formation of complex with cyclodextrin, emulsification, pH modification, surfactant addition, and delivery using mesoporus (Göke et al., 2018; Kawabata et al., 2011; Singh et al., 2011).

Among these methods, the formation of complexation with cyclodextrin and nanoparticles has been applied to antiviral drugs. The solubility of acyclovir-β-cyclodextrin increased 2 times higher than that of original acyclovir (Nair et al., 2014), the solubility of rilpivirine-nanosponge also increased 2 times higher than that of single rilpivirine (Zainuddin et al., 2017). However, this method also has limitation. For example, compounds must be able to form complexes with ligands, the appropriate determination of active pharmaceutical ingredient (API) type to minimize precipitation, and cyclodextrin has the potential to cause toxicity (Gould and Scott, 2005).

Nanoparticles in nanocarrier nanocarriers have also been applied to increase bioavailability. Acyclovir-niosome showed an increase in bioavailability 2 times than a single acyclovir (Attia et al., 2007), whereas lopinavir-liposome showed a bioavailability of 2.24 times that of a single lopinavir (Patel et al., 2017). However, this system has a low drug loading capacity, low physical stability during storage, susceptibility to leakage, difficult to produce on a large scale, and relatively expensive (Grande et al., 2019).

Solid dispersion is other method to increase solubility of API. In the last 10 years research on the method of solid dispersion has continued to increase (Cid et al., 2019; Huang and Dai, 2014; Zhang et al., 2018). Solid dispersions utilize amorphous solids that do not have a crystal lattice so that only requires little energy to dissolve. In solid dispersion systems the homogeneous dispersed amorphous form in the polymer matrix. This can increase wettability, water absorption capacity, and porosity of particles, so the dissolution rate becomes faster and bioavailability increases (Ilevbare et al., 2013; Vo et al., 2013; Vasconcelos et al., 2007). Amorphous, however, can transform into crystalline due to changes in temperature and humidity during storage (Edueng et al., 2017; Zhu et al., 2016). To minimize probability, the selection of polymer is crucial. Some factors which might affect are hygroscopicity and T_g temperature (glass transition). T_g is defined as a physical change in the polymer from rubbery/plastic to be glassy/brittle (Ulven, 2016). The polymers we have in solid dispersion must have higher temperatures than drug T_g to prevent changes in dispersed drug molecules (Mazumder et al., 2017; Xie and Taylor, 2017). In addition, it is important to pay attention to the preparation conditions, preparation methods, and product storage conditions (Newman, 2016).

Some of the advantages offered by solid dispersion have been applied to antiviral drugs, including Intelence® (etravirine) produced by Tibotec, Yardley, PA and Kaletra® (lopinavir and ritonavir) by Abbott, USA. This shows that solid dispersion can solve the problem of commercial antiviral drug products. This article tries to summarize the development of the classification of solid dispersion generation, the mechanism of solid dispersion to overcome the lack of solubility and dissolution rate of antiviral drugs, some reports related to their application to antiviral drugs, as well as some drugs examples that have been in the market.

METHODS

This review article uses literature from year 2000 – 2021 extracted from PubMed and Google Scholar by using the keywords “solid dispersion of antiviral drugs”, “solubility enhancement of antiviral drugs”, as well as “enhanced dissolution of poorly soluble antiviral drugs”. The literature selected in this review article are the ones who studied the increasing solubility and dissolution rate of antiviral drugs using solid dispersion methods. We exclude literature where antiviral drugs are not given by oral route and literature which do not address efforts to increase solubility. The flowchart of the methodology can be seen in Figure 1.

