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Solubility Enhancement Methods Of Efavirenz : A Review

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ABSTRACT

Human Immunodeficiency Virus (HIV) is a global public health concern due to its progression to acquired immunodeficiency syndrome (AIDS) and the associated high morbidity and mortality rates. Efavirenz (EFV), an antiretroviral drug, is widely used to manage HIV/AIDS. However, EFV exhibits poor aqueous solubility and variable bioavailability, necessitating techniques to enhance its solubility and dissolution for improved therapeutic efficacy. This study reviewed methods to enhance EFV solubility using data from research published between 2019 and 2023. Various approaches, including Nano Micelles, Wet Milling, Co-crystals, Physical Mixtures, Nanocrystals, Dry Milling, and Liquisolid techniques, were analysed. The results demonstrated significant solubility enhancements. For instance, Fuentes (2024) achieved a 50% dissolution efficiency using Nano Micelles, while wet milling by Prado (2024) increased dissolution from 83.48% to 99.10% over 150 minutes. Co-crystals, such as those studied by Gowda (2022), improved solubility from 94.16 µg/mL (pure EFV) to 197.32 µg/mL (EFV-DL-Alanine). Sartori's (2022) Nanocrystals technique demonstrated a dissolution efficiency of 98.41%. Furthermore, physical mixtures like Nel's (2022) combination of EFV with pea protein isolate achieved a solubility increase from 1.00 mg/mL to 2.30 mg/mL. These methods highlight advancements in solubility enhancement techniques that improve EFV's pharmacokinetic profile. These findings can guide the development of more effective pharmaceutical formulations, improving treatment outcomes for individuals living with HIV/AIDS.

Keywords: Efavirenz, Human Immunodeficiency Virus, Solubility and Dissolution Enhancement, Particle size

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1. Introduction

Human Immunodeficiency Virus (HIV) is a virus that attacks and weakens the human body's defense system, so that the body is easily infected with various diseases. HIV can cause Acquired Immunodeficiency Syndrome (AIDS), which is a disease symptom caused by decreased immunity. Morbidity and mortality rates caused by HIV are increasing and are the most important public health problems throughout the world.

HIV particles are enveloped RNA viruses, spherical in shape with a diameter of 80-120 nm. Infectious particles consist of two positive single-stranded RNA strands contained in a viral protein core (ribonucleoprotein) and surrounded by a phospholipid envelope layer anchored by 72 glycoprotein spikes (Figure 1). The polypeptide envelope consists of two subunits, namely the outer glycoprotein (gp120), which is the CD4 receptor binding site, and the transmembrane glycoprotein (gp41), which combines with the viral lipid envelope. These proteins in the outer membrane mainly function to mediate binding to CD4 cells and chemokine receptors. On the inner surface of the viral lipid 7.8 envelope is coated with a matrix protein (p17), which likely plays an important role in maintaining the structural integrity of the virion. The lipid envelope is encased in an icosahedral capsid protein (p24) and a p17 matrix. Capsid proteins surround the inner core of the virion thus forming a 'shell' around the genetic material. The nucleocapsid protein is contained in the 'shell' and binds directly to RNA molecules.

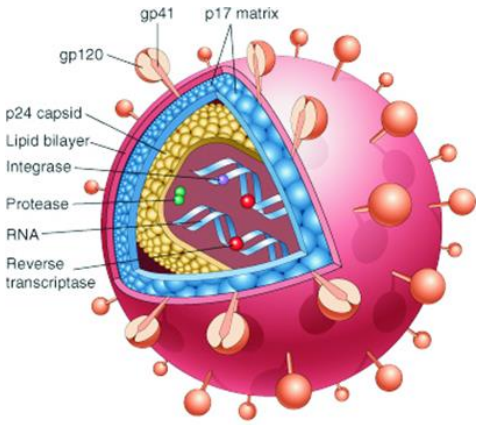

Figure 1. HIV structure (Abbas dan Lichtman,2003)

