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PROSPECTS OF PRODUCTION OF RIFAMPICIN IN INDIA

*Dr. P.K. Ghosh**

INTRODUCTION

Rifampicin is a semi-synthetic antibiotic chemical. It belongs to the group designated as RIFAMYCINS, which are characterised by a long aliphatic bridge connecting two non-adjacent position of an aromatic nucleus. In Rifamycins, a chromophoric naphthohydroquinone is spanned by a long aliphatic bridge. (Fig.1,I). Rifamycins were first isolated in 1959 from a fermentation broth of Nocardia mediterranea, an actinomycete isolated from a soil sample of France by the Lepetit Research Centre of Italy[1,2]. Commercial production of certain Rifamycins started in 1962 in Italy by the Lepetit Group. There are several naturally occuring Rifamycins; however Rifampicin (also called Rifampin), a semi-synthetic one, has assumed greatest importance because of its superior in-vivo activity against Mycobacteria tuberculosis. It is also active against a large number of Gram positive and Gram negative micro-organisms. The drug has also shown promising results in the management of Leprosy.

1.1 Rifampicin as available in trade is in the form of red to orange-red crystalline powder. The moisture content is 2% maximum with assay at 90% minimum; the biological activity is 900 u/mg minimum, on anhydrous basis. As per the United States Pharmacopoeia[3], Rifampicin contains not less than 90% of $C_{43}H_{58}N_4O_{12}$ (Molecular Weight = 822.95), calculated on dry basis. The material melts at 183-188°C with decomposition.

1.2 Rifampicin is administered orally primarily in the form of capsules. Dosages normally available in commerce are single ingredient 150 mg, 300 mg, 450 mg, and 600 mg capsules. In combination with Isonicotinic acid hydrazide (INH), it is also approved[4] for dispensation in the following dosage combinations:

(a) Rifampicin 300 mg plus INH 200 mg
(b) Rifampicin 450 mg plus INH 300 mg
(c) Rifampicin 600 mg plus INH 300 mg

Rifampicin formulation in the form of Syrup has also been approved[5].

1.3 There are about 80 brands[6] of Rifampicin formulations available in the Indian market. The following are the more important brands which, according to the author would cover about 90% of the Rifampicin formulation market:-

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*Dr. P.K. Ghosh, Director, Bureau of Industrial Costs & Prices, Department of Industrial Development, Lok Nayak Bhawan, 7th Floor, New Delhi-110 003.

Brand Name	Company	Composition (Capsules containing rifampicin in mg)
A) Single, ingredient, Rifampicin formulations		
R-CIN-150	Lupin	150, 300, 450
Tibirim	Ranbaxy	150, 300, 450
Rimpin	Lyka	150, 300, 450
Rifacilin	P&C.I.	150, 300, 450
Rimpacin	Cadila	150, 300, 450
Rifacox	Yash Pharma	150, 300, 450
Rifamycin	Biochem	150, 300, 450
Finamycin	Alma	150, 300, 450
Tibamycin	Astra-IDL	150, 300, 450
Relycin	Dolphin	150, 300, 450
Refam	Mercury	150, - , 450
Rifampila	Albert-David	150, 300, 450
Famcin	IDPL	150, 300, 450
Montomycin	Ethico	150, 300, 450
Rifacept	Concept	450, -,, 600
B) Rifampicin with INH		(Capsules containing rifampicin in mg and INH in mg respectively)
R-CINTEX	Lupin	450, 300
Montonex Forte	Ethico	450, 300
Rifacox Plus	Yash Pharma	450, 300

2. Demand/Availability:

2.1 The entire requirement of the bulk drug of the country is met through imports. The main producer-supplier of the bulk drug in the International market are Italy, Switzerland, Poland, Bulgaria, People's Republic of China and South Korea. The trend of imports of the bulk drug into India during the last few years was as under:-

Year	Imports (MT)[7,8,9]
1979-80	5.41
1980-81	8.95
1981-82	16.06
1982-83	36.90
1983-84	76.00
1984-85	60.00 (Estimated)

The above would show at what galloping speed the increase in the imports of the drug had taken place into the country.