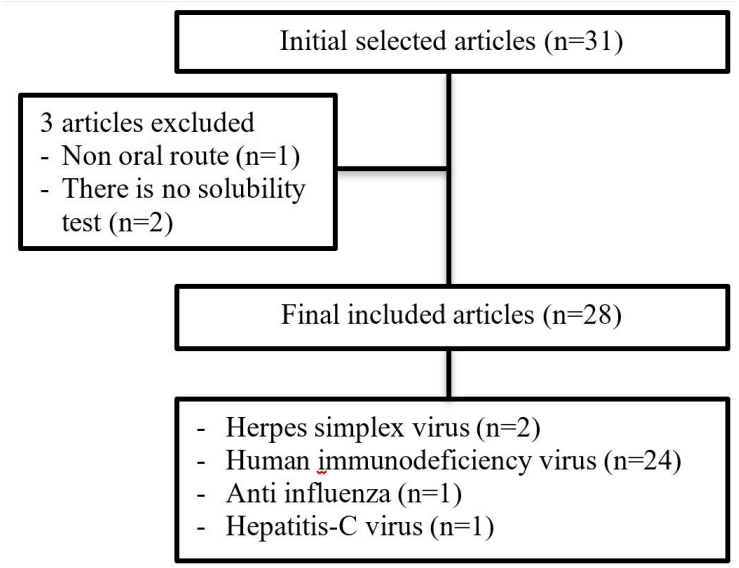

Figure 1. Flowchart of the literature selection

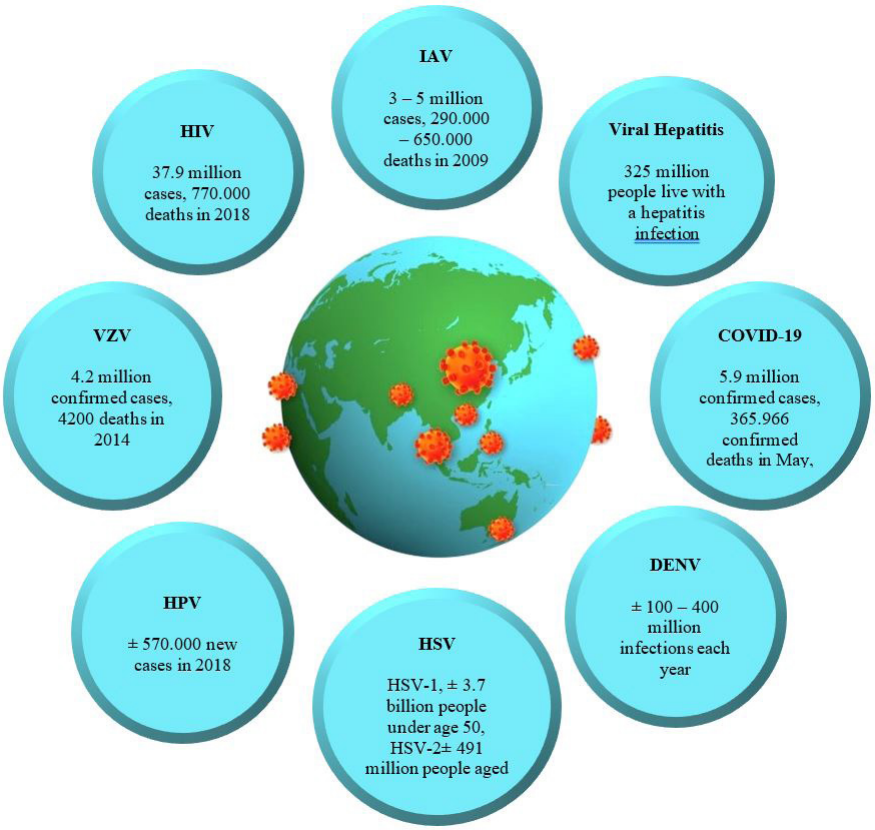

Figure 2. Global Impact of Viral Diseases. HIV (human immunodeficiency virus), VZV (varicella zoster virus), HPV (human papillomavirus), HSV (herpes simplex virus), DENV (dengue virus), COVID-19 (coronavirus disease), and IAV (influenza A virus).

Current Antivirus Therapy

Until now the epidemic of viral infections is still a global problem with the potential for death which continues to increase. Viruses are indeed very small, even smaller than bacteria (Hyman and Abedon, 2012). However, they have the ability to multiply and move from one organism to other organisms very quickly. Based on data obtained from the World Health Organization (WHO), huge global viral infections that happened so far can be seen in Figure 2.

Based on the article summarized by Chaudhuri et al. (Chaudhuri et al., 2018) in 1987-2017 there were 88 antiviral drugs that have been approved by the Food and Drug Administration (FDA) which are mostly intended for the treatment of human immunodeficiency virus (HIV), hepatitis-B virus (HBV), hepatitis-C virus (HCV) infections, and herpes simplex virus (HSV). However, most antiviral drugs have problems, which include poor solubility, low bioavailability, and the short half-life which lead to high doses, as presented in Table 1.

Reviewing some of the antiviral drug problems above, this study will discuss how the application of solid dispersions can be used to achieve therapeutic effectiveness with various advantages to solve these problems.

Solid Dispersion Generation

Solid dispersions generally consist of one or more crystalline or amorphous active substances which are dispersed in an excipient or matrix as an inert carrier (Arora et al., 2012). The function of the matrix, besides of being a carrier, is also improving the stability of drug molecules, since the amorphous form tends to undergo recrystallization during storage. Interactions between drugs and carriers inhibit molecular mobility thereby preventing nucleation (Arora et al., 2012; Meng et al., 2015). Several factors to consider in choosing a carrier, are thermal stability, low vapor pressure, high molecular weight, non-toxic, easily soluble in water (hydrophilic) and gastrointestinal fluid (Hancock & Zografi, 1997; Yang, Grey, & Doney, 2010).

Solid dispersion technology can be classified based on molecular arrangements which are divided into four groups, namely eutectic mixtures, solid solutions, amorphous solid solutions, glass solutions, and glass

Table 1. Physicochemistry and biopharmaceutical properties of antiviral products in the market (Arora et al., 2012)

Group	Drug	Solubility (mg/ml)	Log P	$T_{1/2}$ (h)	Route	Dose	Brand name
HSV	Idoxuridine	1.6	-0.53	0.5	Intravena	0,1-0,5%	Herplex®
	Acyclovir	2.5	-1.56	2.5-3.5	Oral, topical, intravena	200-400 mg	Zovirax®
	Valacyclovir	70	-0.3	2.5-5.3	Oral	500 mg	Valtrex®
	Famciclovir	25	0.6	10	Oral	500 mg	Famvir
	Ganciciclovir	2.6	-1.7	2-4	Oral, intravena	500 mg	Vitrasert
	Foscarnet	1.68	-2.1	3.3-6.8	Intravena	40 mg/kg	Foscavir®
ARV	Zidovudine	10	0.05	0.5-3	Oral, IV	300 mg	Retrovir®
	Didanosine	27.3	-0.2	0.5	Oral	200 mg	Videx EC®
	Zalcitabine	76.4	-1.3	2	Oral	200 mg	Hivid®
	Stavudine	83	-0.8	0.8-1.5	Oral	30 mg	Zerit®
	Lamivudine	70	-1.4	5-7	Oral	300 mg	Epivir®
	Abacavir	77	1.1	1.54	Oral	300 mg	Ziagen®
	Nevirapine	0.007	1.75	45	Oral	200 mg	Viramune®
	Efavirenz	<0.001	4.6	40-55	Oral	600 mg	Sustiva®
	Delavirdine	0.2942	2.8	5.8	Oral	200 mg	Resciptor®
	Ritonavir	1.26	3.9	2-5	Oral	600 mg	Novir®
	Amprenavir	0.04	2.43	7.1-10.6	Oral	1200 mg	Agenerase®
	Lopinavir	1.92	4.69	5-6	Oral	400 mg	Kaletra®
Anti-influenza	Amatadine	6.2	2.4	10-14	Oral	200 mg	Symmetrel®
	Rimatadine	50	3.6	25-30	Oral	100 mg	Flumadine®