The HIV virus particles that initiate the infection are usually found in blood, sperm, or other body fluids, and can spread in many ways. The most common transmission route is sexual contact through the genital mucosa. When HIV reaches the mucosal surface, it binds to CD4 T-lymphocytes or macrophages, which are also skin dendritic cells. After the virus is sexually transmitted through the genital mucosa, it was found that the first cellular target of the virus is tissue dendritic cells (also known as Langerhans cells) found in the cervicovaginal epithelium, and will then move and replicate in the local lymph nodes. These dendritic cells then fuse with CD4 lymphocytes which will migrate into the lymph nodes through the surrounding lymphatic tissue. Within a few days after the virus reaches the regional lymph nodes, the virus will

spread hematogenous and reside in various tissue compartments. Lymph nodules and their equivalents (such as Peyer's plaques in the intestine) will eventually contain viruses. In addition, HIV can directly reach the bloodstream and be filtered through regional lymph nodes. This virus reproduces in the lymph nodes and then new viruses are released. Some of these new viruses can bind to produce new CD4 T cells to replace damaged CD4 T cells. However, CD4 lymphocytes are nearby and infect them, while others can bind to follicular dendritic cells in the lymph nodes.

Providing antiretroviral therapy (ARV) to people living with HIV and AIDS (PLWHA) will inhibit the replication of the HIV virus so that the disease does not progress and the death rate is reduced. ARVs are useful for the treatment and prevention of HIV/AIDS, but this therapy carries various risks of side effects, one of which is neuropsychiatric side effects. 3 Efavirenz (EFV) is one of the ARV drugs in the Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) group which has been widely recommended. Efavirenz is a type of drug that is widely used for HIV (Salbila et al, 2015).

According to the biopharmaceutical classification system (BCS), EFV is considered a class II drug exhibiting incomplete and unpredictable oral absorption with bioavailability varying from 30% to 56%. It is reported that EFV has a low aqueous solubility (9.2 µg/ml), (pH 8.7) at 25 °C,6−8 higher as the pH increases above 9, for the proton loss on the carbamate group's amine. The solubility of a drug substance is one of the significant parameters impacting absorption as well as bioavailability, defined as the fraction of the administered dose of a drug that enters the systemic circulation, thereby accessing the site of action. Unfortunately, EFV tends to be eliminated in the human systemic circulation before the dissolution and absorption into the systemic circulation processes are completed, therefore requiring an increased dosage to achieve therapeutic levels in the body, often implying adverse effects for the patient. Several approaches to improve EFV dissolution were reported (Atoullahi et al, 2021).

Solubility is the main factor that determines the dissolution rate of a drug, because it can affect pharmacokinetic and pharmacodynamic performance. Efforts to increase the solubility, dissolution rate and bioavailability of drugs that are difficult to dissolve in water can be done using physical and chemical approaches (Sutoro, et al., 2023). This research aims to determine methods of increasing the solubility of efavirenz. The study was carried out using research journals published in 2019-2023 as library sources.

2. Method

The Search article using PubMed on 26 november 2024, with the keyword "efavirenz solubility" resulted in 151 articles. Screening was done to eliminate duplication and eligibility, 46 articles were included with several techniques of solubility enhancement. Data of solubility enhancement applicable for tablet formulation of efavirenz of 200 mg API in 400 mg tablet weight, equipment on laboratorium availability, and article within 2019-2024 were included on this topic and then found 13 articles which is continued for data analysis. Article searching is presented in figure 2.

