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Pre-formulations Study of Active Pharmaceutical Ingredients Amiodaron in the Development of Oral Tablet Pharmaceutical Preparations as an Anti-Arrhythmia Drug

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Abstract

Amiodaron is a broad-spectrum antiarrhythmic drug that is widely used in the management of various cardiac rhythm disorders, including ventricular and supraventricular arrhythmias. Despite its therapeutic effectiveness, Amiodaron presents complex physicochemical characteristics that pose significant challenges in the development of oral solid dosage forms, particularly tablet preparations. Therefore, a comprehensive pre-formulation study is essential to ensure the development of stable, safe, and effective pharmaceutical products. This study aims to examine the pre-formulation aspects of Amiodaron hydrochloride as a scientific basis for tablet formulation development. The research method employed was a literature-based study focusing on the physicochemical properties of Amiodaron, including ionization constants (pKa), partition coefficients (log P), solubility, dissolution behavior, polymorphism, chemical and physical stability, as well as particle and powder characteristics. Relevant data were obtained from scientific journals, pharmacopeias, and authoritative pharmaceutical references. The results indicate that Amiodaron hydrochloride is classified as a Biopharmaceutics Classification System (BCS) class II drug, characterized by low aqueous solubility and high membrane permeability. The compound is highly lipophilic, weakly basic, and sensitive to environmental factors such as light, heat, and alkaline pH conditions, which may lead to degradation. Furthermore, Amiodaron powder exhibits poor flowability and compressibility, making direct compression during tablet manufacturing difficult. Based on these findings, appropriate formulation strategies are required, including the use of inclusion complexes, hydrophilic polymers, granulation techniques, and careful selection of excipients to enhance solubility, stability, and bioavailability. This pre-formulation study is expected to provide a strong scientific foundation for the development of optimal Amiodaron tablet formulations.

***Keywords**: Amiodaron, Pre-Formulations, Oral Tablets, Solubility, Stability, Bioavailability*

1. Introduction

Amiodaron is one of the most widely used antiarrhythmic drugs in clinical practice due to its high effectiveness in treating various heart rhythm disorders, both from the atria and ventricles, including chronic and acute conditions. Chemically structured, Amiodaron is a benzofuran derivative containing two iodine atoms (bi-iodinated benzofuran derivative), a characteristic that contributes to its powerful and unique pharmacological activity. Based on the Vaughan Williams classification, Amiodaron is conventionally included in the class III class of antiarrhythmias because of its ability to prolong the duration of the potential action and the period of myocardial refracts, but in its application this drug also exhibits pharmacological activity that includes the mechanisms of class I (sodium canal blockade), class II (beta-blockade effect), and class IV (calcium canal blockade). The combination of these mechanisms of action provides a broad spectrum of action, making Amiodaron able to effectively suppress various types of arrhythmias, maintain normal sinus rhythms in patients with paroxysmal atrial fibrillation, and prevent the occurrence of potentially life-threatening ventricular arrhythmias, making it one of the therapies of choice in the management of complex cardiac rhythm disorders [1].

The clinical advantages of amiodaron are greatly influenced by its unique and complex pharmacokinetic characteristics, which distinguish it from other antiarrhythmic drugs. Amiodaron has a very large volume of distribution, reflecting its ability to be widely distributed to various tissues of the body, particularly fatty tissues and organs with high perfusion, and has a very long elimination half-life, which can even reach a few weeks to months. This characteristic causes the therapeutic effects of Amiodaron to last a long time, so that heart rhythm

control is maintained even after the administration of the drug has been stopped. However, behind these advantages, the accumulation of drugs in tissues also increases the risk of systemic side effects that are chronic in nature. Long-term use of Amiodaron is known to be closely related to various adverse reactions, such as impaired thyroid function due to high iodine content, hepatotoxicity characterized by increased liver enzymes, and pulmonary fibrosis that has the potential to threaten patient safety. Therefore, although Amiodaron has high clinical effectiveness, its pharmacokinetic properties demand strict and continuous monitoring of therapy to ensure the safety of drug use and minimize the risk of serious side effects [2].