2.2 The bill on account of import of rifampicin has been on the increase and is now contributing to about 10-12% of the total imports bill of Drugs and Pharmaceuticals as could be seen from the following:

Year	Total imports[10,11] of drugs including bulk drug, drug intermediates and finished formulations (Rs. crores)	Imports[8,9] of bulk Rifampicin (Rs.crores)	Imports of bulk Rifampicin as % of total
1982-83	148.48	12.06	8.1
1983-84	162.16	15.90	9.8
1984-85	176.00 (Estimated)	21.00 (Estimated)	11.9

2.3 Reverting back to the question of availability, it is useful to understand the main current producer/suppliers of the drug in the International market. No published information in this regard is available. The author had talked to a large number of consumers and suppliers of the drug and had concluded that the following could be an approximate scenario of world production of the drug during 1984-85:-

	World Source	1984-85 (MT)
1.	West European countries including Italy, Switzerland and France	100-120
2.	Communist countries including USSR, Bulgaria, Poland but excluding Peoples' Republic of China	40- 60
3.	Asian Countries including South Korea & Peoples' Republic of China	25 - 35
	TOTAL	165-215
		Average 190 MT

According to the author, nearly 30-35% of the world production of rifampicin during 1984-85 found a market in India. And of the total imports taking place in India, nearly 60% to 65% come from production units of West European Countries.

2.4 As regards current consumption in India of the bulk Rifampicin for formulations purposes, it could be placed at a level of about 60 MT during 1984-85. The consumption may rise to a level of about 100 MT by the end of 7th PLAN ie. by 1989-90. The consumption is expected to be fully catered through imports during the 7th Plan period if there is no substantial change in the Government Policy on the production of the drug in the country as discussed later on.

3. Price in India

3.1 The annual average C.I.F. price of the bulk drug, imported in India, during the last few years had been as under:-

Year	CIF Price[7,8,9] (Rs./Kg.)
1979-80	5747
1980-81	5010
1981-82	4127
1982-83	3268
1983-84	2092
1984-85	3600 (estimated)

3.2 There was a substantial drop in the price during 1983-84. The author could not find a plausible reason for this. However, the sudden fall in the price was responsible for the heavy imports of the bulk drug into the country during the year 1983-84. The price had however, started rising subsequently and has now (Middle of 1985) reached a level of around US $260 to US $280 per kg[12], which price with current exchange rate works out to around Rs.3300/- to Rs.3500/- per kg. c.i.f.

4. Process of Manufacture

4.1 The production of Rifampicin is lengthy and complex. Detailed descriptions are also not available. Based on the information in the published literature[1,2,13 to 28], it appears that a selected mutant variant of STREPTOMYCES MEDITERRANEI (Classified by Thiemann[13] et al. based on the structure of the cell walls as NOCARDIA MEDITERRANEA) is fermented as usual, in a chosen neutrient media under controlled agitation, aeration, pH and temperature conditions. Sodium diethyl barbitone concentration is maintained at around 0.2% in the media so that the production in the broth is exclusively of Rifamycin-B[15]. A titre of 5000µ/ml to 15000 µ/ml of Rifamycin-B could be obtained depending upon the strain and the technology in active fermentation time of around 160 to 240 hours. The naked broth is harvested, and after proper treatment is filtered to separate the active substance (Rifamycin-B) from the mycellium. Rifamycin-B is isolated under appropriate conditions and oxidised with a suitable oxidising agent to Rifamycin-O. The latter is hydrolyzed to Rifamycin-S and is isolated under appropriate conditions. Oxidation of Rifamycin-S under appropriate condition gives Rifamycin S.V. Rifamycin S or SV are converted[19] into 3-N,N-disubstituted aminomethyl derivatives of Rifamycin-S or -SV by Mannich Reaction and the derivatives are oxidised under appropriate condition to 3-Formyl Rifamycin-SV. The latter on being reacted with 1-amino 4-methyl piperazine gives Rifampicin[20,24]. Rifamycin-O has also been directly converted into Rifampicin in one pot reaction by reacting it with formaldehyde, butyl amine and manganese dioxide and contacting the reaction product with aminomethyl piperazine[21,25]. Rifamycin-S has been converted into 1,3 Oxizine (5,6-c) rifamycin derivatives instead of 3-formyl

