

Rifampicin and technologies employed in improving its dissolution profile

Rifampicina e tecnologias empregadas para melhoria do seu perfil de dissolução.

Lyghia Maria Araújo Meirelles^{1*}, Anderson Wilbur Lopes Andrade¹

¹Universidade Federal do Piauí, Teresina, Brasil

* Correspondência:
E-mail: lyghia@ymail.com

ABSTRACT

Rifampicin is an antibiotic of the group of naphthalenics ansamicins, produced by *Streptomyces mediterranei*. This drug was discovered in the 60's, with bactericidal activity about 95% of sensitive strains of *Mycobacterium tuberculosis* and *Mycobacterium leprae*, the etiologic agents of tuberculosis and leprosy, respectively. Investigations have shown that the main limitation of some formulations of rifampicin is due to their low solubility in aqueous medium, which fits in class II Biopharmaceutical Classification System. Objective: In this regard, the objective of this review was to demonstrate the main techniques used to optimize the dissolution profile of the drug rifampin. Methods: The scientific review was developed by database search *Pub Med*, *Science direct*, *Scopus*, CAPES Periodicals and *ACS Publications*, using the keywords rifampicin, release system, dissolution and their associations in the period March to June 2014 in documents published in the year 1971 to 2013. Results: Scientific Publications show that the restricted solubility of this compound can be circumvented by delivery systems for non-conventional, such as vesicular systems, inclusion complexes or solid dispersions. Conclusion: These technologies allow for pharmaceutical forms more stable and soluble bioavailability less variable.

Keywords: rifampicin; delivery systems; solubility; dissolution.

RESUMO

Rifampicina é um antibiótico do grupo das ansamicinas naftalênicas, produzido por *Streptomyces mediterranei*. Este fármaco foi descoberto na década de 60, com atividade bactericida sobre 95% das cepas sensíveis de *Mycobacterium tuberculosis* e *Mycobacterium leprae*, os agentes etiológicos da tuberculose e hanseníase, respectivamente. Investigações realizadas mostram que a principal limitação de algumas formulações de rifampicina deve-se à sua baixa solubilidade em meio aquoso, o que a enquadra na classe II do Sistema de Classificação Biofarmacêutico. Objetivo: Diante disto, o objetivo desta revisão foi demonstrar as principais técnicas empregadas para otimizar o perfil de dissolução do fármaco rifampicina. Metodologia: A revisão científica foi desenvolvida pela busca nos bancos de dados do *Pub Med*, *Science Direct*, *Scopus*, Periódicos CAPES e *ACS Publications*, utilizando-se as palavras-chave rifampicina, sistema de liberação, dissolução e suas associações no período de março a junho de 2014 em documentos publicados no ano de 1971 a 2013. Resultados: Publicações científicas demonstram que a solubilidade restrita deste composto pode ser contornada por sistemas de liberação não convencionais, como sistemas vesiculares, complexos de inclusão ou dispersões sólidas. Conclusão: Estas tecnologias permitem obter formas farmacêuticas mais estáveis e solúveis, com biodisponibilidade menos variável.

Palavras-chave: rifampicina; sistema de liberação; solubilidade; dissolução.

INTRODUCTION

For many years, the lack of a profitable market and of effective public policies led to the stagnation of the treatments for neglected tropical diseases, making them obsolete (CHATELAIN & IOSET, 2011). Tuberculosis (TB), which belongs to this group, is caused by the bacillus *Mycobacterium tuberculosis* and is characterized by its chronic infectivity. According to health indicators published in 2012, 8.6 million people developed the disease, and in the same year, 1.3 million deaths were associated with TB. The greatest obstacles to global control of this infection involve the detection and cure of a number of representative cases to interrupt the transmission (SOSNIK et al., 2010; VILLEMAGNE et al., 2010; WHO, 2013)

The initial therapeutic regimen recommended by World Health Organization (WHO) since 2009 is the combined administration of isoniazid, rifampicin, pyrazinamide, and ethambutol for the first two months, followed by isoniazid and rifampicin combination, during four months. However, some gaps remain to be filled, due to the rapid development of resistance, complications of TB/HIV co-infection, and the limitations of the association of first-line drugs (DUCATI et al., 2006; PANDIT & TIWARI, 2011; LAWN & ZUMLA, 2011).