From a pharmaceutical point of view, the development of amiodaron preparations faces a variety of complex and interrelated challenges, especially in an effort to produce preparations that have consistent and optimal therapeutic performance. One of the main problems that is often faced is the relatively low oral bioavailability and shows considerable variation between individuals, which is influenced by the physicochemical properties of the active substance as well as environmental conditions during the formulation, production, and storage processes. Amiodaron hydrochloride is known to be a highly lipophilic compound with very low water solubility, so the release of the active substance from the solid form becomes non-optimal and leads to a slow dissolution rate. The limitation of this solution directly impacts the drug absorption process in the gastrointestinal tract, making it a major limiting factor in achieving adequate drug levels in the systemic circulation [3]. In addition, variations in the physiological conditions of the gastrointestinal tract, such as pH and the presence of food, can further magnify the fluctuations in the bioavailability of Amiodaron. Therefore, this condition demands an appropriate and rational formulation approach, including excipient selection, treatment techniques, as well as strategies to increase solubility and dissolution, in order for amiodaron to achieve optimal and consistent therapeutic effects in patients.

In addition to bioavailability issues, the stability of Amiodaron is also a very crucial aspect in the development of pharmaceutical preparations because it directly affects the quality, safety, and effectiveness of drugs during the process of production, storage, and use by patients. Various studies show that amiodaron hydrochloride has a high susceptibility to environmental factors such as light exposure, high temperature, and pH changes, which can trigger chemical degradation and decreased levels of active substances. Amiodaron is known to be relatively more stable in acidic pH conditions, while at neutral to alkaline pH the degradation rate increases significantly, especially when accompanied by exposure to higher temperatures, so this condition must be carefully considered in formulation design and manufacturing processes [4]. In addition, the sensitivity of Amiodaron to light causes photodegradation which can result in degradation products and degrade the quality of the preparation, so special attention is needed in the selection of packaging types that are able to protect the drug from exposure to light and the establishment of appropriate storage conditions to maintain the stability and effectiveness of the preparation throughout its shelf life [5].

Based on the various challenges inherent in the physicochemical properties and pharmacokinetic profile of Amiodaron, the study of pre-formulations is a very crucial stage in the development of its pharmaceutical preparations. This study not only serves to identify the basic characteristics of the drug, but also to understand in depth important parameters such as low solubility, crystallinity that can affect the rate of dissolution, stability to environmental factors such as light, temperature, and pH, as well as the potential interactions between amiodaron and various excipients commonly used in tablet or capsule preparations. The information obtained through pre-formulations studies becomes a scientific basis in determining the selection of compatible additives, appropriate formulation methods, and strategies to increase the solubility and stability of the drug. Thus, a comprehensive pre-formulations approach allows the design of amiodaron preparations that are not only physically and chemically stable, but also safe and therapeutically effective, thus being able to provide optimal clinical benefits while minimizing the risk of side effects and therapeutic failure in their use [6].

The purpose of this pre-formulations study is to gain a comprehensive understanding of the physical and chemical characteristics of Amiodaron which plays an important role in determining the success of the formulation process and the final quality of tablet preparations, including solubility, stability, crystallinity, and drug behavior to environmental changes such as pH, temperature, and light exposure. In addition, this study aims to systematically analyze the potential interactions between Amiodaron and various excipients used in tablet formulations, so that it can be identified as possible incompatibilities that can reduce the stability, effectiveness, and safety of the preparation. Based on the results of the pre-formulations study and evaluation of the stability data obtained, this study is expected to be able to provide recommendations for the formulation of Amiodaron tablets that are optimal, rational, and applicative, in order to produce a stable pharmaceutical preparation, have good biopharmaceutical performance, and be able to provide maximum therapeutic effects for patients.

