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Fenofibrate Solid Dispersion Method: A Review

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Abstract:- Fenofibrate is an effective remedy for the treatment of hypertriglycerides, hypercholesterolemia and mixed hyperlipidemia. However due to its poor water solubility fenofibrate has a poor oral absorption problem followed by low bioavalication. The manufacture of solid disperse system is a common method that can be used to increase the solubility of fenofibrate in water with the process of increasing solubility is expected to be higher fenofibrate dissolution rate. The purpose of knowing the related review of the method of making solid dispersion Fenofibrate. This review provides evidence in the literature of methods of making solid disperse fenofibrate from the year 2010-2020. Various databases such as *PubMed, ScienceDirect* and *Google Scholar*. The search terms used are using the keywords "solid dispersion" and "fenofibrate".

Keywords:- *Fenofibrate, Solid Dispersion, Mission Rate.*

I. INTRODUCTION

Fenofibrate is a phenophoid acid drug that is one of the hypolipidemic agents most widely used among fibrates. Clinically, it is used for the treatment of hypertriglyceridemia, hypercholesterolemia as well as mixed hyperlipidemia. Also, fenofibrate has a strong therapeutic effect on hyperlipidemia associated with diabetes, hypertension, and other cardiovascular diseases [1].

Class II BCS fenofibrate has a high solubility of low permeability, with particle size reduced by micronization can increase specific surface area, resulting in increased dissolution rate and oral bioavailability. Fenofibrate has a solubility of only 0.263 µg/ml in distilled water and its permeability is high log P = 5.24 which causes inadequate dissolution and poor oral bioavailability [2].

In the *Biopharmaceutics System Classification* (BCS) proposed by Amidon in 1995 BCSis divided into 4 classes namely:
Class 1 : High solubility, High permeability
Class II : Low solubility, High Permeability
Class III : High solubility, Low Permeability
Class IV : Low solubility, Low Permeability

Fenofibrate has a low solubility so that the bioavailability of the drug is slight. Bioavailability is one of the factors that determine the therapeutic effect of a drug to reach the systemic circulatory system. The drug must be dissolved in body fluids to be absorbed and enter the blood circulation. For oral drug preparations, solubility and dissolution of a drug will affect its bioavailability [3].

The biopharmaceutical circulatory system provides information on the rate-limiting step of a drug. The rate-limiting step is the stage that determines the rate for the overall reaction, in drugs that belong to class I and class III that have high solubility tends not to have problems in the formulation process, on the contrary in class II and class IV with low solubility, it is necessary to make efforts to improve its solubility so that its bioavailability can be improved [4].

One of the most common methods used to increase solubility at the rate of dissolution of fenofibrate is the solid dispersion method. The solid dispersion method is a method of making a dispersion system where drugs that have low solubility will be dispersed into a water-soluble carrier so as to show the solubility and dissolution of the drug. Research on the manufacture of solid dispersion in fenofibrate drugs with a variety of methods has been carried out and has obtained characteristic variations of the resulting solid disperse. Therefore, in this review will be collected data sourced from research journals on the manufacture of solid dispersion fenofibrate along with the results that have been mentioned as a consideration in the formulation process of fenofibrate drug preparations in order to produce increased bioavailability of fenofibrate in pharmaceutical dosage form and therapeutic effects.

II. RESEARCH METHOD

Search using scientific literature databases (PubMed, Science Direct and Google Scholar) search conducted on the literature on the manufacture of solid disperse of fenofibrate drugs by using the keywords "Solid Dispersion" and "Fenofibrate" journals library as a reference with the year published 2010-2020 both national journals and international journals so that complete journals can be collected, examined, summarized, and concluded in accordance with the criteria.

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III. RESULTS AND DISCUSSION

From the results of the literature, data obtained on several types of carriers commonly used in the process of making solid disperse, namely: Polyvinyl pyrrolidone (PVP) Polyethylenglicol (PEG), Poloxamer [5], Vitamin E TPGS [6], Hydroxypropyl Methyl Cellulose (TPMC) [7]. After that, several types of research have been collected fenofibrate solid dispersion using various methods and obtained the following results:

No	Method	Solvent	Result	**State**	Ref
1	*Melt Extrusion*	PVP-VA	The heat extrusion method is very well used to improve the bioavailability of fenofibrate.	China	[2]
2	*Melt Extrusion*	PVP K12-17	Instant heating significantly improves the performance of the formulation even though the procedure is simple, and thus can be a powerful step to put into the formulation of the manufacturing process.	Jepang	[8]
3	*Supercritical anti-solvent (SAS)*	P407 and TPGS	The supercritical anti-solvent (SAS) method shows that solid dispersion systems have excellent potential as formulations for fenofibrate that are difficult to dissolve.	Korea	[9]
4	*Fusion*	PLU and SLS	The level of intrinsic missive fenofibrate from solid dispersion increased significantly compared to pure drugs, increasing the dissolution rate by about 134 cal properties for solid dispersion containing 30/70% b/b fenofibrate.	Polandia	[10]
5	*Solvent Evaporation*	SLS and PVP VA64	All results indicate that polymer/SLS interaction will affect dispersion system performance.	China	[11]
6	*Melt Extrusion*	PVP K30, HPMC E6, HPMC E15, PEG 6000, PEG 4000 andNals	The rate of dissolution of pellets containing fenofibrate is significantly higher than that of lymphatic tablets reference 160 mg, at the initial stage has a criterion of USP 38. Next pellets are packed in hard capsules for bioequivalence studies in experimental animals.	Vietnam	[12]
7	*Solvent Evaporation*	CS	SSD formulations have the best dissolution compared to conventional PM compression and fenofibrate acid formulations in its commercial tablets, SSD preparations with CS can increase the dissolution of phenyl borate acid from the dosage form of its tablets.	Indonesia	[13]
8	*Melt Extrusion*	PVP VA64	PVP VA64 can be considered a promising polymer to increase the biological availability of water-soluble drugs such as FNB that are processed with heat melt extrusion. Also, the investigation of the mechanism of increased penetration is expected to lay the grounding on the subsequent development of effective and practical solid dispersion.	China	[14]
9	*Solvent Evaporation*	PVP and SLS	Increased wetness of fenofibrate or PVP/SLS compression by adding SLS contributes to a slight increase in the release and absorption of early drugs, implying that wetness will be a promising tool in formulation studies.	China	[15]
10	*Melt Extrusion*	PVP	Amorphous tablet model of fenofibrate dispersion system in copovidone content that is contained with a concentration of fenofibrate crystals known to be examined with XRM to measure the concentration, size, and distribution of crystalline particles in tablets	USA	[16]

Table 1

Increase in solubility and dispersion rate through solid dispersion techniques that have the following mechanisms: when a drug is made in a solid dispersion system, then the drug will be molecularly dispersed in its matrix so that when the result of solid dispersion is dissolved in the media, then the carrier will be dissolved and the drug will be released as fine colloidal particles so that the result of the surface area of the drug will increase and there will be an increase in the dissolution rate and bioavailability of the drug. This technique was first introduced by Sekeghuci and Obi, where it is known that there is an increase in absorption from drugs that have low solubility in water that has water-soluble properties such as urea [17].

There are several classifications in the dense dispersion system based on the molecular composition of solid dispersion results:

No	Type	Matrix	Drug	Description	Number of Phases
1	*Eutechnical mixture*	Crystal	Crystal	The type of solid dispersion that was first made utilizing the melting point phenomenon	2
2	*Amorphous precipitation of crystalline matrics*	Crystal	Amorphous	This type of dense dispersion is rare used	2
3	*ContinousSolid solution*	Crystal	Dispersed Molecular	Soluble in various compositions, rarely used	2
	DiscontinousSolid solution	Crystal	Dispersed Molecular	The molecular diameter of the drug differs from that of carriers (difference less than 15%) so that drugs and matrices are substitutional	1 and 2
	InterstitialSolid solution	Crystal	Dispersed Molecular	The diameter of the drug is less than 59% of the diameter of the matric. Usually, The mix is limited, discounting.	2
4	*Glasssuspension*	Amorphous	Crystal	Dispersed phase particle size depending on the cooling or evaporation rate. Obtained after crystallization of the drug on the amorphous matrix-matrix	-
5	*Glasssuspension*	Amorphous	Amorphous	Dispersed phase particle size depending on the cooling or evaporation rate.	2
6	*Glass solution*	Amorphous	Dispersed Molecular	Requires mixing, and complex formation during the process of cooling or evaporation of solvents.	1

Table 2

Based on the method of manufacture, solid dispersion is divided into 9 parts namely: fusion method, solvent method, melting solvent method, melt extrusion method, lyophilization method, melt agglomeration process, surfactant usage, electrospinning, supercritical fluid technology. By the above discussion, it will be explained as follows:

The fusion method in the manufacture of solid dispersion by mixing the drug with a carrier that is water-soluble and heated directly until melted. The melt is then quickly consolidated (using continuous stirring). The solid period that formed was then destroyed and pulverized then sifted [18].

The solvent method whereby the physical mixture of the drug and carrier is dissolved in the appropriate solvent and mixed then the solvent is evacuated until a thin film remains. The advantages of this method are that decomposition due to high temperatures can be avoided, but some shortcomings of this method are the high cost, difficulty in eliminating solvents perfectly, the selection of suitable solvents, and others [19].