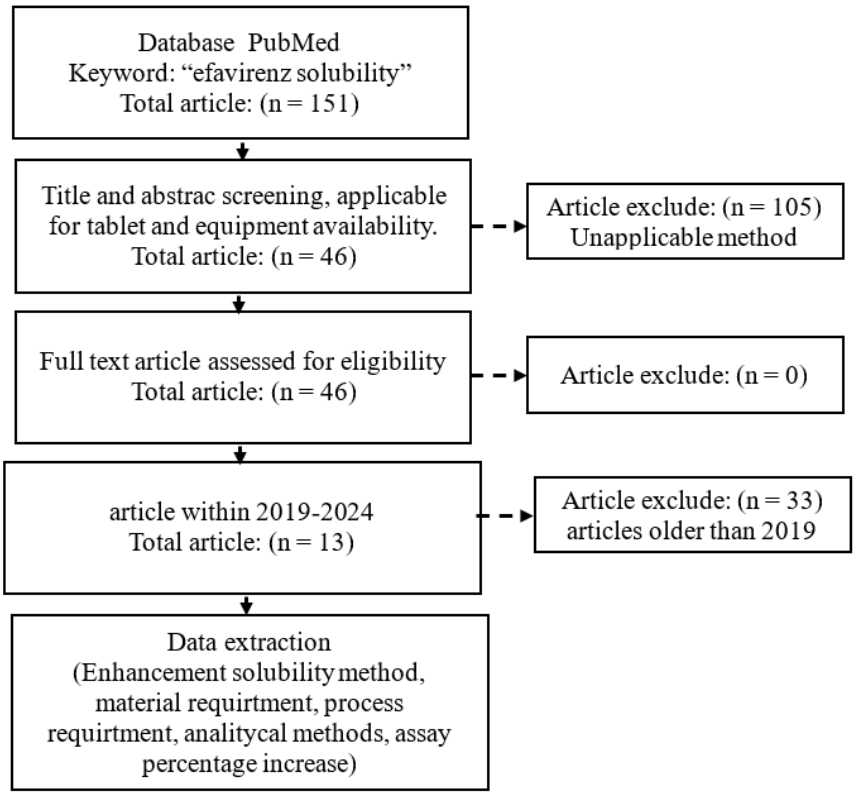

Figure 2. Article searching process

3. Result

Data on enhancement solubility methods, excipients used in research, ratio of API and excipient used, and result of solubility of dissolution increased of efavirenz shown in table 1. After conducting a literature search, there are many studies that focus on increasing the solubility of efavirenz to provide good bioavailability in the body. From several of these studies, the research results are shown in the form of increasing solubility, increasing dissolution, and comparing pharmacokinetic profiles in the living body.

Figure 2. Article searching process

	Enhancement solubility method	**Excipients used**	**Ratio (API : Excipients)**	**Result Solubility / Dissolution**
Fuentes 2024	Nano micelles	Efavirenz (EFV) Curcumin (CUR), Polyvinyl caprolactam–polyvinyl acetate–PEG (Soluplus®)	EFV 5 mg/mL, CUR 5, 10 and 15 mg/mL, Soluplus® in distilled water (10 % w/v)	Dissolution efficiency (% average ± SD) in 15 mL PBS (phosphate buffer USP 30 pH 7.4) containing 0.5% Tween 80 (v/v) and 30% ethanol (v/v) after 6 hours • EFV-NMs : 50% • EFV-CUR-NMs : 40%