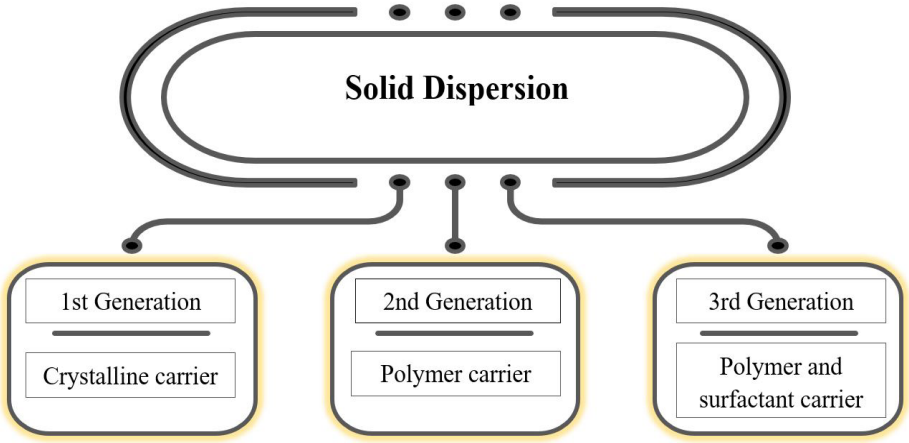

Figure 3. Classification of solid dispersion

dispersions (Vasconcelos et al., 2007; Yu et al., 2015). In addition, solid dispersions are also classified into three generations based on various types of carriers as shown in Figure 3.

First generation solid dispersion

The first generation of solid dispersion was introduced by Sekiguchi and Obi in 1961 and 1964 against sulfathiazole and chloramphenicol with eutectic mixing

using urea as a carrier. The results indicated that urea, which is hydrophilic, is able to increase absorption thereby affecting the bioavailability (Hayata, 2002). Eutectic mixes are defined as mixtures of two or more components (drugs and excipients or between excipients) which usually do not form new structures. At certain ratios can inhibit the crystallization process and produce solids that have a melting point lower than one of the component melting points (Abbott et al., 2017; Hoang Pham, 2013; Williams et al., 2013).

Application of crystalline carriers in antiviral drugs by Awasthi et al. (2017) conducted a study with a hydrotropic mixture technique using citric acid, lactose, mannitol, and urea to increase nevirapine solubility (0.09941 mg/mL) (Awasthi et al., 2017). Hydrotropic is a molecular phenomenon where substances that have high solubility in water can increase the solubility of substances that are not soluble in water. Hydrotropic compounds are generally organic salt ion compounds. The addition of acid compounds can also increase the solubility of insoluble substances (Hodgdon and Kaler, 2007). With a ratio of 5:35 of lactose and citric acid, the increase in nevirapine solubility is 10.654 mg/mL, 107.13 times higher than single nevirapine (Awasthi et al., 2017). A ritonavir-sorbitol solid dispersion with a ratio of 1:4 for 45 minutes shows a release of 92%. Ritonavir-sorbitol solid dispersions undergo high release because sorbitol has an alcohol group that elicits strong interactions between ritonavir-sorbitol and is influenced by its hydrophilicity (Sinha et al., 2010). It was concluded that crystalline carriers could be an option for increasing drug solubility and dissolution.

Second generation solid dispersion

Unlike the previous generation, this generation of solid dispersion used amorphous material as a carrier. This is the carrier most used in the application of solid dispersions. These carriers are polymers which can be natural or synthetic polymers. Examples of natural polymers are including ethyl cellulose (EC) (Yan et al., 2016; Ohara et al., 2005) and hydroxypropyl methylcellulose (HPMC) (Javeer and Amin, 2014; Shin et al., 2019; Wlodarski et al., 2015), while synthetic polymers including polyvinylpyrrolidone (PVP) (Indulkar et al., 2019; Usmanova et al., 2018), polyethylene glycol (PEG) (Guedes et al., 2011; Xu et al., 2007), and Eudragit® (Jafari, 2013; Pradhan et al., 2016). Amorphous polymers offer high T_g and viscosity which causes the slow relaxation of the polymer long chain thereby blocking the mobility of the dispersed drug molecules. In addition, the presence of functional groups that form hydrogen bonds causes specific interactions to increase drug solubility in the polymer, increase wettability, inhibit phase separation, and prevent recrystallization (Saluja et al., 2016; Van, 2012; Marsac et al., 2010).

Several studies have shown the successful use of polymers to increase the dissolution of antiviral drugs, such as studies conducted by Alves et al. (Alves et al., 2014) efavirenz solid dispersion - PVP K-30 prepared by the kneading method at a ratio of 4:1 within 60 minutes gives the highest dissolution percentage of 58.83% or 1.72 times that of a single efavirenz (34.19%). This is associated with the hydrophilic nature of PVP K-30 which reduces the interface tension and increases the wettability of efavirenz. In the study of Gadade et al. (2015), the solubility of solid dispersion of acyclovir-Eudragit® EPO (2.7 mg/mL) at a ratio of 1:4 increased 2.6 times higher compared to single acyclovir (1.03 mg/mL). The dissolution study in 60 minutes showed the highest dissolution percentage of 97.92%, 1.84 times higher than a single acyclovir (53.03 mg/mL) (Gadade e al., 2015).

Third generation solid dispersion

Considering the very promising potential for solid dispersion, developments in the pharmaceutical field are continuing. Limitations of previous generations, such as the solubility of drugs with polymers and physical stability can be overcome by the addition of surfactants. Surfactants can increase miscibility, physical stability, and prevent precipitation below the saturation point (Feng et al., 2018; Mah et al., 2016; Pouton, 2006). Therefore, third generation of solid-state dispersion which involve surfactants success to reduce the surface tension between liquids and solids. Some examples of surfactants, including Gelucire® (Fukushima et al., 2007; Damian et al., 2002; Damian et al., 2000), tween 80 (Akbari et al., 2015; Rashid et al., 2015), and poloxamer 407 (Simonazzi et al., 2018; Eloy et al., 2015).

