

XEED™

**A QUALITY PRODUCT WITH FULL THERAPEUTIC DOSE/DAY
LEADING TO RELATIVELY SPEEDIER CURE FROM TB, LESSER
CHANCES OF GETTING DRUG RESISTANT TB AND REDUCED
RISK OF TREATMENT FAILURE**

1. Introduction

XEED™ is a fixed dose combination (FDC) of four drugs Rifampicin, Ethambutol, Pyrazinamide and Isoniazid with proven bioavailability of Rifampicin for the **treatment of tuberculosis**. It offers the convenience of a fixed dose combination, at the same time ensuring optimal bioavailability of all the active drugs.

It ensures release of Rifampicin & Isoniazid at different sites to avoid interaction leading to **42% enhanced bioavailability of Rifampicin as compared to conventional FDCs**.

2. Medical need

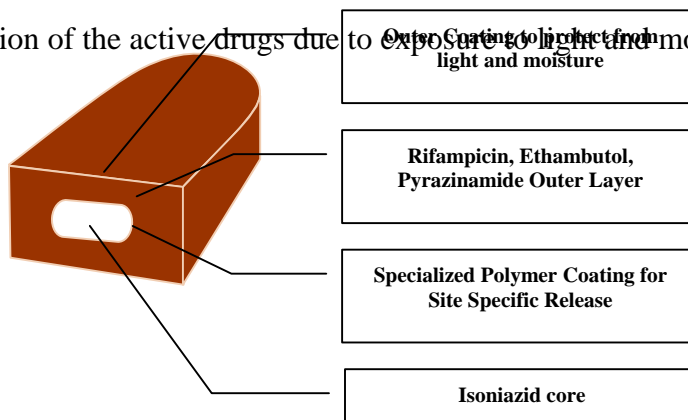
It is estimated that between 19% to 43% of the world population is infected with tuberculosis. As per recent forecasts, between 2000 and 2020, nearly one billion people will be newly infected, 200 million people will develop active tuberculosis, and 35 million will die from the disease - if control is not further strengthened. The HIV epidemic has also increased the risk of tuberculosis

WHO & IUATLD recommend the use of FDCs to ensure the delivery of correct dosage and avoidance of monotherapy, thereby, preventing the development of Multi Drug Resistant bacilli.

However, it has been observed that the co-administration of Rifampicin with Isoniazid in the form of FDC or in loose combination, leads to a significant loss of bioavailability of the former to the extent of 32%.

3. XEED™ Drug delivery system

XEED™ is a compression-coated tablet, wherein Isoniazid is present in the core and is coated with special polymers for site-specific release and avoid the known adverse interaction with Rifampicin. The outer layer of the tablet contains Rifampicin, Ethambutol and Pyrazinamide. The tablets are further coated with selected polymers to prevent the degradation of the active drugs due to exposure to light and moisture.



3.1 Mechanism of action

The problem of bioavailability of Rifampicin has been solved by spatial control of release of both the drugs in such a way that the release takes place at different locations in GIT. The site-specific release of Rifampicin and Isoniazid prevents the drugs from coming in contact with each other in solution stage in the acidic pH of gastric region, thereby, preventing the degradation. **XEED™**'s innovative technology releases Rifampicin, Ethambutol and Pyrazinamide in the stomach while the special polymer coating on the Isoniazid core prevents its release in the stomach, thereby avoiding any interaction between Isoniazid and Rifampicin. Rifampicin releases in acidic pH of stomach and gets absorbed immediately which ensures absolute bioavailability of Rifampicin. The Isoniazid core moves on to the proximal part of the intestine and the release of the drug

takes place in the duodenum where pH rises above 5.0. The release of two drugs at different sites results in no loss of bioavailability of either of the drug.

4. Clinical experience

4.1 Study I

The bioavailability of Rifampicin in **XEED**TM was compared to the reference conventional preparation in a six volunteer pilot study. The C_{max} and AUC (bioavailability) of Rifampicin from the **XEED**TM were found to be significantly higher from the formulation containing conventional Rifampicin.