Rifampicin is a semisynthetic antibiotic derivative of rifamycin, which works by blocking the synthesis of messenger RNA from mycobacteria (BACCHI & PELIZZI, 1998; SOUSA, 2005; ARISTOFF et al., 2010). The Biopharmaceutics Classification System (BCS) fits rifampicin in class II, due to the low solubility and high permeability (SOSNIK et al., 2010). Thus the dissolution rate becomes the rate limiting step for absorption in the gastrointestinal tract. Formulation strategies have been adopted to optimize the solubility of the drug, reducing the dosage, frequency of administration, side effects and hence interruption of treatment (AULTON, 2005).

Various adjuvants, delivery systems and alternative routes of administration, emerged in the last decades to optimize the bioavailability of the drug. The objective of this paper is to present the process of technological innovation on this drug and demonstrate the feasibility of these

improvements when compared to the development of new molecules.

METHODS

The scientific review was done by searching the banks of the PubMed Data, Science Direct, Scopus, CAPES Journal and ACS Publications. The keywords used were: rifampicin, delivery system, and dissolution of these associations. The quest journals was conducted from March to June 2014 documents published in the year 1971 - 2013.

RESULTS AND DISCUSSION

Authors related that a drug should be formulated so as to obtain the maximum benefit. This is the concept behind a delivery system, which includes the drug, the site of action, the disease and the delivery system, the latter being the only variable parameter for the same treatment (PANDEY & AHMAD, 2011). The interactions involved are complex and depend on the physicochemical characteristics of the drug, the delivery device employed and pathophysiological conditions of the patient (GAMSIZ et al., 2009).

Generally, the bioavailability of drugs that belong to Classes II and IV of the BCS is limited by the rate of dissolution affected by such factors as the surface area of contact, the diffusion coefficient, the thickness of the diffusion layer, the saturation solubility and the volume of dissolution medium. According to Kawabata et al. (2011), crystal modification, reduction of particle size, lipid formulations, complexation with cyclodextrins, pH modification and amorphization are effective alternatives to improve the dissolution profile of poorly soluble drugs (SAFFOON et al., 2011). The following will be discussed using these techniques to improve the dissolution profile of rifampicinas an alternative to optimize the treatment of tuberculosis.

Documents analyzed demonstrate that systems with targeted release may release the drug at its site of action in higher concentrations and for a longer period before the conventional systems. Therefore, they represent an interesting carrier system for the release of antituberculous agents in order to reduce the frequency of administration by prolonged release of the drug and minimizing the dose required and thereby side effects by

selectively distributing the drug to target cells. Several studies have reported the advantages of the use of carrier systems such as liposomes, microparticles, dendrimers, solid lipid nanoparticles, among others (VERMA& GARG, 2001; SARAOGIA et al., 2010).

Some of the challenges of most conventional systems for drug delivery include circumvent the instability caused by low bioavailability, low solubility, variable intestinal absorption, side effects and fluctuations in plasma concentration of the drug. The oral bioavailability of drugs presented in a solid dosage form depends mainly on the size and size distribution of particles, which is improved by increasing its surface area. Hence, a variety of micronization technologies such as spray-drying, freeze-drying, crystallization and milling processes were developed to decrease the particle size (KRISHNAIAH, 2010).

The nanotechnology used in drug development, can be used as a tool to solve these problems. A nanoparticle is a microscopic particle whose size is measured in nanometers, consisting of macromolecular materials, usually polymers, in which the active ingredient is dissolved or encapsulated. The enhance of dissolution rates for drug compounds is complemented with other technologies used to enhance the bioavailability of insoluble compounds such as solubility enhancers (i.e. surfactants), liquid-filled capsules or solid dispersions of drugs in their amorphous state (OCHEKPE, OLORUNFEMI & NGWULUKA, 2009; KRISHNAIAH, 2010).

Viçosa et al. (2012) prepared ultrafine particles of rifampicin using antisolvent precipitation method for accelerating dissolution without the use of conventional volatile organic solvents. The solubility was found to be higher than 90 mg/g for this technique and lower than 1mg/g in water at 25 °C. The ultrafine particles (280–360 nm) are amorphous with enhanced solubility and faster dissolution rate. Moreover the technique is an innovative process for obtaining nanosizing particles of poorly water-soluble drugs.