Damian et al. (2002) conducted study on the UC-781 thiocarboxanilide antiviral prepared by melting technique using PEG 600 and Gelucire® 44/14. The results showed solid dispersion increased 280 times compared to pure UC-781 thiocarboxanilide (0.168 µg/mL) (Damian et al., 2002). Increased solubility is accompanied by an increase in dissolution rate. The UC-781 thiocarboxanilide solid dispersion had an increase in dissolution rate of 80-90% for 6 hours, while the pure UC-781 thiocarboxanilide was only 40%. Another study conducted by Sinha et al. (Sinha et al., 2010) showed solubility ritonavir-Gelucire® 44/14 increased to 220 µg/mL or 220 times higher than a single ritonavir (1 µg/mL). This is because Gelucire® 44/14 decreases the interface tension between the drug and the solvent and increases the wettability of micelles (Damian et al., 2000).

***In vitro* and *in vivo* Study of Solid Dispersion**

In addition to solubility, dissolution is also one of the very important scientific standards in the development of preparations given by oral route because it will affect absorption and have an impact on bioavailability.

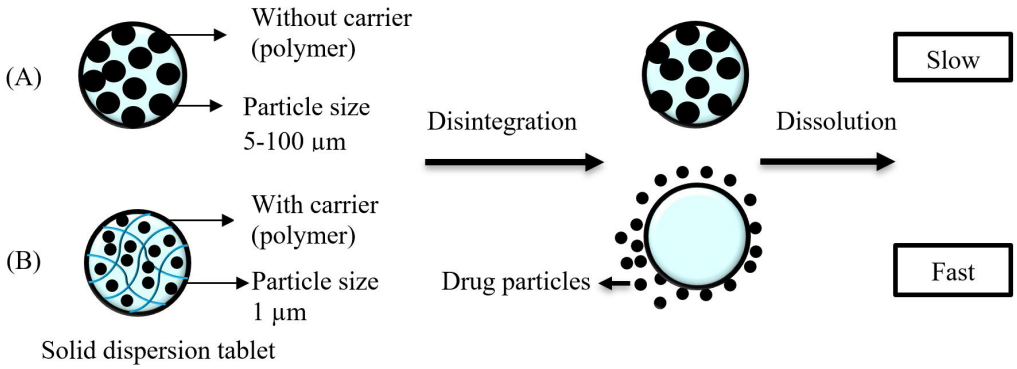

Figure 4. Drug dissolution rate in a solid dispersion system (A) without a carrier and (B) with a carrier (Craig, 2002).

The mechanism of drug release from a solid dispersion system is complex, depending not only on the nature of the drug but also on the nature of the carrier. The process of drug dissolution is illustrated in Figure 4.

As illustrated in Figure 4 particles dispersed in a carrier have smaller sizes resulting in an increase in particle wetting. The smaller particle size also minimizes agglomeration (Santos et al., 2018; Craig, 2002; Xu et al., 2012). Molecularly dispersed drugs are released in a saturated state where the hydrophilic carrier dissolves first (Jackson et al., 2016). The efficacy of solid dispersion to increase the rate of dissolution of antiviral drugs has demonstrated its success. The increase in dissolution rate is presented in Table 2.

The use of first, second and third generation polymers have been developed as a carrier in antiviral drug solid dispersion systems. Based on Table 2., hydrophilic carriers are most widely used because they can increase the wettability of dispersed drug particles, such as HPMC, Kollidone®, PVA, and PEG (Zi et al., 2019; Xiong et al., 2019; Xu et al., 2007; Damian et al., 2000). In addition surfactant carriers have also been used, including Soluplus® and Gelucire® (Lavra et al., 2017; Goddeeris et al., 2008).

In developing a product, studying the relationship between *in vitro* and *in vivo* studies is very important to do. It is assumed that the faster dissolution will be the faster absorption will occur and will have an impact on bioavailability (Zi et al., 2019; Law et al., 2004). This is evidenced from several studies (Table 2). Drugs that belong to the BCS III and IV groups, generally use surfactants to help increase drug absorption. The study conducted by Zi et al. (Zi et al., 2019) Lopinavir dispersed in Soluplus® showed a significant increase in dissolution and permeability compared to lopinavir alone, so C_{max} also increased 3.64 times. Soluplus® is quite effective in increasing the solubility of lopinavir by forming H-bonds and micelles that function to increase permeability 2.22 times higher than single lopinavir.

Solid Dispersion Manufacturing

Solid dispersions do not only develop carriers, but also manufacturing methods to prepare large scale production. Several methods that can be used for manufacturing solid dispersions are presented in Figure 5. And some methods have been applied to antiviral drugs are presented in Table 3.