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2. Research Methods

The research method used in this study is descriptive-analytical research with a literature review approach that specifically focuses on the pre-formulation aspect of the active ingredient Amiodaron hydrochloride as the basis for the development of oral tablet preparations. This research does not involve direct experimental testing in the laboratory, but is carried out through the collection, review, and critical analysis of secondary data obtained from various credible scientific sources, such as national and international journals, pharmaceutical textbooks, official pharmacopoeia, and trusted online databases, including PubChem and Pharmacopoeia Indonesia. The data studied included various important physicochemical parameters of amiodaron, including ionization constant (pKa), partition coefficient (log P), solubility in various solvents, dissolution rate, polymorphism properties, and chemical and physical stability to the influence of environmental factors such as light, pH changes, and temperature. All of these parameters are systematically analyzed because they have a crucial role in determining the characteristics of drug pre-formulations, potential obstacles during the formulation process, and their implications for the quality, stability, and performance of oral tablet preparations to be developed.

The research stage begins with the process of identifying problems with Amiodaron hydrochloride pre-formulations which is carried out comprehensively based on the physical and chemical characteristics of the active substance. At this stage, a critical analysis of various sources of scientific literature is carried out, including research journals, pharmaceutical textbooks, and official references, in order to assess in depth potential formulation obstacles that may arise during the development of tablet preparations. The problems studied include the very low solubility of Amiodaron in water, poor flow properties and compressibility of powders, and high susceptibility of drugs to degradation due to exposure to light, oxidation, and other environmental factors. All data obtained were then systematically analyzed to relate the intrinsic properties of Amiodaron with its implications for each stage of the tablet manufacturing process, from weighing and mixing ingredients, uniformity of distribution of active substances in the mixture, formation of tablets with adequate mechanical strength, to the physical and chemical stability of the product during storage. In addition, this analysis also considers the classification of Amiodaron in the Biopharmaceutical Classification System (BCS), which is a drug with high permeability but low solubility, thus becoming an important basis in determining a rational formulation approach and the selection of appropriate solubility and bioavailability improvement strategies.

The final stage of the research method is focused on the formulation of a pre-formulations solution strategy and the justification for choosing the most appropriate form of preparation based on the results of the literature analysis that has been carried out systematically and critically. At this stage, various approaches to improve the solubility and stability of Amiodaron are comprehensively evaluated, including the formation of salt forms to improve ionic solubility, the use of inclusion complexes with cyclodextrin to improve the fraction of dissolved drugs, the utilization of hydrophilic polymers to increase the dissolution rate, the application of wet granulation techniques to improve the flow properties and compressibility of powders, and the selection of excipients that are compatible and stable to active substances. All of these findings were then analyzed in an integrated manner by considering the physicochemical characteristics of amiodaron, the need for clinical therapy, and the technical aspects of the production process, so that the most suitable form of target preparation, namely tablets or oral capsules, could be determined. The selection of this form of preparation is based on considerations of long-term therapeutic effectiveness, ease of use by patients, good dose control, and opportunities for future development of advanced formulations. With this methodological approach, the research is able to provide a comprehensive and scientifically based overview of the basis for the development of Amiodaron tablet formulations that are stable, safe, and have optimal pharmaceutical performance.

3. Results and Discussion

3.1. Identification of Amiodaron HCL Pre-formulations Problems

Based on the results of the pre-formulations study, amiodaron HCl shows a number of fundamental problems that are very closely related to its physicochemical properties, especially the very low solubility in water. This low solubility is a major limiting factor in the development of pharmaceutical preparations, both for the oral and parenteral routes, since the active substance is difficult to be in the dissolved form necessary for the absorption process in the body. As a result, the rate of Amiodaron dissolution becomes slow and has the potential to reduce the bioavailability of the drug. The condition is further exacerbated by the highly lipophilic properties of amiodaron, so the drug tends to be distributed to the lipid phase and is less dispersed in aqueous mediums. Therefore, the main challenge in the pre-formulations of Amiodaron HCl is how to increase the fraction of the dissolved drug without sacrificing the chemical and physical stability of the active substance, so that therapeutic effectiveness can still be achieved optimally.