rifamycin-S.V. and the former on treatment with aminomethyl piperazine gave rifampicin[22,23]. The major structural transfermations in the production of Rifampicin from Rifamycin-B are presented schematically in Fig.1.

4.2 The yield attained in the industry in the conversion of Rifampicin from Rifamycin-B is not precisely known. However, based on the nature of transportation as described in the Literature cited above, it appears that the overall yield may vary from 35% to 55% w/w from Rifamycin-B in the naked broth to finished Rifampicin.

5. *Discussion*

5.1 Tuberculosis (T.B.) happens to be a major public health problem in India. According to one estimate there are currently about 10 million cases[29] of TB in India. According to another estimate[30], 1.5% of the population at any point of time now shows radiologically active chest X-ray and about 0.4% is sputum positive. This is stated to be based on findings of limited surveys conducted by leading TB Institutes like National Tuberculosis Institute, Bangalore, Mabnapallai Tuberculosis Research Centre, Andhra Pradesh, New Delhi Tuberculosis Centre, New Delhi etc. Based on these figures, the radiologically active cases could be placed at about 11 million while the sputum positive cases could be placed at 2.95 million.

5.2 Deaths due to TB are currently stated to 80 per 100,000 population in India[29]. Total deaths in India due to this disease is not precisely known. As TB is not a notifiable disease, nor the causes of deaths in India are scientifically investigated in most cases, the difficulties in getting precise figures are obvious. However, it is reported[31] that currently the Health Minister expressed her concern over the persistingly high mortality due to TB and mentioned in a meeting of the Health Ministers of U.P., Bihar, M.P., Rajasthan and Orissa that over five lakh people die of TB every year. The gravity of the situation from TB deaths is thus apparent. From the above it can also be said that the infectious pool is maintained by equal number of new infections every year. It can also be stated that the National Tuberculosis Programme launched by the Government has made little dent-on the dimensions of the problem and the incidence of the disease continues to be high.

5.3 Introduction of rifampicin in India for combating tuberculosis has however, brought forth new hopes, for the drug used in combination with INH and Ethambutol has emerged as a higlly effective therapy for the arrest and complete cure of the dasease in the shortest possible time (about 6 to 9 months). Earlier the regimen used (Streptomycin with INH & PAS) required a treatment time of about 2 years and more and the cure rate was not as high as it is with the rifampicin regimen.

5.4 During the last twenty years, the usage of new drugs and development of new treatment regimens have changed the world knowledge and direction in the treatment of tuberculosis. A hierarchy of individual drugs and combinations thereof have been founded. The time period for optimum duration of treatment has been radically shortened. Retreatment of chronic cases has undergone a thorough change and attention has been concentrated

to particular administration schedules. Rifampicin has largely contributed to these developments in the tuberculosis chemotherapy.

5.5 The hierarchy[32] of drugs in the tuberculosis chemotherapy widely accepted worldwide using the criteria of effectiveness, safely and acceptability, largely attributed to the works of Prof. J. Grosset[32] is as under:-

-- Major agents	:	Rifampicin and INH
-- Secondary agents	:	Cyclocerine, Ethambutol, Ethionamide, Kanamycin, Pyrazinamide, Streptomycin, Viomycin
-- Minor agents	:	PAS, Thiacetazone

Rifampicin and INH possess the highest effectiveness, have high safety index and satisfy excellently the acceptability criteria.

