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Commentary

Biopharmaceutic and pharmacokinetic aspects of variable bioavailability of rifampicin

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Abstract

Even today the treatment outcome of tuberculosis is questionable due to variable bioavailability of rifampicin, which was discovered four decades back. In this manuscript, results of bioequivalence trials reported are presented in the form of a figure that provides a comprehensive look at the rifampicin bioavailability literature, provides understanding of the problem and clears 'myths and assumptions' regarding rifampicin bioavailability from fixed-dose combination (FDC) formulations. It was found that FDCs of good as well as bad quality rifampicin containing formulations with reduced or increased relative bioavailability are available. In addition, 'rifampicin alone' formulations also show variability in bioavailability. In the context of anomalous bioavailability of rifampicin, reasons postulated in literature are summarized. Approaches needed to solve the issue of rifampicin bioavailability are discussed on the basis of LADMER and BCS.
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For centuries tuberculosis (TB) has remained a complex socio-economic problem that impedes human development. Apart from annual death toll of two million, poor people of developing countries are paying intangible economic, psychological and social costs in terms of manpower loss, pain, suffering, grief and discrimination. After the discovery of tubercle bacilli by Robert Koch in 1882, the era of anti-TB chemotherapy dawned in 1945 with the introduction of streptomycin. Until 1970 streptomycin, *p*-amino salicylic acid and isoniazid were the main anti-TB drugs available. Inclusion of rifampicin and pyrazinamide in earlier available regimen substantially reduced the relapse rate and treatment period. Hence, rifampicin along with isoniazid and pyrazinamide was considered as a major anti-TB component. Early clinical trials at the Tuberculosis Research Center, Chennai and the British Medical Research Council, London in 1972 explored regimens with rifampicin and isoniazid wherein rifampicin at a dose of 10 mg/kg was considered to be effective, with a success rate of more than of 95%. Thus current day anti-TB treatment includes 6 months therapy with rifampicin, isoniazid, pyrazinamide and ethambutol and these regimens are 100% curative with very low relapse rates (Fox et al., 1999).

Although, the term 'short-course' is coined for standard anti-TB regimens, from an operational point of view, 6 months multi-drug therapy is a complex procedure leading to treatment failure and resur-

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gence of drug resistant strains. To increase patient compliance, the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease (IUATLD) encourage the use of fixed-dose combination (FDC) tablets that ensures ingestion of all the components of the therapy. By preventing monotherapy and by facilitating the delivery of correct drug doses, FDCs are expected to reduce the risk of emergence of drug resistant TB. However, the major quality issue associated with FDCs is the bioavailability of rifampicin. Rifampicin, one of the key components of the anti-TB chemotherapeutic cocktail, is reported to have bioavailability problem in FDC formulations that raises the question of therapeutic success of the current treatment (Blomberg et al., 2001).

There is ample evidence in the literature that good quality FDCs can be and are produced with proven bioavailability (Fig. 1). It is pertinent to note that the bioavailability of some FDCs when compared with rifampicin alone is not negatively affected while in some cases comparisons with separate formulations at same dose levels have shown reduced bioavailability. Interestingly, some of the trials report increased relative bioavailability of rifampicin from FDC formulations. On the other hand, rifampicin generic formulations (RIF alone) have also shown variable bioavailability. This indicates that FDCs of good as well as bad quality rifampicin containing formulations with reduced or increased relative bioavailability are possible. Therefore, it is difficult to make any generalization regarding the bioavailability of rifampicin either from 'FDCs' or from 'rifampicin alone' generic formulations as variability has been found in both the cases (Panchagnula et al., 2001).