Prado 2024	Wet milling	Efavirenz (EFV), Hydroxypropyl Cellulose (HPC), Polyvinylpyrrolidone (PVP), and sodium lauryl sulfate (SLS)	EFV, HPC (8 g) + SLS (8 g), PVP K30 (16 g) and red dye (2.8 g)	Dissolution efficiency (% average ± SD) in 900 mL 0.25% (m/v) of SLS after 150 min • Raw material : 83.48 ± 1.37 • GRANULE 1 : 95.86 ± 2.12 • GRANULE 2 : 94.94 ± 0.70 • GRANULE 3 : 99.10 ± 3.12 • GRANULE 4 : 97.18 ± 2.94 • GRANULE 5 : 87.31 ± 0.93
Gowda 2022	Co-crystal	Efavirenz (EFV), DL-alanine (ALA), oxalic acid (OX), maleic acid (MAL), nicotinamide (NIC)	1:1 molar ratio of EFV-ALA, EFV-OX, EFV-MAL, EFV-NIC.	Solubility (ug/mL) ± SD in 10 mL of 1% w/v sodium lauryl sulphate (SLS) • EFV Pure: 94.16 ± 0.8 • EFV-ALA: 197.32 ± 0.9 • EFV-OX: 182.92 ± 1.7 • EFV-MAL: 84.25 ± 0.6 • EFV-NIC: 34.96 ± 1.1
Gowda 2022	Co-crystal	Efavirenz (EFV), tartaric acid (TAR), And adipic acid (ADP)	1:1 molar ratio of EFV-TAR EFV-ADP	Solubility (ug/mL) ± SD in 5 mL of 1% w/v sodium lauryl sulphate (SLS) • EFV Pure: 94 • EFV-TAR: 163 • EFV-ADP: 107
Nel 2022	Physical Mixture	Efavirenz (EFV), pea protein isolate (PPI) and inulin (IN)	EFV and IN (EI) 1:4, EFV and PPI (EP) 1:4, and EFV, PPI, and IN (EPI) 1:4:4	Solubility in distillate water (mg/mL) with 1% v/v Tween® 20 solutions • EFV : 1.00 • EI : 0.92 • EP : 2.30 • EPI : 0.42
Rashed 2022	Wet milling	Efavirenz (EZ), Polyvinyl alcohol (PVA), poloxamer 188, Sodium, carboxymethylcellulose (CMC), Hydroxypropyl methylcellulose (HPMC E5), mannitol, and sodium lauryl sulfate (SLS	raw efavirenz (EZ) Physical mixture (PM) Freeze-drying of Nanosuspensions (FD-NS)	Solubility (ug/mL) in deionized water at 25 ± 0.5°C • EZ : 9.05 ± 1.23 • PM : 23.6 ± 0.56 • FD-NS : 102.8 ± 1.49

Sartori 2022	Nanocrystals	Efavirenz (EFV), hydroxypropyl methylcellulose (HPMC) E5, polyvinyl pyrrolidone (PVP) K30, sodium lauryl sulphate (SLS)	EFV 8-70% SLS 2% HPMC E5/ PVP K30 40%	Dissolution efficiency (% average ± SD) in 900 mL aqueous 0.1% (w/v) SLS solution after 90 min • TX1 70.26 ± 1.39 • TX2 11.70 ± 2.30 • TX3 91.25 ± 3.98 • TX4 56.47 ± 4.90 • TX6 29.23 ± 4.00 • TX7 98.41 ± 1.07 • TX8 19.79 ± 1.52 (TX=code of formula)
Shinde 2022	Co-crystal	Efavirenz (EFV), salicylic acid (SA), benzoic acid (BA) and chloroform	n/a	Dissolution efficiency (% average ± SD) in 900 mL deionized water with 1% sodium lauryl sulphate after 60 min • EFA : 60% • EFA:SA : 97% • EFA:BA : 78%
Ataollahi 2021	Dry Milling	Efavirenz (EFV), PVP-K30	800 mg of EFV powder, with (50 w/w%) PVP.	Dissolution efficiency (% average ± SD) in water after 30 mins • Pristine EFV A :25 • EFV-A60 : 30 • EFV-A80 : 35 • EFV-A60-PVP : 53 • EFV-A80-PVP : 58
Jaydip 2020	Liquisolid	Transcutol HP, Neusilin, aerosil, Kyron T314, MgO	EFV 200 mg Transcutol HP 267,3 mg, Neusilin 267,02-333,78, aerosil 22,25-66,75, Kyron T314 32,93-34,71, MgO 8,56-9,02	Dissolution efficiency (% average ± SD) in 900 ml (0.1 N HCl + 0.5%w/v SLS) after 30 min • F1 69.51 ± 0.85 • F2 90.33 ± 0.99 • F3 98.02 ± 1.3 • F4 71.25 ± 1.2 • F5 91.90 ± 0.28 • F6 92.33 ± 0.66 • F7 63.80 ± 1.41 • F8 86.8 ± 1.07 • F9 84.74 ± 0.48

4. Discussion

After conducting a literature search, there are many studies that focus on increasing the solubility of efavirenz to provide good bioavailability in the body. From several of these studies, the research results are shown in the form of increasing solubility, increasing dissolution, and comparing pharmacokinetic profiles in the living body.