Patel et al. (2013) developed oral sustained release chitosan nanoparticles of rifampicin prepared by modified emulsion

ionic gelation technique. In vitro release date of optimized formulation showed an initial burst followed by slow sustained drug release.

Use of polymers to obtain particles micro/nanometric ranges containing rifampicin has been adopted for quite some time, especially for pulmonary administration. For doing so, the carrier must be compatible with the drug properties and method of production, making it capable of delivering the proper dose at the site of action, for the desired time. Such characteristics require a nontoxic, biodegradable, and low cost material (PANDEY&AHMAD, 2011).

Various natural and synthetic polymers, such as alginate, chitosan and polyesters have been used for the development of systems for controlled release of drugs. Investigations carried out by Qurrat-UI-Ain et al. (2003) showed alginate microparticles, encapsulated rifampicin, are significantly increasing their bioavailability up to nine times compared to the free drug, by weekly administration.

Delivery systems based on lipids present as a strategy of highly suitable formulation for increasing the bioavailability of drugs poorly soluble in water include various systems such as oil solutions, emulsions, microemulsions, systems and release self-emulsifying micellar systems (GRIFFIN, 2012).

Containing solid lipids as matrix material which possesses adhesive properties that make them adhere to the gut wall, this nanoparticles kept rifampicin under therapeutic concentrations in plasma of mice over a period of 8-10 days, whereas the free drug was purified in 1-2 days. The result allows us to state that the frequency of administration of this delivery system would be lower when compared to the conventional treatment for promoting better adherence (JOHNSON et al., 2005; KRISHNAIAH, 2010).

Singh et al. (2013) incorporated rifampicin in a solid lipid nanoparticulate system to limit its degradation and interaction with isoniazid at acidic pH and reduced its degradation to about 9% (from 26.50% when present alone) and to around 20% (from 48.81% when isoniazide was also present).

Sarfaraz et al. (2010) obtained microspheres of carbopol and sodium

alginate, which were effective for controlled release of rifampicin, which reached a maximum of 91.2% released, and also high encapsulation efficiency, demonstrating their effectiveness as the release profile. Date, Samad & Devarajan (2010) obtained rifampicin nanoparticles by lyophilization using cryoprotectants with high encapsulation efficiency. The system showed sustained release, good redispersibility, and there was no significant change in the particle size, which remained stable for 12 months.

The number of candidate drugs with low solubility has grown, covering about 70% of the new drugs in recent years and, with them, the need to develop new strategies for solubilization (KAWABATA et al., 2011). Cyclodextrins are the primary agents to increase the aqueous solubility, bioavailability and stability of water-insoluble drugs (BREWSTER & LOFTSSON, 2007).

Cyclodextrins are cyclic oligosaccharides starch derivatives with a hydrophilic surface and a lipophilic cavity. The addition of alkalizing agents or acidifiers and hydrophilic polymers may increase the solubilizing action of these molecules by the formation of a multicomplex. The techniques employed, such as precipitation, evaporation, lyophilization, spray drying and kneading, result in amorphous solids which are quickly dissolved and provide a supersaturation (UEKAMA, HIRAYAMA & IRIE, 1998; BREWSTER & LOFTSSON, 2007; LI & ZHAO, 2007).

Inclusion complexes of rifampicin and cyclodextrin have been studied for some time, with evidence that they form stable complexes with β -cyclodextrin and its synthetic derivatives (methyl-, hydroxypropyl-, hydroxyethyl- β -cyclodextrin) by forming non-covalent bonds between the guest molecule and the carrier with defined stereochemistry. Studies show various techniques attest the formation of inclusion complexes between the drug and the guest molecules, as compared to free molecules and their physical mixtures. X-ray diffraction analysis; Fourier transform infrared spectroscopy; thermal analysis; scanning electron microscopy; diagrams of solubility and dissolution profile are the most frequently used techniques in the characterization of the complex (FERREIRA et al., 2004; CHADHA et al., 2010; LIMBACHIYA, 2012).