Although the problem associated with the quality of FDCs was addressed in its development stages and marketing from the 1980s, up till now the exact cause of the compromised rifampicin bioavailability from some of the formulations is not clear and the reasons are only speculative. The reasons hypothesized in the literature include raw material characteristics, changes in the crystalline habit of the rifampicin, excipients, manufacturing and/or process variables, degradation in the gastro-intestinal tract, inherent variability in absorption and metabolism, etc. (Laing et al., 1999; Blomberg et al., 2002). Other anti-tubercular components of FDC like isoniazid, pyrazinamide and ethambutol do not show any bioavailability problems as all these drugs belong to class I (highly soluble and highly permeable) of the biopharmaceutic classification system (BCS). Rifampicin is the only hydrophobic component of the FDC which belongs to BCS class II (low solubility and high permeability) and is reported to be adsorbed by common pharmaceutical excipients. Further, rifampicin shows pH-dependent solubility affecting its absorption from gastro-intestinal tract. Rifampicin being the only water insoluble component of FDC, manufacturing of rifampicin containing FDC with all other highly water-soluble components

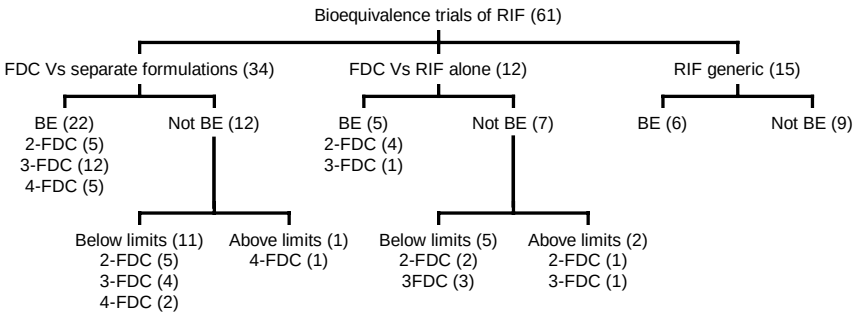

Fig. 1. Bioequivalence trials of rifampicin containing formulations reported in the literature. Figures in parentheses indicate number of bioequivalence trials in particular categories, whereas the prefix of FDC indicates the type of FDC formulation. This figure summarizes all the bioequivalence trials reported after 1970 published in the journals listed in Medline. Figures in parentheses indicate the number of rifampicin formulations for which bioequivalence has been tested in human volunteers. Note that number of published papers does not match with these figures as some of the papers report bioequivalence tests of more than one rifampicin product. Care has been taken to avoid the repeated inclusion of trials from the papers that report the reanalysis of data based on earlier published trials. BE, bioequivalent; FDC, fixed-dose combination; RIF, rifampicin.