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In an effort to overcome the solubility problem, various studies have evaluated formulation approaches that are rational and based on the characteristics of active substances. One of the strategies that has been widely reported to be effective is the formation of inclusion complexes with cyclodextrin, such as *β-cyclodextrin, methyl-β-cyclodextrin, and 2-hydroxypropyl-β-cyclodextrin*. The formation of this complex is able to significantly increase the solubility and dissolution rate of amiodaron by adhering drug molecules in the hydrophobic cavity of cyclodextrin, thereby increasing the drug's ability to interact with aqueous mediums. This increase in solubility and solution has the potential to improve the bioavailability of amiodaron and support the achievement of more consistent and predictable therapeutic effects [7]. Thus, the lipophilic and low-solubility properties of Amiodaron demand the existence of an appropriate formulation strategy so that the drug can be well dispersed and optimally available in the biological environment.

In addition to solubility issues, the physical properties of amiodaron HCl powder are also a significant challenge in the development of solid preparations, particularly tablets and capsules. Relatively fine Amiodaron crystal powder tends to have poor flow properties, which can complicate critical stages in the production process, such as weighing, homogeneous mixing, as well as tablet printing or capsule filling. The flow properties of these powders are greatly influenced by the processing conditions and the type of solvent used during the crystallization process, as these factors can affect the crystal habitus, particle surface area, as well as the cohesion forces between particles that determine the overall flow ability of the powder [8]. If the flow properties are not well controlled, the risk of weight variations and inhomogeneity in the final preparation will increase.

Another problem that is no less important is the relatively low compressibility of Amiodaron HCl. This condition causes tablets produced through the direct compression method to have the potential to have inadequate mechanical strength, are fragile, and are easily destroyed during the handling, packaging, and storage process. To overcome these obstacles, a more complex formulation approach is needed, such as the application of wet granulation or dry granulation methods that aim to increase particle size, improve particle size distribution, and improve powder flow properties. In addition, the addition of binding agents such as microcrystalline cellulose or povidone is important to improve the bonds between particles so that the resulting tablets have the appropriate hardness and mechanical resistance. The selection of a stable polymorphic shape of Amiodaron also plays an important role in improving the powder's ability to form a tablet that is dense, uniform, and has consistent physical quality [7].

The aspects of stability and partition coefficients are crucial components in the identification of HCl Amiodaron pre-formulations problems because they greatly determine the success of the development of safe and effective pharmaceutical preparations. The results of the study using the stability-indicating HPLC method showed that amiodaron is prone to degradation when exposed to stress conditions such as oxidation, heat, humidity, and light, both in the form of pure active substances and in tablet preparations. Therefore, the formulation and packaging system aspects must be carefully designed to provide maximum protection against these environmental factors [9]. This sensitivity is reinforced by the finding that sterilization at 121 °C for 15 minutes can significantly reduce the level of the active substance, so the control of production process conditions and the use of lighttight packaging are critical to maintaining drug stability [10]. On the other hand, the high value of partition coefficient indicates that amiodaron HCl is highly lipophilic with good membrane permeability, but has low water solubility, so it is classified as a Class II BCS drug. This condition confirms that although absorption through biological membranes is relatively efficient, solubility limitations remain a major limiting factor in conventional oral formulations and demand the existence of specific formulation strategies to ensure optimal bioavailability [7].