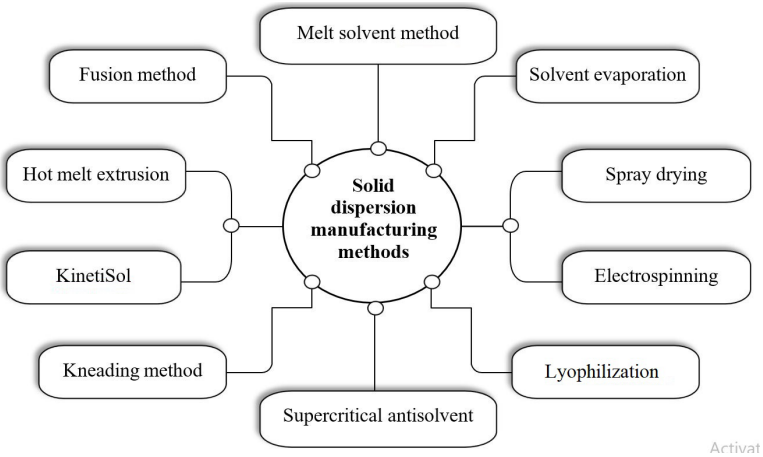

Figure 5. Solid dispersion manufacturing methods

Table 2. Comparison of dissolution rates of pure drugs with solid dispersion products

Drug	Dissolution pure drug (%)	Solid dispersion	Dissolution efficiency (%)	Dissolution enhancement (folds)	C_{max} (Folds)	Reference
Acyclovir	D_{60min} 53.03	ACV – Kollidone® VA64	D_{60min} 70.70	1.33		(Gadade et al., 2015)
		ACV – Soluplus®	D_{60min} 77.45	1.46		
		ACV – Eudragit®	D_{60min} 97.92	1.84		
Acyclovir	D_{90min} 78.88	ACV – Pluronic F68®	D_{90min} 99.91	1.25		(Nart et al., 2015)
		ACV – HPMC K100M®	D_{90min} 99.27	1.25		
		ACV – Chitosan	D_{90min} 94.78	1.20		
Efavirenz	D_{30min} 45	EFV – Eudragit® EPO	D_{30min} 96	2.13		(Sathigari et al., 2012)
		EFV – Plasdone S-630	D_{30min} 82	1.82		
Efavirenz	D_{45min} 32	EFV – Soluplus® – HPMCAS-HF	D_{45min} >91	3.7		(Pawar et al., 2016)
Efavirenz	D_{120min} 35.53	EFV – Soluplus®	D_{120min} 93.77	2.63		(Lavra et al., 2017)
Efavirenz	D_{60min} 34.19	EFV – PVP K30®	D_{60min} 58.83	1.72		(Alves et al., 2014)
Lopinavir	D_{120min} 20.8	LPV - Kollidone® VA64	D_{120min} 25.7	1.23	2.26	(Zi et al., 2019)
		LPV – Soluplus®	D_{120min} 37.8	1.81	3.64	
Ritonavir		RTV – CAP Adp 0.33	D_{5h} 20			(Mazumder et al., 2017)
		RTV – CAP Adp 0.85	D_{5h} 27			
		RTV – CA-320S Seb	D_{5h} 30			
		RTV – CMCAB	D_{5h} 40			
Ritonavir	D_{3h} 15	RTV – PVPVA	D_{3h} 35	2.33		(Indulkar et al., 2019)
Ritonavir	D_{45min} 20	RTV – Gelucire	D_{45min} 85.43	4.27		(Sinha et al., 2010)
		RTV – Sorbitol	D_{45min} 45.5	2.27		
		RTV – Gelucire	D_{45min} 80.9	4.04		
		RTV – Sorbitol	D_{45min} 60.9	3.04		
Ritonavir	D_{60min} 50	RTV – PVP VA64 – Span 20	D_{60min} > 80	1.6	1.81	(Zhao et al., 2019)
Ritonavir	D_{2h} 5.68	Milk	D_{2h} 55.26	9.72		(Dhore et al., 2017)
Ritonavir	D_{30min} 20	RTV – 8000	D_{30min} 100	2	13.7	(Law et al., 2004)
Saquanavir		SQV – curcumin			0.36	
Telaprevir	D_{30min} 3.1	TLV – HPMC	D_{30min} 62.6	20.9		(Xiong et al., 2019)
Thiocarboxanilide UC-781	D_{6h} 40	UC-781 – PEG 6000 – Gelucire® 44/14	D_{6h} 80 – 90	2.25		(Damian et al., 2002)
Thiocarboxanilide UC-781	D_{4h} 37.1	UC-781 – TPGS 1000 – Eudragit E100	D_{4h} 58	1.56		(Goddeeris et al., 2008)

HPMC: hydroxypropyl methylcellulose, PVP: Polyvinylpyrrolidone, PEG: Polyethylene glycol, TPGS: D -α-Tocopherol polyethylene glycol *1000* succinate, CMCAB: carboxymethyl cellulose acetate butyrate, CAP Adp: cellulose acetate propionate adipate

Table 3. Solid dispersion preparation methods on antiviral drugs

Drug	BCS	Method	Polymers	Physical stability	Reference
Umifenovir		Fusion method	PEG 4000, PEG 6000, PEG 8000		(L. Xu et al., 2007)
Thiocarboxanilide UC-781	II	Fusion method	PEG 6000 – Geluceri® 44/14		(Damian et al., 2000)
Efavirenz	II	Hot melt extrusion	Plasdone S-630, Eudragit EPO	EFV - Plasdone S-630 does not show crystallization after 9 months of storage	(Sathigari et al., 2012)
Efavirenz	II	Hot melt extrusion	Soluplus® - HPMCAS-HF	HPMCAS-HF has no effect as a stabilizer after 6 months	(Pawar et al., 2016)
Ritonavir	IV	Hot melt extrusion	PVP-VA64, Span 20	RTV undergoes recrystallization after 6 months of storage	(Zhao et al., 2019)
Ritonavir	IV	KinetiSol® dispersing	PVA		(LaFountaine et al., 2016)
Efavirenz	II	Kneading method	PVP K-30	Decomposition 58.47% after 1 month of storage	(Alves et al., 2014)
Acyclovir	IV	Ball-milling	Pluronic® F68, HPMC K100M®	There was no change in the FTIR spectrum after 120 days of storage	(Nart et al., 2015)
Telaprevir	II	Co-milling	PVP K-30, PEG 6000, HPMC	TVR-PEG is stable after 3 months of storage under 75% RH	(Xiong et al., 2019)
Zidovudine	III	Supercritical antisolvent	Poly- (L-Lactic Acid)		(Yoshida et al., 2015)
Acyclovir	IV	Solvent evaporation	Kollidone VA64®, Soluplus®, Eudragit EPO®		(Gadade et al., 2015)
Atazanavir	II	Solvent evaporation	SLS, Gelucire® 50/13		(Fukushima et al., 2007)
Lopinavir	IV	Solvent evaporation	Soluplus®, Kollidone® VA64, Kollidone® 12PF, Kollidon® CL-SF	No change in dissolution performance can occur after 6 months of storage	(Zi et al., 2019)
Ritonavir	IV	Solvent evaporation	Quercetin	Does not show recrystallization after 90 days of storage	(Dengale et al., 2015)