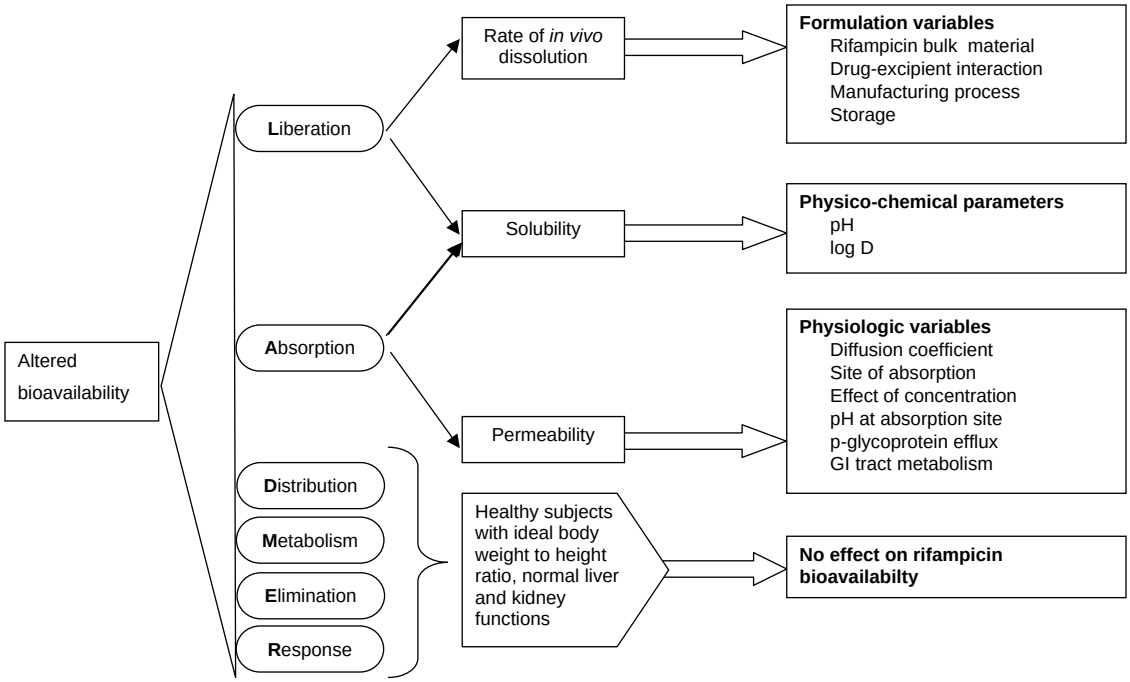

Fig. 2. Probable reasons for the altered bioavailability of rifampicin from either separate dosage forms or from FDC formulations of anti-TB drugs. Physiological variables such as food, gastric emptying time, age, phenotype, gender, nutritional status, disease, etc. are not considered as these variables are minimized in bioequivalence trials having a cross-over design.

is the most critical process, which is further complicated as the number of processing steps such as grinding, mixing, granulation, drying and compression are increased. The crystalline nature or particle size of rifampicin may be affected, thereby altering its bioavailability. Further, common pharmaceutical excipients used in the tablet as binder, glident, e.g. bentonite, talc and kaolin rapidly and strongly adsorb rifampicin and hence reduce its gastrointestinal absorption. Thus, idiosyncratic behavior of rifampicin can be explained by physiological, physicochemical, pharmaceutic and manufacturing factors that affect the absorption of rifampicin from various dosage forms (explained in Fig. 2). Although, reasons vary from raw material to in vivo absorption, there is no comprehensive and systematic study that characterizes the effect of the above-mentioned variables on the in vivo performance of rifampicin-containing formulations, probably because of the fact that TB has been more of a “poor man’s” disease.

In the above backdrop of variable bioavailability of rifampicin, to ensure the effective therapeutic treatment of TB, the WHO and IUATLD have recommended use of FDC formulations with proven bioavailability of rifampicin and also have developed a simplified, effective protocol for assessment of rifampicin bioavailability from FDC formulations (Fourie et al., 1999). This protocol utilizes only six sampling points over a period of 8 h and thus is convenient and cheaper. However, in most of the developing countries regulatory authorities follow their own national guidelines for bioequivalence studies. Therefore, the number of volunteers and sampling time points required are not uniform in national regulatory guidelines, which may affect the statistical results of the bioequivalence study. These quality issues of rifampicin-containing formulations, along with the variable registration requirements discourage some manufacturers.

Dissolution has emerged as a simple, rapid and sensitive tool to judge the quality of formulations. Based on the sound scientific principles of BCS, observed in vivo differences in the rate and extent of absorption of a drug from two pharmaceutically equivalent solid

oral products may be due to in vivo differences in drug dissolution. Rates of dissolution from IR dosage forms are generally affected by raw material characteristics, formulation variables, manufacturing process variables such as grinding, compression, and by storage. It therefore becomes apparent that sensitive and reproducible dissolution data derived from physicochemically and hydrodynamically defined conditions can be used as a surrogate for in vivo bioavailability, bioequivalence testing and in vitro–in vivo correlations of rifampicin containing formulations to reduce the cost and ensuring treatment of tuberculosis with quality formulations.

Hence, in order to provide scientific evidence to recommend and implement FDCs in TB programs, we have studied the effect of different parameters at all levels of product development such as raw material, formulation, manufacturing, in vivo release and absorption at physiologic conditions. We have addressed issues of the variable bioavailability of rifampicin, minimum protocol requirements for bioequivalence determination and finally dissolution as a surrogate for evaluation of rifampicin containing FDCs (Agrawal, 2003). The outcome of such a thorough study should clarify the doubts surrounding rifampicin bioavailability and suggest possible strategies to provide good quality anti-TB formulations for the ailing population.

It is my dream that when my grandchild goes to Medical School, Professors of that generation should be teaching "... for centuries there was one disease that used to affect people of developing and underdeveloped countries which was known as tuberculosis..." and that this dreadful disease is now confined to textbooks and completely eradicated from the face of the earth.

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