3.2. Solution Strategies for Pre-formulations Problems

Amiodaron has physicochemical characteristics that pose significant challenges at the pre-formulations stage, especially due to its highly lipophilic nature and very low solubility in water, as stated in the Indonesian Pharmacopoeia and the PubChem database which states that Amiodaron is classified as difficult to dissolve in water and has a high partition coefficient value [14]. This condition has a direct impact on the low rate of drug solution in the gastrointestinal tract, so it has the potential to reduce oral bioavailability and hinder the achievement of optimal therapeutic levels if not addressed through the right formulation approach. The low solubility also makes it difficult for amiodarons to disperse homogeneously in the biological medium, so that the drug fractions available for the absorption process are limited and can cause variations in therapeutic responses between individuals. In addition, the high lipophilic properties have implications for the tendency of the drug to accumulate in the lipid phase, which further confirms that the dissolution process becomes a limiting stage in the absorption of the drug orally. Therefore, the solubility aspect is a critical factor that must be considered from the early stages of preparation development, so that through a pre-formulation strategy and rational formulation approach, the

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biopharmaceutical performance of amiodaron can be improved effectively and consistently without reducing the stability and safety of the drug [14].

One formulation approach that can be applied to overcome the problem of low solubility of Amiodaron is the formation of a salt form of the active substance, which aims to increase ionic solubility through modification of the physicochemical properties of drug solids. This strategy allows the change from a stable but difficult-to-dissolve crystalline form to an amorphous phase with higher free energy, making it easier for drug molecules to interact with the solvent medium. The amorphous phase generally exhibits better solubility and dissolution speed than its crystal form, due to the absence of an orderly and strong crystal lattice arrangement. This increase in the rate of dissolution will increase the amount of drugs that are in dissolved form in the biological medium, so that the fraction of drugs available for absorption through the gastrointestinal tract membrane becomes larger. Thus, the formation of salt forms not only plays a role in improving the properties of the solution, but also directly contributes to a significant and more consistent increase in the oral bioavailability of amiodaron, as has been reported in previous studies [11].

In addition to solubility issues, the stability aspect of Amiodaron is also a very crucial factor and must receive serious attention in every stage of the development of pharmaceutical preparations. Amiodaron is known to have high sensitivity to various environmental factors, especially exposure to light, oxidation, and moisture, which can trigger the chemical degradation of active substances. The degradation process not only causes a decrease in Amiodaron levels in the preparation, but also has the potential to reduce the effectiveness of therapy and affect the safety of drug use in the long term. Therefore, the right formulation strategy is needed to minimize the influence of these factors, one of which is through the addition of appropriate antioxidants. The use of antioxidants such as butyl hydroxytoluene (BHT) or butyl hydroxy anisol (BHA) is an important approach because these compounds are able to inhibit oxidative reactions that accelerate the breakdown of Amiodaron. By suppressing the oxidation rate, antioxidants play a role in maintaining the chemical stability of active substances during the production, storage, and distribution of pharmaceutical preparations. The implementation of this strategy is expected to maintain the quality, safety, and consistency of the therapeutic effectiveness of amiodaron, so that the quality of the preparation is maintained in accordance with the set standards [12].

In addition, the selection of non-hygroscopic excipients is a very important aspect in the development of Amiodaron tablet preparations to minimize moisture absorption from the surrounding environment during production, storage, and distribution processes. Excessive humidity is known to trigger chemical degradation reactions, accelerate the oxidation process, and reduce the physical and chemical stability of tablet preparations, which can ultimately have an impact on reducing the level of active substances and product quality. This condition is becoming increasingly crucial considering that amiodaron has a high sensitivity to environmental factors, so humidity control through the selection of the right excipients is necessary. Therefore, the combination of the appropriate use of antioxidants and the selection of non-hygroscopic excipients is a strategic step to maintain the long-term stability of Amiodaron in tablet preparations. This formulation approach not only aims to maintain the level of the active substance within the required limits, but also plays an important role in ensuring the consistency of quality, therapeutic effectiveness, and safety of pharmaceutical products throughout their shelf life.