4.1 Nano Micelle

In Fuentes' research in 2024, increasing the dissolution of efavirenz using the nano micelle technique. Currently, natural bio-enhancers are gaining attention because of their

ability to increase oral drug absorption (Ajazuddin et al., 2014). This research uses curcumin as a bio-enhancer and polyvinyl capro-lactam–polyvinyl acetate–polyethylene glycol graft copolymer known Soluplus® as a biocompatible copolymer to form nano micelles (NMs). The results of this study showed a stable colloid between efavirenz and curcumin. Then, the release after 6 hours of EFV-NMs and EFV-CUR-NMs is 50% and 40% respectively.

4.2 Wet Milling

In the Prado research in 2024, efavirenz dissolution was increased using wet milling by making efavirenz in suspension form and then reducing the particle size using a colloidal mill for 1 hour. This reduction in particle size has been done before, but the drying method is not commonly used in the pharmaceutical industry, so this research used a more general drying method and used more solid content. The results of this study showed that there was an increase in dissolution after 150 min of raw material: 83.48 ± 1.37 % to 87.31 ± 0.93 % to 99.10 ± 3.12 %.

Still using the wet milling technique, Rashed's research in 2022 reduced the particle size of efavirenz by dispersing the drug in a solution containing a stabilizer and then milling it using a planetary ball mill for 3 hours. The wet milling technique was chosen because it is a technique that is well accepted in the pharmaceutical industry because the process is simple, cheap, easy to scale-up and has high drug loading. The results of this research succeeded in reducing the size of the efavirenz particles in the nanosuspension to a uniform size. There was an increase in Solubility in deionized water at 25 ± 0.5°C from single efavirenz 9.05 ± 1.23 ug/mL to 23.6 ± 0.56 in physical mixture and 102.8 ± 1.49 ug/mL in freeze drying nanosuspension.

4.3 Co-crystal

Gowda research in 2022 created a co-crystal to increase the solubility of efavirenz. co-crystal is an alternative form of medicinal compound to improve physicochemical properties such as flowability, compressibility, hygroscopicity, solubility, and stability. Co-crystals are made by combining active pharmaceutical ingredients with coformers which can be connected via non-ionic intermolecular interaction mechanisms such as hydrogen bonds. In this study, efavirenz was combined with tartaric acid, adipic acid, DL-alanine, oxalic acid, maleic acid, and nicotinamide in a molar ratio of 1:1. The research results show that co-crystals can be formed using the slow solvent evaporation method and characterized using FT-IR, DSC, PXRD, and SEM. there was an increase in solubility in 1% w/v sodium lauryl sulphate (SLS) from EFV Pure: 94.16 ug/mL to EFV-TAR: 163 ug/mL, EFV-ADP: 107 ug/mL, EFV-ALA: 197.32 ug/mL , EFV-OX: 182.92 ug/mL, EFV-MAL: 84.25 ug/mL, and EFV-NIC: 34.96 ug/mL.

Another co-crystal study from Shinde 2022 used salicylic acid and benzoic acid as coformers with GRAS status. The results of this study showed that the physicochemical properties of efavirenz increased after co-crystals were formed with SA and BA. The results of the dissolution efficiency test in 900 mL deionized water with 1% sodium lauryl sulphate after 60 min show that there was an increase in dissolution from single EFA: 60% to EFA: SA: 97% and EFA: BA: 78%. An increase in co-crystal dissolution is thought to occur due to changes in crystal shape and size.