The secondary agents have recognised bactericidal activity but have certain limitations compared to the major agents in the property criterion mentioned above. Ethambutol for example cannot guarantee a sufficiently strong and constant and bactericidal effect in doses normally used compared to the major agents although its safety and acceptability criteria are very high. Fox and Mitchisen[34] have called these agents as "Semibactericides" and have suggested that these be combined with the major agents so that complete bactericidal effect is produced by their complementary activities.

The minor agents do not have bactericidal activity in any condition; besides they possess limited safety and acceptability criteria.

All the above are stated to focus the therapeutic status of Rifampicin among other drugs used for the management of Tuberculosis.

5.6 As India understood that Rifampicin commands a high therapeutic status in the treatment of TB, the usage of the drug had increased at a galloping rate. The usage is, however, being fully met from imports as mentioned earlier; the annual imports increased at a very high rate. The current (1984-85) usage rate is estimated at about 60 M.T. The drug has thus established its roots into the formulators and the medical profession engaged in the management of Tuberculosis.

5.7 Leprosy, another major public health problem in India, affects about 3-4 million people in the country, of which nearly 20% are considered to be infectious. The medicines currently in use, namely, dapsone and clofazimine are greatly complemented by the use of Rifampicin; the latter is stated to convert infectious patients non-infectious within the shortest possible time besides offering resistance to the further spread of the disease within the body.

5.8 Assuming that 25% of the patients having radiologically active chest X-ray are suffering from infectious tuberculosis and 20% of the leprosy cases are infective, the quantity of Rifampicin required to treat the whole infectious pool would be about 250 MT. The planners engaged in the management and control of TB and Leprosy may like to view the above as the potential demand of the drug in the national context. The figures would further inflate if it is assumed that the whole of the TB and leprosy population is to be treated within Rifampicin.

5.9 Government of India has exempted[35] the customs duty on the drug so as to enable the formulators to convert the bulk drug into the dosage forms at lower costs. Obviously the expectations are that the manufacturers would make the formulations available to the consumers at a cheaper prices. As the bulk drug is totally imported, the Government had felt the need to get its production started into the country and had liberalised the licencing policy for the production of this item and had recently exempted[36] its production from obtaining an industrial licence. Besides, for the quick setting up of capacities, the currently financial budget had also exempted custom duties[37] on the importation of 3-Formyl Rifamycin-SV, Rifamycin-S and 1-Amino 4-Methyl piperazine which are late intermediates in the production of Rifampicin.

5.10 All these measures taken by the Government are for the quick production of the drug into the country. However, these relaxations are not adequate to motivate the investors to be into this business. This is because the capital investment for the setting up of basic production capacities in India is considered substantial. Therefore even if internationally competitive technology is inducted, the cost of production would work out much higher compared to international costs, largely on account of higher capital block and capital servicing charges (depreciation and interest costs). The cost of raw materials in India would also be about double if not more, the international oosts. The cost of rifampicin of the Indian producers would have to be protected therefore, for their very existence. Indian enterpreneurs may be keen to know in advance in adequate quantitive terms the kind of protections they are going to get from the Government before they put in money into this venture.

A few enterpreneurs[38] had shown their willingness for the setting up of basic production facilities in the country. Important among them are HAL, Hindustan-Ciba Geigy, Cadila, Themis Pharma, Alembic and Curewell.Foreign collaboration proposals were cleared[39] by the Government in favour of Cadila, Themis, Shri Arun K. Mittal, Alembic and Curewell on 19.4.82, 17.12.82, 31.3.84, 16.6.84 and 23.7.84 respectively; the approval of Cadila had since lapsed. There is no information about whether any of these companies have made any worth-while progress in the setting up of basic production facilities for the drug. What factors are really holding them up?