From the aspect of the tablet manufacturing process, the use of wet granulation method is more recommended than direct compression, considering that amiodaron powder has poor flow and compressibility properties and there are challenges in maintaining uniformity of levels due to relatively low drug doses. The wet granulation method is considered to be able to increase the homogeneity of the powder mixture through the formation of more uniform granules, improve flow properties, and increase the size and distribution of particles so that the mold filling and packaging process can take place more consistently and controlled. In this approach, the use of microcrystalline cellulose (MCC) as a filler plays an important role in improving the compression ability and mechanical strength of the tablet, while the addition of binding agents such as PVP K30 or HPMC helps to form stronger bonds between particles so that the resulting tablets are not easily brittle and have good physical stability. The combination of methods and excipients is a rational strategy to overcome the limitations of the physical properties of Amiodaron powder. However, to support the development of more optimal, consistent, and scientifically based formulations, advanced pre-formulations tests such as Differential Scanning Calorimetry (DSC) and X-ray diffraction (XRPD) are needed to evaluate the crystallinity properties and possible deformation of solids, along with compatibility tests and forced degradation tests to assess the drug-excipient interactions as well as the overall chemical and physical stability of the formulation [13].

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3.3. Justification for the Selection of Preparation Form

Based on the results of the analysis and pre-formulations discussion, the form of oral tablet or capsule preparation is considered the most suitable to meet the long-term therapeutic needs of the use of amiodaron HCl, especially in patients with chronic arrhythmia disorders who require continuous and stable treatment. Oral preparations have the main advantages in the form of ease of use that allows patients to take drugs independently, a relatively high level of patient compliance because they do not require special procedures, and the ability to control accurate and consistent doses so that the risk of fluctuations in drug levels in the body can be minimized. In addition, the tablet or capsule form also provides the advantages of pharmaceutical and logistical aspects, such as better physical and chemical stability during storage, ease in the distribution process, as well as relatively lower production costs compared to parenteral forms or more complex drug delivery systems. With these advantages, both from a clinical and pharmaceutical point of view, oral preparations remain the primary and most rational choice in the widespread use of amiodaron for long-term maintenance therapy in patients with heart rhythm disorders.

However, the development of amiodaron oral preparations is inseparable from various obstacles stemming from the physicochemical properties of its active substances which are complex and unfavorable for conventional formulations. Amiodaron HCl is known to be very lipophilic and has very low water solubility, so it is included in the class of drugs that are difficult to formulate orally. The Indonesian Pharmacopoeia and PubChem database state that amiodaron is classified as difficult to dissolve in water and has a high log P value [14], which indicates the tendency of the drug to be more easily distributed in the lipid phase than in the water phase. These characteristics have a direct impact on the drug dissolution process in the gastrointestinal fluid, where the slow dissolution rate can be the main limiting factor in drug absorption. As a result, the oral bioavailability of Amiodaron has the potential to be low and inconsistent, which can lead to variations in therapeutic responses between individuals. In addition, this condition also increases the risk of not achieving optimal therapeutic levels, especially in patients with physiological differences in the gastrointestinal tract. Therefore, the pre-formulations stage is crucial to identify and understand the main barriers that can affect the performance of Amiodaron tablet or capsule preparations, as well as the scientific basis for designing appropriate formulation strategies to improve the solubility, dissolution rate, and bioavailability of the drug.

To overcome these problems, a special formulation strategy is needed that is rationally designed and based on the results of pre-formulations studies, so that every formulation decision is supported by a comprehensive understanding of the physicochemical properties of amiodaron. Some of the approaches that can be applied include the selection of suitable hydrophilic excipients to improve the wetting and solubility of drug particles, the use of wet or dry granulation techniques to improve the flow and compressibility of the powder so that the tablet printing process can take place more homogeneously and consistently, and the application of various methods of improving the solution such as the use of hydrophilic polymers, surfactants, or the formation of solid dispersion systems. These approaches aim to increase the effective surface area and increase the contact between drug particles and the dissolved medium, so that the fraction of dissolved drugs in the gastrointestinal tract can increase significantly. With increasing rates and degrees of dissolution, the oral bioavailability of Amiodaron is expected to improve and variations in therapeutic responses can be minimized. Thus, through the application of appropriate and integrated formulation strategies, the limitations of the physicochemical properties of Amiodaron can be effectively minimized without having to change the chemical structure of the active substance, so that the quality, stability, and therapeutic effectiveness of oral preparations can be maintained.