4.4 Physical mixture

Nel's 2022 research combines EFV with two natural excipients, pea protein isolate (PPI) and inulin (IN) to increase solubility. These natural ingredients are used because they are biocompatible, biodegradable, cost effective, available in abundance, non-toxic, and generally regarded as safe (GRAS) for human consumption. The results of this study show that PPI can increase the solubility of efavirenz in distilled water from single efavirenz 1.00 mg/mL to EP: 2.30 mg/mL. Meanwhile, IN can reduce the solubility of efavirenz to IP: 0.92 mg/mL, making it suitable for making slow-release preparations.

4.5 Nanocrystals

In research conducted by Sartori in 2022, efavirenz nanocrystals were made by mixing a solution containing efavirenz with a suitable solvent into an aqueous solution of particle stabilizers under high shear agitation. Particle size reduction techniques to increase solubility and dissolution are commonly used for drugs with low solubility in water. The results of this research show that the combination of bottom-up (antisolvent precipitation) and top-down (colloid milling) techniques were shown to be the most efficient for producing EFV nanosuspensions which have 98.41 % dissolution efficiency.

4.6 Dry Milling

Ataollahi's 2021 research used ball milling to reduce the size of efavirenz particles. This method was chosen because it is the most common physical method for reducing particle size and does not require expensive equipment. In this method efavirenz was subjected to high-energy grinding in a planetary ball mill with Polyvinylpyrrolidone (PVP). The results of this research can be concluded that the use of energy (Ω) 80 rpm and 30 min (non-stop) was found to increase the dissolution efficiency of Pristine EFV batch A from 25 % to EFV-A80 and EFV-A80-PVP by 35% respectively and 58%. However, the use of extreme grinding conditions (Ω = 200 rpm) with a long milling time (6 h) results in recrystallization and agglomeration of EFV, associated with a decrease in solubility.

4.7 Liquisolid

Jaydip's research in 2020 can increase the dissolution efficiency of efavirenz with the liquidsolid technique, namely by mixing efavirenz into a non-volatile co-solvent and then mixing it with powder excipient. The liquidsolid technique is used because it is simple, easy to scale up, and low-cost formulation. The results of this study showed that there was an increase in the dissolution speed between the selected formulas and single efavirenz tablets. It is known that the dissolution efficiency in 900 ml 0.1 N HCl + 0.5%w/v SLS after 30 min for a single efavirenz tablet is 30%, while the experimental results for making liquisolid range from the lowest being F7 with a value of 63% and the highest being F3 with a value of 98%.

5. Conclusion

Techniques to increase the solubility and dissolution of efavirenz have been carried out using a variety of methods, tools and excipients. In the end, all of these solubility increasing techniques will be applied to pharmaceutical preparations which are generally in

tablet form, whether developing new delivery systems, as developing copy drugs by improving existing formulas. The solubility enhancement method that has been carried out over the last 5 years has succeeded in increasing the solubility and dissolution of efavirenz. The increase in solubility can be seen from the modification of the active ingredients using the Nano micelles, Wet Milling, Co-crystal, Physical mixture, Nanocrystals, Dry Milling methods, as well as the Liquisolid preparation formulation. The results of the highest increase in solubility were shown in nel research in 2022 with a physical mixture of efavirenz and pea protein isolate which could provide a solubility of 2.30 mg/mL in distillate water with 1% v/v Tween® 20 solutions. This increased solubility of efavirenz occurs because it exhibits smaller contact angles suggesting better wettability of these powder mixtures. Then the highest increase in dissolution was shown in Sartori's research in 2022 which made a nanocrystal formulation with a composition of EFV 13.5%, SLS 2%, and HPMC E5 40% providing dissolution of 98.41% in 900 mL aqueous 0.1% (w/v) SLS solution after 90 min. This high dissolution occurs because the addition of a milling step was able to prevent particle growth and produce a uniform suspension, the particles maintained their stability through freeze-drying.

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