4.2 Study II

In an another single blinded, randomized, two-way, cross-over bioequivalence study carried out in 12 healthy volunteers, it was found that the C_{max} and AUC (bioavailability) of Rifampicin from the **XEED**TM formulation was found to be higher when compared to C_{max} of Rifampicin from the reference conventional formulation. No difference in C_{max} & AUC (bioavailability) of Isoniazid was observed between the **XEED**TM formulation and Isoniazid of the reference conventional formulation.

4.3 Study III

Bioequivalence results from above pilot studies were strongly convincing and hence a third BA/BE study was planned in 24 healthy volunteers. They were evaluated in a 3-way crossover design for bioavailability of Rifampicin in the **XEED**TM formulation against conventional Rifampicin. It was reported that the **XEED**TM had 42% higher relative bioavailability of Rifampicin (with respect to AUC) than Rifampicin 450 mg (Rimactane) given alone.

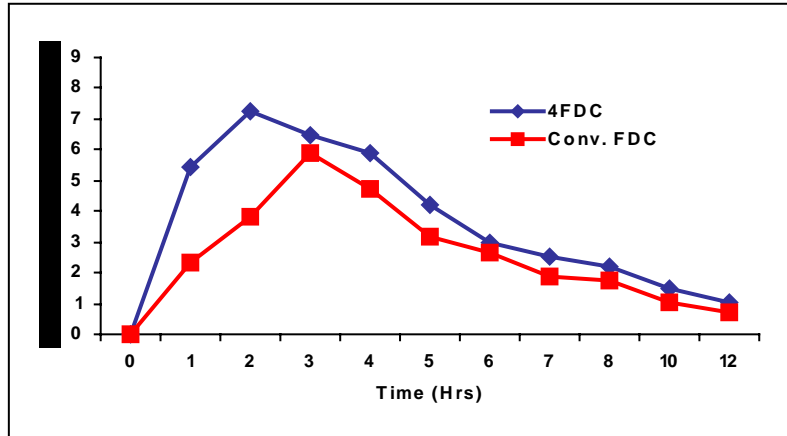


Figure 1 : a relative bioavailability equal to 141.97% was observed for Rifampicin in case of XEED™ when compared with reference conventional formulations (in loose combination)

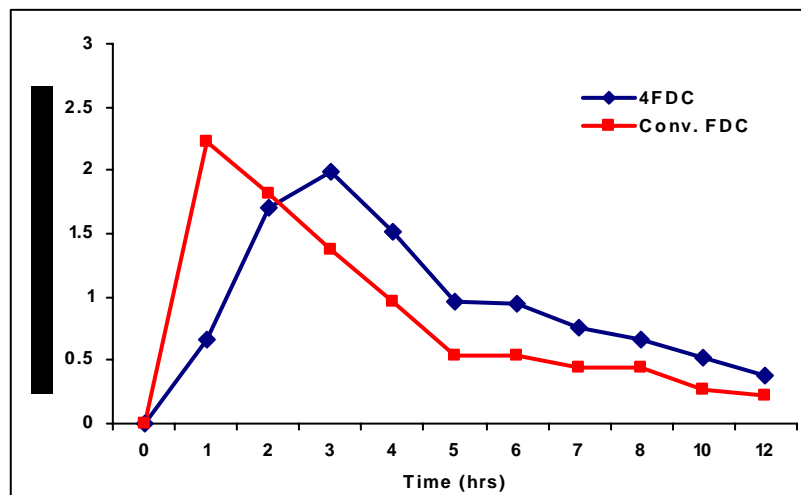


Figure 1 : There was no loss in bioavailability of Isoniazid as Cmax and AUCs are same in both the cases, and as designed only Tmax has been delayed