In addition to conventional tablet or capsule preparations, the development of alternative formulations such as soft-gel capsules, lipid-based preparations, and inclusion technologies shows very promising potential in improving the pharmaceutical and therapeutic performance of Amiodaron. The highly lipophilic characteristics of Amiodaron HCl make the lipid-based system a rational formulation approach, as it is able to dissolve the active substance in the oil phase, increase the pseudo-solubility, and enlarge the fraction of the drug available for the absorption process in the gastrointestinal tract. Various studies show that modification of oral formulations through the selection of appropriate excipients, including the use of hydrophilic polymers and the application of solid dispersion techniques, can significantly improve the physical properties of tablets, increase the dissolution rate, and result in a more consistent drug release profile. Fița et al. (2022) reported that the selection of the right polymer type in solid dispersion-based amiodaron fast-release tablets was able to significantly improve the dissolution rate and performance of the preparation [15], demonstrating the importance of the role of polymers in controlling drug–excipient interactions and active substance release behavior. In addition, the development of fast disintegrating tablets has also been reported to be able to accelerate the destruction time of tablets in the oral cavity, thereby increasing the availability of drugs in the early stages and potentially improving the initial bioavailability of Amiodaron [16], especially in patients with difficulty swallowing or who require a faster therapeutic effect.

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On the other hand, for certain clinical conditions that require rapid onset, injection formulations remain a relevant option even if their use is limited to acute situations and certain healthcare facilities. The development of amiodaron injection preparations demands special attention to the stability of the active substance, given that amiodaron is sensitive to heat and other environmental factors. Creţeanu and Ochiuz (2016) emphasized that the thermal stability of Amiodaron needs to be strictly controlled because exposure to high temperatures can accelerate the degradation of the active substance. In this context, formulation technology that is able to increase solubility while maintaining stability is very important. Nonetheless, for general use and long-term therapy, the oral tablet or capsule form remains the preferred choice because it is more practical, economical, and fits the patient's needs [10]. Therefore, these results and discussion confirm that the development of Amiodaron preparations must combine the selection of the right preparation form with advanced formulation strategies based on scientific evidence in order to obtain pharmaceutical products that are stable, have better solubility and bioavailability, and can be adjusted to the clinical needs of patients.

4. Conclusion

The overall study of amiodaron pre-formulations shows that the development of these medicinal pharmaceutical preparations faces complex and interrelated challenges, especially related to very low solubility, sensitive stability to environmental factors, and limited oral bioavailability. Amiodaron is classified in the Biopharmaceutical Classification System (BCS) class II, which has high permeability but low solubility, so the dissolution process is the main limiting factor in achieving optimal therapeutic effects. Its highly lipophilic nature with a high log P value and weak alkaline character with a pKa of around 6.5 causes amyodonons to be easily degraded due to exposure to light, heat, and alkaline conditions, which can ultimately reduce the potency and quality of the preparation. In addition, the physical characteristics of amiodaron powder characterized by poor flow properties and low compressibility pose technical obstacles in the tablet manufacturing process, especially in maintaining weight uniformity, mechanical strength, and product quality consistency. Therefore, a comprehensive formulation approach and pre-formulations data-based approach is needed, such as the utilization of inclusion complexes with cyclodextrins, the application of solid dispersion techniques, and the use of appropriate surfactants and hydrophilic polymers to improve the solubility, dissolution rate, and stability of active substances. By conducting a thorough and systematic pre-formulations study, the formulation of Amiodaron tablets can be rationally optimized so that it can achieve better stability, increase the bioavailability of the drug, and ensure the effectiveness and safety of therapy for patients with arrhythmic disorders.

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