Melt extrusion method in this method, the drug, and carrier is melted then carried out the extrusion process and formed tablets, granules, pellets, sheets, or powder. The result can be directly processed into conventional tablet forms [20].

Supercritical anti-solvent (SAS) methods of anti-solvent supercritical processes (SAS) are most often performed by involving supercritical CO2 fluids because they require moderate, non-toxic, low-cost critical conditions. The SAS process can alter the properties of drugs or polymers, including the crystallinity of pharmaceutically active ingredient polymorphisms [21].

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Based on data obtained from library search results, some commonly used methods are fusion, solvent method, supercritical anti-solvent (SAS), and melt extrusion This is because this method is simple and does not cost much. On the contrary, other methods such as lyophilization, supercritical fluid, electrospinning is a method of making solid dispersion that requires special tools or materials in the process so that it is rarely used, basically, the selection of this method depends on the type and chemical properties of the active substance used. In addition to method factors, the carrier factor used also exerts an influence on the resulting solid dispersion. In research conducted by [22], [5]

The research conducted by [2] has the aim to develop solid dispersion with fenofibrate active substances with high bioavailability using heat melt extrusion method with carrier Eudragit E100 or (PVP-VA) polyvinylpyrrolidone-vinyl acetate. Which fenofibrate comes out as a noncrystal state in these two types of solid dispersion that can be proven by DSC and X-ray diffraction, Eudragit E100 1:2 which has a dissolution rate of 84% and 65% at the 60th minute in a solution of 0.1 M HCL in water. Eudragit E1001 1:4 solid dispersion has a lower dissolution rate in 0.1 M HCL and a higher dissolution rate in water with percentage values of 73.6% and 87.3%. Solid dispersion using 1:2 PVP-VA carriers has a dissolution rate of 60% and 65%. At the 60th minute in a solution of 0.1 M HCL in water. The solid dispersion of PVP-VA 1:4 has a higher dissolution rate of 0.1 M HCL and a lower water dissolution rate with a percentage of 64% and 53% values because the solubility dissolution rate is different when eudragit E-100 has a value of 177.1%.

In the study [8] electrospray techniques were used in insoluble fenofibrate to improve bioavailability. Solid dispersion uses methacrylic acid-methyl methacrylate or Eudragit L-100 as a polymer PVP-K12-17 for fenofibrate in the core phase although 58% of fenofibrate remains in the crystalline state using the electrospray method of significantly increased dissolution rate due to particle reduction, decreased crystallization, and increased dispersion efficiency warming at 1000C within 30 seconds to turn the remaining Crystals into an amorphous state to increase solubility.

The study [9] has the aim of increasing solubility and bioavailability of fenofibrate with solid dispersion system using supercritical anti-solvent (SAS) process with polymer P407 and TPGS. Solid dispersion techniques have been widely used to raise the solubility and dissolution profile of drugs that are difficult to dissolve. Fenofibrate is classified as a class II compound biopharmaceutical classification system due to its low lubilitas and high gastrointestinal permeability. Two copolymers were selected based on solubility and dissolution tests. Its physicochemical properties are compared to those made with conventional solvent evaporation (CSE). Formulations of dispersion systems containing fenofibrate were successfully prepared using SAS and CSE methods. Dissolution rate (%) fenofibrate at 60 minutes increased significantly compared to raw fenofibrate solution (19.5% ± 3.7%) 95.1% ± 2.5% and 93.7% ± 4.1% using SAS and CSE processes, respectively. An increase of about fourfold in the rate of mission indicates that oral bioavaon can be increased. Also, pharmacokinetic studies analyzed using areas below the curve (AUC) and Cmax SAS and CSE dispersion system values in mice, AUC 2.1 times higher and Cmax 1.9 times higher in SAS dispersion systems showed higher fenofibrate concentrations in the blood.

Further research conducted by [10], showed that the level of dissolution of fenofibrate in solid dispersion systems is higher than in pure substances. After 120 minutes of testing depending on the composition of the formulation, there was a 1.1-fold increase in the composition of the fenofibrate with PLU of 90/10 and more than 100-fold for 30/70, 40/60, and 70/30. Fenofibrate/PLU w/w with dissolved amounts of 27, 24, and 25% of the total pharmaceutical active ingredients with an additional only 0.48% of the dissolved fenofibrate. As the concentration of polymers increases, the emission increases due to increased degradation and wetting of pedophilic particles in the form of hydrophilic groups and the surface-active properties of PLU polymers. Fenofibrate of the solid dispersion system was observed after 1440 minutes of the dissolution test. Solid dispersion contains 30/70.40/60.70/30 % w/w of fenofibrate and PLU according to the percentage obtained 66.79, and 41%.