Table 3. Continued

Drug	BCS	Method	Polymers	Physical stability	Reference
Ritonavir	IV	Solvent evaporation Melt method	Gelucire®, sorbitol		(Sinha et al., 2010)
Ritonavir	IV	Solvent evaporation	PVPVA		(Indulkar et al., 2019)
Ritonavir	IV	Solvent evaporation	PEG 8000		(Law et al., 2004)
Ritonavir	IV	Solvent evaporation	PEG 8000	Does not show recrystallization after 1.5 years of storage	(Law et al., 2001)
Saquanavir	IV	Solvent evaporation	Curcumin, Solutol® HS15		(Kim et al., 2013)
Efavirenz	II	Spray drying	Plasdone® K29/32		(Yang et al., 2010)
Efavirenz	II	Spray drying	Soluplus®	Does not show recrystallization after 12 months of storage	(Lavra et al., 2017)
Etravirine	IV	Spray drying	Soluplus® dan Povidone		(Ramesh at al., 2015)
Darunavir	II	Spray drying	HPMC, HPMC AS, PVP K-30		(Smeets et al., 2018)
Thiocarboxanilide UC-781	II	Spray drying	TPGS 1000, Eudragit® E100		(Goddeeris et al., 2008)
Efavirenz	II	Freeze drying	PVP K-30		(Fitriani et al., 2016)
Efavirenz & Ritonavir	II and IV	Freeze drying	CAP Adp 0.33, CAP Adp 0.85, CA-320S, CMCAB		(Mazumder et al., 2017)
Ritonavir	IV	Freeze drying	Milk	There were no significant changes in dissolution and permeability after 6 months of storage	(Dhore et al., 2017)
Neviprepine	II	Mixed hydrotropic	Urea, lactose, citric acid, mannitol		(Awasthi et al., 2017)

Fusion method

The melting method is a simple and cost-effective preparation method that was first carried out in 1961. The drug and carrier are heated to melt which is then cooled quickly accompanied by strong stirring until a solid is obtained. This method can obtain crystals that are much finer and saturated in the carrier. However, it has weakness which is a change in carrier ability and phase separation when the mixture is cooled (Gurunath et al., 2013; Xu et al., 2007). In the study conducted by Xu et al. (2007) the antiviral drug umifenovir (T_m 133-137 °C) was prepared by a melting method using PEG 4000 (T_m 61.4°C), PEG 6000 (T_m 61.9 °C), and PEG 8000 (T_m 65.6°C) (Xu et al., 2007). The solubility of umifenovir dispersed in PEG 8000 (655.44 µg/mL) increased 2.77 times higher than that of a single umifenovir (235.95 µg /mL). This is associated with greater molecular weight which can increase drug compatibility that has an impact on thermal stability (Gurunath et al., 2013; Knopp et al., 2015; Zeng et al., 2020).

Hot melt extrusion

Hot melt extrusion (HME) is one of the most widely used methods in solid preparation because it shows the success of increasing drug dissolution. This method attracts commercial interest in the pharmaceutical industry because it does not involve solvents as not causing solvent residues (Genina et al., 2018; Crowley et al., 2007).The HME method produces a very homogeneous mixture due to the intense mixing of drugs, polymers and plasticizers which melts at high temperatures in about 1 minute which is then extruded and can be formed into powders, pellets, and sheets. The intermediates can be directly processed into conventional tablets. The use of the HME method must consider the thermodynamic characteristics of the drug and the polymer, including the glass transition temperature (T_g) and the melting temperature (T_m) to avoid degradation of both components (Thiry et al., 2016).

For example, efavirenz (T_m 139-140 °C) is prepared by the HME method in a ternary system using Soluplus® and HPMCAS-HF (T_g 133 °C). Study on the dissolution of the solid dispersion of efavirenz-Soluplus®- HPMCAS-HF (30:60:20) showed drug release >91% within 45 minutes, about 3.7 times greater than a single efavirenz (32%). In addition, this solid dispersion is stable after 6 months of storage. The stability is caused by high T_g and low hygroscopic properties of HPMCAS-HF so that moisture absorption does not occur (Pawar et al., 2016). In another study conducted by Zhao et al. (Zhao et al., 2019) showed that ritonavir (T_m 128°C) which was also prepared by the HME method in a ternary system using PVP VA64 and Span 20 (1:4.5:0.5 (w/w)). In solid dispersions drug release within 60 minutes reaches >80%, 1.6 times higher than single ritonavir (50%). The interaction of hydrogen formed between drugs and excipients is a phenomenon that causes an increase in dissolution (Fule et al., 2015). Other strengths include the increased permeability caused by the amphiphilic nature of span 20 and the significant increase in bioavailability of C_{max} 1.81 times, T_{max} 3.33 times, half-life 6.48 times, and AUC ($_{0-t}$) 1.58 times compared to single ritonavir (Zhao et al., 2019; Kanzer et al., 2010).