The cost of production of the drug, requiring small capital investment starting from the intermediates, namely, 3-formyl rifamycin-SV

and 1-Amino 4-methyl piperazine would have to match the landed cost of rifampicin at US $ 260 to $ 280 per kg. To have this matched, the companies going into production from these intermediates must get 3-formyl rifamycin-SV at a price of US $ 170-200 per kg. It is doubtfulif there would be enough material at this price. And even if some material comes in, it is anticipated that this may be procured only by those few firms in India who have collaborations with the producing International firms of the bulk drug. It is therefore expected that with the current policy in vogue there would not be much production from these intermediates. To encourage production from these intermediates, if the customs duties on rifampicin are increased to say 25%, this may help such producers; however this would not help the country in the long run as firstly the landed cost of rifampicin would go up and secondly at any subsequent point of time even if such parties are pressurised for a backward integration, it would hardly be meaningful since the backward integration is complex, highly investment oriented and is a high technology area which every producer, specially the small producers, would not be able to go in for.

5.11 Since the price of rifampicin produced in India from the basic stage would have in it a large component of capital block and capital servicing costs, the cost would be very sensitive to capacity utilisation of the plant. Therefore, assuming that an attractive policy package is available to the industry, there should be a method of screening and selecting the right enterpreneur for this business. If this is not done the indigenous costs are bound to be high and such situation would only help the outside suppliers to continue their business in the country.

5.12 The handling of rifampicin technology requiring sophisticated knowledge of fermentation and unit operations of complicated chemical transformation is an integrated culture unique in itself. Many business houses may not have the expertise and it would take quite sometime to develop the same. Many enterpreneurs may not therefore come forward to take up this challenging task.

5.13 By producing the drug in the country from the basic stage, the saving in foreign exchange at the level of current requirement (60 MT/a during 1984-85) would be of the order of US $ 15 million per annum. This is a strong motivating force for the Government to take such steps as would enable the quick setting up of the basic production facilities for the drug.

5.14 The materials required for the manufacture of rifampicin such as various carbohydrate sources (starch, dextrose, sucrose etc.) proteins (defatted soyabean powder, ground-nut cake, cotton seed meal etc. oils, filter aids, defeaming agents, ascorbic acid, salts and minerals etc. are abundantly available in the country. A few solvents such as tetrahydrofuran etc., may be required to be imported. The import content is however going to be very low.

5.15 India has now developed excellent expertise in the management of complex processes of fermentation and chemical transformations. As such

there would be plenty of skilled manpower to adapt and absorb the technology for the manufacture of rifampicin from the basic stage.

5.16 The major consumer of the bulk rifampicin being India and the producer-suppliers of the bulk drug being only a few international sources, the normal forces of supply and demand could be played upon for artificially increasing the international prices. Brokers may contribute to this situation by buying up large quantities of materials, thereby causing an unbalancedsupply and demand situation. If this is not anticipated in India now, the country may end up in loosing millions of dollars in importing the bulk drug in the coming years. India would acquire enough bargaaning power to influence the international price of the drug only when it has taken up its production in substantial quantities from the basic stage, no matter even if the production cost is higher in India than the international costs.

6. *Conclusions:*

6.1 Rifampicin commands a high therapeutic status in the management of Tuberculosis. It is also a useful drug for controlling the spread of Leprosy. The current consumption is around 60 MT and this may go up to 100 MT by the end of the 7th Plan. The current annual import bill is estimated at US $ 16-17 million. If it is decided to take up the basic production of the drug in the country, the present infra-structure shall fully be supportive. The country has adequate technical skill and expertise to absorb and assimilate the technology. Most of the raw materials required for the basic manufacture are available indigenously except a few solvents and chemicals; the strain and technology is also available for purchase from international sources. The situation could be utilised for the setting up of basic production facilities in the country, if economic impediments are modified.

6.2 It is however doubtful if private enterpreneurs would invest for the setting up of basic production facilities in the existing situation unless entrepreneural attractions are increased by working out adequate incentives so that fair return on investment is assured.