The complexes obtained by evaporation and trituration mainly show an amorphization of the complexes compared to rifampicin and pure cyclodextrins; increase in solubility profile, morphological alterations in the crystals; displacement, reduction and disappearance of the characteristic peaks in the spectroscopic and thermal analysis. Such complexation occurs by encapsulation of the piperazinic portion in the cavity of cyclodextrin. There are also patents for the preparation of complexes employing β -cyclodextrin and its derivatives, and rifampicin (RAO et al., 2006; RAO et al., 2008; CHADHA et al., 2010).

In pharmaceutical technology, the solid materials can be classified into amorphous or glassy form, and crystalline. The first ones hold special interest because they increase the dissolution rate and solubility of poorly water-soluble drugs and protect active agents from a polymorphous transformation. The solubility of amorphous form has been reported to be between 1.1 and 1000 times higher than that of the crystalline form (SZABÓ-RÉVÉSZ et al., 2007; BABU & NANGIA, 2011, KAWABATA et al., 2011).

Solid dispersions are a favorable approach to improved oral bioavailability of poorly soluble in water drugs. The term solid dispersion refers to the preparation of one or more hydrophobic drugs dispersed in an inert matrix, making it essentially amorphous (CHIOU & REIGELMAN, 1971). The matrix is typically a hydrophilic polymeric material, such as cellulose derivatives, hydroxypropyl methylcellulose, or vinyl derivatives, polyvinylpyrrolidone. This increase is attributed to the interaction of the drug with the polymer chains by the number and location of the hydrogen bonding between them, the reduced particle size and increased surface contact, and reduces the energy needed to disrupt the crystal structure of the molecule in question (DAHLBERG et al., 2010).

The method for obtaining solid dispersions is selected according to the physicochemical properties of the drug and the polymer, the main method involve technologies such as solvent evaporation, spray drying, freeze-drying and hot melt extrusion, resulted in formulations that showed a significant increase in drug

dissolution rate (LEUNER & DRESSMAN, 2000; ZOELLERA, DRESSMAN & KLEIN, 2012; ALVES et al., 2012; MOOTER, 2012).

Theja et al.(2012) produced solid dispersions of rifampicin and polyethylene glycol 6000 at different ratios through the method of evaporating the solvent, obtaining dispersions with uniform content and good dissolution profile. Although the drug in the amorphous state has a faster dissolution compared to its crystalline structure, the first is not physically stable, being possible the recrystallization of the obtained product during the lifetime of use (LIMA et al., 2011).

Krasnyuk Junior (2009) evaluated the solubilizing effect of some polymers in the presence of antibiotics, as rifampicin. Solid dispersions of polyvinylpyrrolidone and polyethylene glycol 1500 were obtained by evaporating the solvent, and β -cyclodextrin by co-grinding. The solubility of rifampicin from the solid dispersion with polyethylene glycol, polyvinylpyrrolidone and β -cyclodextrin increased by factors of 2.5, 2.7, and 2.1 respectively.

There is a variety of techniques used for characterizing amorphous solids, which include X-ray diffraction analysis, molecular spectroscopy, thermal analysis, scanning electron microscopy, among others. Although solid dispersions are a practical, low cost and effective way of improving the solubility of poorly soluble in water drugs, its application in large scale production is limited by problems of crystallization of the components, which must remain amorphous. The mechanical stress to which the substances are exposed during processing or the environmental conditions during storage can lead to changes in crystal behavior, and the forms with better solubility profile are those with impaired stability, or metastable (JACOB et al., 2011; SAFFOON et al., 2011).

FINAL CONSIDERATIONS

Currently, the expenditure on R&D of new drugs is high, and the time spent for such development varies from one to two decades, in addition to uncertainties about the resistance and toxicity. One of the alternatives to minimize cost, delay and risk of development failure is the incremental development of existing drugs and of proven effectiveness. The increasing prevalence of

tuberculosis, coupled with the absence of new drugs makes the search for new presentations and new formulations attractive, offering advantages to the holder on the market. From this logic, rifampicin may have optimized its biopharmaceutical properties through accessible and low cost technologies, leading to greater efficiency, reducing the frequency of administration and adverse effects, facilitating patient compliance and presenting itself as a favorable alternative when compared to the development of a new molecule.

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