KinetiSol dispersing

KinetiSol is evidence of technological progress to produce a solid dispersion system. The same as the melting method and HME, KenetiSol® is also included in thermal processing (Miller, 2018). However, KinetiSol® is far better because it can process thermolabile drugs and polymers, high melting points, and make very thick polymers without the aid of plasticizers. This is caused by very fast rotational dynamics (for example, 1000 rpm, 1750 rpm, 2250 rpm) and the ejection temperature given below the degradation temperature of the drug and the polymer. The time required for the process is relatively very short (20 seconds) (LaFountaine et al., 2016; Hughey et al., 2012; DiNunzio et al., 2010).

The application of the KinetiSol® method to antiviral drugs, namely ritonavir with a PVA (semi-crystalline) polymer, a rotational speed of 1000-2000 rpm, and an ejection temperature of 80-100°C was confirmed by XRD and MDSC that both components had become amorphous. Studies showed a significant increase in solubility within 90 minutes of solid dispersion having released 50 µg/mL, an increase of 50 times compared to crystalline ritonavir (~ 1 µg/mL) (LaFountaine et al., 2016).

Kneading method

Kneading method is a very simple method for solid dispersion preparation. This method involves water to help turn a carrier into a paste. The drug is then added and kneaded within a certain time, dried, and filtered using a sieve (Nikghalb et al., 2012). Studies conducted by Alves et al. (Alves et al., 2014) on efavirenz prepared by kneading method using PVP K-30 at a ratio of 4:1 within 60 minutes showed a percentage of dissolution (58.83 ± 6.72%), 1.72 times higher than pure efavirenz (34.19 ± 3.97%). This is related to the hydrophilic nature of PVP K-30 which increases wetting and reduces interface tension.

Milling

Milling is a mechanical process that aims to reduce particle size without involving temperature and the use of organic solvents. The mechanical energy exerted causes changes in the crystal structure into amorphous (Al-Obaidi et al., 2013; Mallick et al., 2008). Advances in technology, allows the grinding method to produce

large-scale particles and is relatively easy in the process. Therefore this method has been applied in the pharmaceutical industry which has shown success in increasing poor solubility of drugs in water. The grinding method offers several techniques, including ball milling and co-milling. Drugs and polymers to be ground are placed in vessels containing spheres made of ceramic, zirconia, and agate, rotated at a certain speed. The change in particle size is caused by the collision of spheres that collide with each other (; Łyszczarz et al., 2020; Loh et al., 2014; Suryanarayana, 2001). Nart et al. (2015) aimed to improve the dissolution and permeability of acyclovir with ball milling techniques using Pluronic® F68, HPMC K100M®, and chitosan (Nart et al., 2015). Within 90 minutes all solid dispersion released >99%, 1.23 times higher than pure acyclovir (76.88 ± 1.6%). The acyclovir - Pluronic® F68 permeability study showed an increase of 2.69 ± 0.29, 1.7 times higher than pure acyclovir (1.59 ± 0.26). This is related to the surfactant effect by Pluronic® F68 which can disrupt the structure of cell monolayer (Palmberger, Hombach, & Bernkop-Schnürch, 2008). Xiong et al. (2019) used co-milling techniques to increase the solubility of telaprevir using HPMC. Solid dispersions show an increase in solubility 45.9 times higher than pure telaprevir (4.7 µg/mL). Dissolution studies showed a very significant value, solid dispersion within 30 minutes has been released at 62.6 ± 2.2%, 20.19 times higher than pure telaprevir (3.1 ± 0.4%). The study also showed that solid dispersion did not affect telaprevir activity and did not cause side effects on liver cells (Xiong et al., 2019).

Supercritical anti-solvent

Supercritical anti-solvent (SAS) is defined as a substance in a single-phase liquid that is above the critical temperature (T_c) and critical pressure (P_c). The simple production process and low temperature used are the advantages of this method (Yasuji et al., 2008). Carbon dioxide (CO_2) is the gas most often used because it is non-toxic, inert, non-flammable, and abundant. The critical temperature is low (31.06°C) and the critical pressure (7.38 MPa) so that CO_2 is suitable for thermolabile substances (Badens et al., 2009). The process of making solid dispersions in this method, namely drugs and polymers that have dissolved in organic solvents, is atomized through a high pressure nozzle in a tube containing supercritical CO_2. Particle precipitation is obtained from the process of evaporation of organic solvents and supercritical CO_2 which is influenced by pressure, temperature, and solute concentration (Esfandiari, 2015; Ha et al., 2015; Badens et al., 2009). Yoshida et al. (2015) aimed to improve zidovudine permeation by SAS method using poly (L-lactic acid) (PLLA). Solid dispersion with a ratio of 1:2 shows a release of 91.54% within 24 hours. Solid dispersion permeability studies showed an increase of 2.57 times (9.87%) higher than pure zidovudine (3.84%). Thus, a solid dispersion system not only increases solubility and dissolution rate, but also increases permeability (Yoshida et al., 2015).

Solvent evaporation

Solvent evaporation is a method that uses volatile organic solvents to dissolve drugs and polymers (Széliga and Nacucchio, 2015). Commonly used organic solvents include methanol, ethanol, n-hexane, and acetone (Akterian, 2018). The advantage of applying this method is avoiding the thermal decomposition of drugs and polymers because they only use low temperatures to evaporate organic solvents. However, this method also has disadvantages, including the possibility of side effects from the remaining solvents, the selection of suitable solvents, and the relatively high cost (Savjani et al., 2012). In developing a study product about the relationship between *in vitro* and *in vivo* studies is very important to do. It is assumed that if dissolution occurs faster then absorption will also occur faster. For example, a study conducted by Law et al. (Law et al., 2004) where solid dispersion preparation with solvent evaporation, i.e ritonavir-PEG 8000, showed 100% release within 60 minutes, 5 times higher than crystalline ritonavir which only releases 20%. Increased dissolution also has an impact on bioavailability. In vivo studies of solid dispersion showed C_{max} 5.48 ± 0.64 µg/mL and T_{max} 1.6 ± 0.4 hours, 22 and 13.7 times higher than crystalline ritonavir (C_{max} 0.40 ± 0.24 µg/mL and T_{max} 1.5 ± 0.3 hours). In addition, the success of solid dispersion was also obtained by Fukushima et al. (2007) on atazanavir using sodium lauryl sulfate (SLS) and Gelucire® 50/13 carriers to increase absorption (Fukushima et al., 2007). Solid dispersions with a ratio of 1:2 less than 30 minutes had been released 69%, 3.4 times higher than pure atazanavir. In addition, in vivo studies with a ratio of 1:1:2 showed C_{max} 0.63 ± 0.14 µg/mL, T_{max} 2.6 ± 0.4 hours, 7.0 and 0.72 times higher than pure atazanavir. This is being related to Gelucire® 50/13 which can form emulsions to prevent molecular aggregation (Zi et al., 2019; Mah et al., 2016).