6.3 The decision for the setting up of basic production facilities must be taken with fullest care to entrust the project to the right enterpreneurs who should have the most appropriate technology, sound R&D backup and should also have excellent knowledge and records of handling fermentation and complicated chemical transformations. The decision is extremely important in the context of international competition and anticipated internal expectations of getting the material at the cheapest possible price so as to keep the prices of the finished formulations as low as possible.

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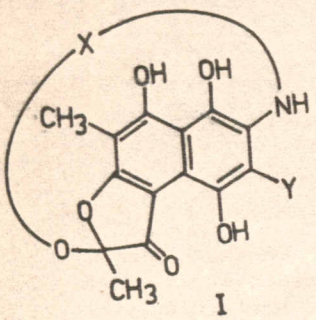
Figure - 1

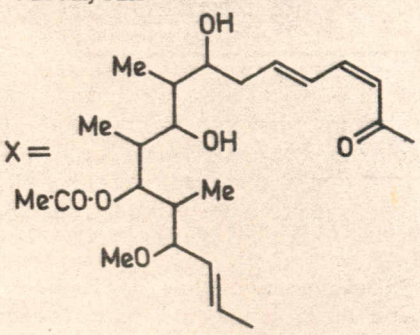
(Major Structural Transformations in the production of Rifampicin)

I. = Rifampicin
II. = Rifamycin - B
III. = Rifamycin - O
IV. = Rifamycin - S
V. = Rifamycin - SV
VI. = 3-Formyl Rifamycin SV
VII. = 1.3 Oxazino Rifamycin



I

Where



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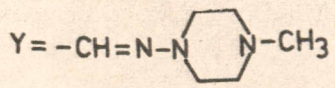
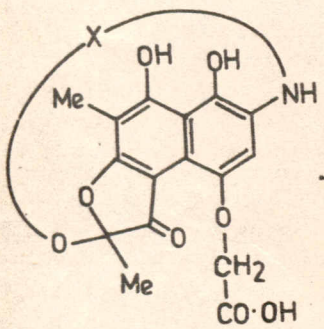
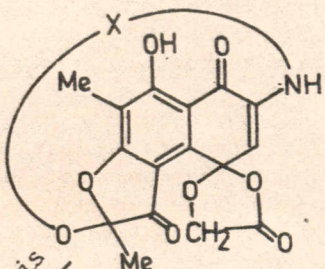




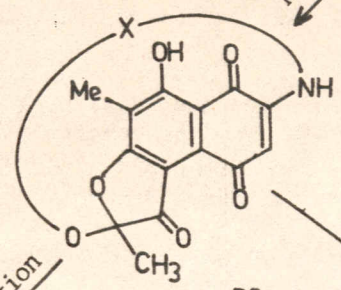
II

OXIDATION



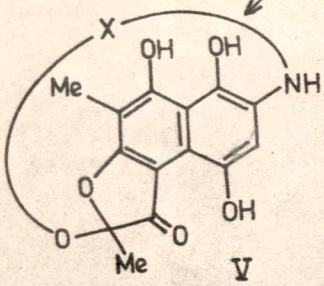
III

Hydrolysis

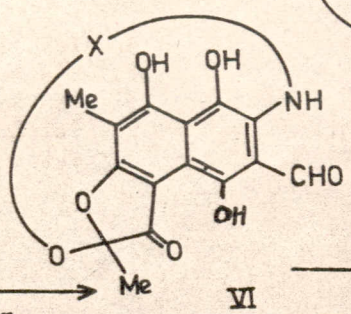


IV

Reduction

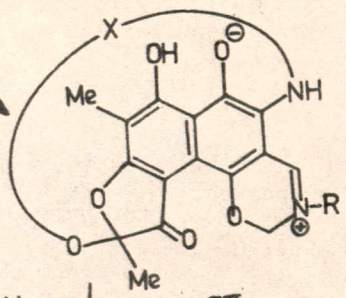


V



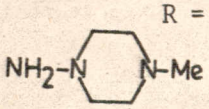
VI

Mannich Reaction



VII

where,
R = alkyl



I