4.4 Study IV

In order to evaluate the clinical significance of higher bioavailability of Rifampicin in the XEED™, a randomized, open-labeled, comparative, prospective, multi-centric Phase IV study involving 420 TB patients (Male - 78.3%, Female - 21.7%) with clinical symptomatology of cough, fever, anorexia, haemoptysis, lethargy and weight loss was planned. The aim was to evaluate the safety and efficacy of the XEED™ against

conventional FDC, in the treatment of primary pulmonary tuberculosis. All the patients were given FDC as per WHO guidelines:

Two ± one month → Intensive Phase

Four ± two month → Continuation Phase

Results

- ▪ An early symptomatic relief in fever, cough (both productive and non-productive), night sweats and haemoptysis was observed in patients with the XEED™ as compared to conventional FDC
- ▪ There was 91% improvement observed in the XEED™ group as compared to 70% in conventional FDC group, at the end of initiation phase (2 months) of therapy.
- ▪ Also, at the end of continuation phase 99% of subjects taking the XEED™ showed improvement as compared to 84% taking conventional FDC.

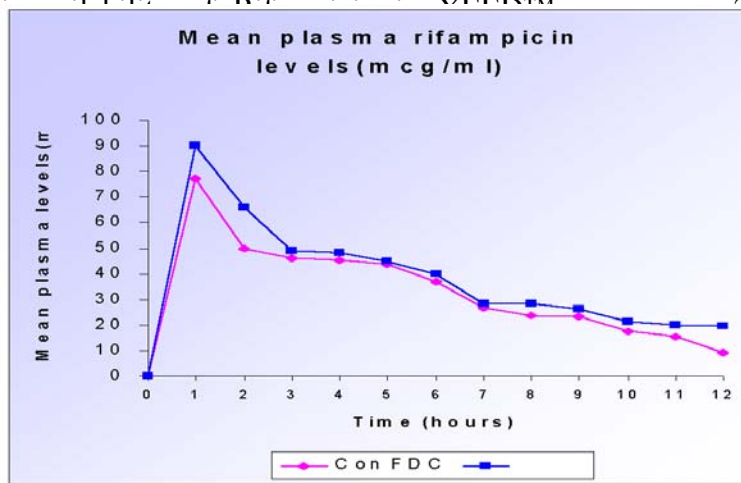
Regimen	At the end of IP		At the end of CP	
	Improved	Deteriorate / Stable	Improved	Deteriorate / Stable
XEED™	91%	9%	99%	1%
Conventional FDC	70%	30%	84%	16%

Table 1 : Overall improvement in fever, cough, night sweats, haemoptysis in patients with XEED™ as compared to conventional FDC

- ▪ There was a quicker radiological improvement seen in patients taking the XEED™. Subjects in the XEED™ group showed early significant improvement in all the defined markers of radiographs as compared to conventional group at day 45 and

Clinical study volunteers at one of the center of Phase IV study were also simultaneously evaluated for Rifampicin and Isoniazid levels in the XEED™ and conventional FDC. This was a parallel, non-cross over bioavailability study in 24 patients at the beginning of their clinical therapy at first therapeutic dose. These patients were admitted for a day after first dose of anti tubercular FDC and their blood levels were monitored for 12 hours thereafter. Equal numbers of subjects were given XEED™ and conventional FDC. It was observed that b

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5. IPR Status

Product patents are filed in all major countries across the globe and patent is already granted in the following countries :

Australia, Nigeria, North Korea, Poland, South Africa, Sudan, Tanzania, Turkey

6. Development Stage

- Commercialized in the Indian market
- CTD compilation under process for regulated markets

7. Product presentation

XEED™ 4

Each film coated tablet contains

Rifampicin 150mg

Ethambutol HCl
275mg

Pyrazinamide 400mg

Isoniazid 75mg

(in modified release form)



XEED™ 3E

Each film coated tablet contains

Rifampicin 150mg

Ethambutol HCl
275mg

Isoniazid 75mg

(in modified release form)



XEED™ 2

Each film coated tablet
contains

Rifampicin 150mg

Isoniazid 75mg

(in modified release form)