Spray drying

Spray drying as one of the solid dispersion preparation techniques that has been applied in the pharmaceutical industry due to a fast and time-saving process. The process is that drugs and carriers are dissolved in organic solvents, passed through the nozzle, atomized into particles so small that they expand the surface, and are dried (Ramesh et al., 2015; Sathyaraj and Palraja, 2012). Ramesh et al. (2015) conducted a study of etravirine prepared by spray drying techniques using Soluplus® and Copovidone®. Solubility studies showed etravirine-Soluplus® (0.28 ± 0.06 mg/mL) at a ratio of 1:2, 4 times more than crystalline etravirine (0.07 ± 0.03 mg/mL)

Table 4. Commercial products of solid dispersion antiviral drugs

Drug	Product	Company	BCS	Dosage form	Year of accepted
Lopinavir dan ritonavir	Kaletra®	AbbVie	II and IV	Tablet	2005
Etravirine	Intelence®	Tibotec, Yardley, PA	IV	Tablet	2008
Ritonavir	Novir®	AbbVie	IV	Tablet	2010
Telaprevir	Incivek®	Vertex	II	Tablet	2011
Ombitasvir	Viekirax®	Abbvie	IV	Tablet	2014

(Ramesh et al., 2015). In addition, dissolution studies also experienced an increase in 90 minutes with 93.0 ± 0.6 of release, 3.07 times higher than etravirine crystals (30.2 ± 3.4). Lavra et al. (2017) conducted a study of efavirenz prepared with spray drying techniques using Soluplus®. Solid dispersion with a ratio of 1:10 showed a solubility of 15.95 ± 0.93 and a dissolution study within 120 minutes showed a release of 93.77 ± 0.07%, which means an increase of 9.16 and 2.63 times higher than efavirenz crystals. This is due to the amphiphilic structure of Soluplus® which has a hydroxyl group (Zi et al., 2019; Lavra et al., 2017; Thakral et al., 2012).

Freeze drying

Freeze drying is generally used for thermolabile materials. The drug and the polymer are first dissolved in a solvent. The mixture is frozen by using liquid nitrogen until it is frozen. The advantage of this method is the minimum risk of phase separation (Semenov et al., 2016). Mazumder et al. (2017) showed that ritonavir which was prepared by freeze drying using 4 cellulose derivatives, namely CAP Adp 0.33, CAP Adp 0.85, CA 320S Seb, and CMCAB. Dissolution studies showed that within 5 hours each release reached 20%, 27%, 30%, and 40%. CMCAB showed the highest release because the polymer is hydrophilic so it interacts more with water (Mazumder et al., 2017). Other success was also obtained by Fitriani et al. (2016) against efavirenz using PVP K-30. Solid dispersion with a ratio of 1:2 showed a solubility of 14,672 ± 0.416 µg/mL, an increase of 58.6 times higher than a pure efavirenz (0.250 ± 0.047 µg/mL) (Fitriani et al., 2016).

Application of Solid Dispersions of Antiviral Drugs on The Market

The market demand for antiviral drugs globally in 2019 was worth USD 56.4 billion. Several antiviral preparations using solid dispersion technology that have been circulating in the market are presented in Table 4. Three of them are drugs intended for the treatment of HIV. Based on global statistical data by the United Nations Acquired Immune Deficiency Syndrome (UNAIDS) in 2019 the needs for antiretroviral drug therapy reached 24.500.000 worldwide. Based on the products that have been circulating, it is proven that solid dispersion products are potential and feasible to become commercial products.

AUTHORS PERSPECTIVE

Currently, solid dispersion technology is the most effective method to increase the solubility and bioavailability of drugs, including antiviral drugs. Considering various studies that have been carried out, many solid dispersions show a significant success rate. The challenge in applying this solid dispersion is the limited stability during storage. This can be minimized by carrier selection and preparation techniques according to the physicochemical properties of each component, for example drugs that are thermostable can be prepared by the hot melt extrusion method and drugs that are thermolabile can be prepared by the solvent evaporation or supercritical anti-solvent methods. Solid dispersion offers promising prospects, especially for the pharmaceutical industry as the latest method of development and innovation for antiviral drugs which currently has a lot of emerging new antiviral drugs. Thus, it is expected that there will be more solid dispersion products on the market, especially for antiviral drug products.

CONCLUSION

At present, improving the solubility of antiviral drugs is very necessary to increase the effectiveness of therapy, especially when most of antiviral drugs are given by oral route. The potential and technological advancements offered by solid dispersion systems offer great hope as a strategy for the development of antiviral drugs. Recently, various studies have explored various preparation and carrier techniques that can be used, including hydrophilic polymers and surfactants. Solid dispersions have shown success both at increasing solubility and dissolution rates. In addition, solid dispersion has also succeeded in increasing the permeability and pharmacokinetic effects of antiviral drugs. It is hoped that in the future solid dispersion can be an innovative method in the development of antiviral drugs.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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