In the research conducted by [11], using solvent evaporation method using polymers from SLS and PVP-VA64 showed that fenofibrate with PVP-VA64 molecular weight increases and polymer wetness decreases resulting in a significant decrease in the dispersion rate of solid fenofibrate, although SLS does not increase the rate of mission but can increase the bioavailability of drugs released at an early stage.

In this study the results of PXRD and DSC measurements showed that fenofibrate formed amorphous and remained stable in long-term conditions for 12 months. Solid dispersion is increased to the rate of the mission of fenofibrate this is to increase the capsule fenofibrate has criteria USP 38. In animal studies, there was no significant difference in pharmacokinetic parameters of 90%, for AUC, t, and Cmax were in the t max capsule test criteria much shorter than the number of products used [12].

Furthermore [13], the formulation of a solid dispersion system with CS can increase phenylfibrate mission. Phenophylate dissolution is enhanced due to partial amorphization, crystal changes, and fenofibrate particle deposition in cs enhancement during the solvent evaporation process. The consolidated profile of all tablets compared to DE60 of F1 was 93.74 or 4.39% for F2 at 83.74% or 1.40% and F3 was 78.40% or 1.05% and fenofibrate was 74.72% or 1.56%. The difference between all tablets is quite significant except between F3 and fenofibrate, F1 and F2 can achieve the efficiency of more than 80% mission within 60 minutes due to the presence of CS components of 105 mg/tablet that

facilitates the process of dissolution of fenofibrate in the next medium F3 can not charge DE60 the same as F1 and F2 because it only weighs 15 mg/tablet or about 5% OF CS comparable to fenofibrate.

Research [14], a dense dispersion of fenofibrate prepared to be made in an amorphous state after the heat melt extrusion process, in vitro on caco-2 cytotoxicity test showed excellent biocompatibility of PVP-VA64 carriers. Also, cell transport tests and dissolution in vitro tests showed that fenofibrate released from amorphous solid dispersion was equipped with membrane transport and a better dissolution rate. also, pharmacokinetic studies in animals showed that compared to commercial micronization products oral biological fentanyl availability of solid dispersion of fenofibrate increased significantly by 2.45-fold.

This study look at the wetness of the surface modulated by surfactant and its effect on the release of the drug and absorption of the dense dispersion of fenofibrate. Cocipitation of polyvinylpyrrolidone/sodium lauryl sulfate (PVP/SLS) and fenofibrate dispersion system is made by the solvent evaporation method. The contact angle of PVP /SLS cocipitation with various PVP/SLS weight ratios is determined to filter the suitability of SLS incorporated in the fenofibrate dispersion system. The dispersive energy scan of electron spectroscopic microscopy (SEM-EDS) was used to analyze the surface composition of PVP/SLS coprecipitate, suggesting that SLS molecules tend to be concentrated on the carrier's surface. The physical characteristics of phytochemicals, PVP, SLS, dispersion systems, and physical mixtures of fenofibrate were evaluated with thermal, XRD, FTIR, and SEM analyses, which showed that fenofibrate was molecularly dispersed in the dispersion system. The interaction between SLS and PVP or fenofibrate confirmed by FTIR will affect the surface morphology of the dispersion system. Finally, the contact angle of the fenofibrate dispersion system was measured to see the effect of surface wetness on the solution and absorption of the drug from the phenophibrate. The interesting thing is that the wetness of PVP/SLS precipitation is positively related to the fenofibrate dispersion system. Increased fenofibrate wetness or PVP/SLS cocipitation by adding SLS contributed to a slight increase in the release and absorption of early drugs, implying that wetness would be a promising tool in formulation studies [15].

Research conducted [16], Particles of fenofibrate active substances that may exist in amorphous solid dispersion is very important to understand the product performance and develop improved formulations. In this study, X-Ray Microscopy (XRM) was used to measure these attributes in the dispersion system in a non-destructive way. Models of amorphous fenofibrate tablets in copovidone content that are affected by the concentration of fenofibrate crystals are known to be examined with XRM to measure the concentration, size, and distribution of crystal particles in tablets. Data collection and analysis conditions are evaluated and reported. XRM images show the contrast between the active substance of the crystal and the amorphous content of the tablet. In analysts use the basic threshold provided quantitative data and distribution of existing crystallinity. Crystals are as small as 10 mm were detected and a practical quantitative limit of 0.2% (b/b total tablets) crystallinity was indicated.

IV. CONCLUSION

Solid dispersion methods can be used to increase the solubility and dissolution rate of fenofibrate that has low solubility in water, taking into account the appropriate preparation and carrier methods and the type of solid disperse produced.

➢ *Thank You*

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