NOVEL PHARMACEUTICAL COMPOSITIONS OF ANTI - TUBERCULAR DRUGS AND PROCESS FOR THEIR PREPARATION

Tuberculosis is a major problem largely of developing countries but lately emergence of Mycobacterium infections in HIV infected individuals is also on the rise in developed countries. The management of tuberculosis treatment is further complicated due to emergence of drug resistance. Drug resistance in tuberculosis is due to inappropriate prescribing or taking of medications, effectively resulting in monotherapy. To reduce the possibility of monotherapy, the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Diseases (IUATLD) have recommended that antitubercular drugs should be taken in combination (Fixed dose combination tablets for the treatment of tuberculosis, Report of an informal meeting held in Geneva 27 April 1999, World Health Organization Communicable Diseases Cluster, 1999). A number of combinations of first line drugs containing rifampicin isoniazid pyrazinamide and ethambutol are in useThis fixed dose combination (FDC) tablets provide a simple approach to delivering the correct number of drugs at the correct dosage as all the necessary drugs are combined in a single tablet. By altering the number of pills according to the patient's body weight, complete treatment is delivered without the need for calculation of dose. However, such FDC tablets are not free from disadvantages. The major issue is the adverse effect on bioavailability of rifampicin in presence of other drugs. Various researchers have worked on several aspects of this problem of FDC tablets and several recommendations are recorded in literature. WHO attributes that when rifampicin combined with the other drugs within the same formulation the bioavailability negatively affected if the manufacturing procedures are not strictly controlled. Against this background, WHO and IUATLD issued a joint statement in 1994 advising that only FDC tablets of good quality and proven bioavailability of rifampicin should be used in the treatment of tuberculosis (Anonymous; 1994; Tuber. Lung Dis.; 75: 180–181). There are several forthcoming articles in a special supplement of the International Journal of Tuberculosis and Lung disease devoted to the quality assurance of FDC tablets. These include a simplified protocol for assessing rifampicin bioavailability and its use in studies carried out in South Africa and India (Ellard, G.A.; 1999; Int. J. Tuberc. Lung Dis.; Nov 3; 11; Suppl. 3 : S284–5; Mclleron,

H. et al.; 1999; Int. J. Tuberc. Lung Dis.; Nov. 3; 11; Suppl 3; S239-35; Panchagnula, R. et al.; 1999; Int. J. Tuberc. Lung Dis.; Nov. 3; 11; Suppl 3; S336-42), high performance liquid chromatographic methods for assaying of rifampicin, isoniazid and Pyrazinamide (Smith, P. et al.; 1999; Int. J. Tuberc. Lung Dis.; Nov. 3; 11; Suppl 3; S325-28) procedures for ensuring laboratory proficiency for rifampicin bioavailability studies (Ellard, G.A.; 1999; Int. J. Tuberc. Lung Dis.; Nov. 3; 11; Suppl 3; S343-46) improved procedure of dissolution testing of rifampicin in presence of isoniazid (Shishoo, C.J. et al.; 1999; Int. J. Pharm.; Nov 10; 190 (1) : 109–23) and a review of the pharmacology of rifampicin (Ellard, G.A. et al.; 1999; Int. J. Tuberc. Lung Dis.; Nov 3; 11 Suppl 3; S301–8 : S317–21).

It has been reported that the poor absorption of rifampicin from combination products may be due to decomposition of the drug in acidic stomach conditions, which is accelerated in the presence of isoniazid (Shishoo, C.J. et al.; 1999; Int. J. Pharm.; Nov 10; 190 (1): 109–23; Singh, S. et al.; 2000; Pharm. Pharmacol. Commun.; 6: 491-494). The mechanism of this degradation was proposed by Singh et al. (Singh, S. et al.; 2000; Pharm. Pharmacol. Commun.; 6: 405-410). Studies revealed that the decomposition of rifampicin in acidic conditions in the absence of isoniazid stopped at the formation of 3–formylrifamycin, while the reaction in the presence of isoniazid proceeded to form a hydrazone between 3–formylrifamycin and isoniazid. Further, it was suggested that once 3-formylrifamycin is formed, it interacts with isoniazid to form the hydrazone, through a fast second order reaction. As hydrazone are unstable in acid conditions, 3-formylrifamycin and isoniazid are regenerated in a reversible manner through a slower first order reaction. In this complex reaction process, rifampicin is further degraded, while isoniazid is recovered.

Devani et al.(Devani, M.B. et al.; 1985; J. Pharm. Sci.; 74 : 427–432) has also discussed kinetics of hydrazone formation from isoniazid in presence of reducing sugars.

None of the reports has suggested a pharmaceutical technological solution to the above problem. The inventors after careful experimentation and expenditure of considerable amount of mental faculties and time have found a novel way to solve the bioavailability problems of drugs in FDC tablets.

The invention described herein discloses compositions of anti-tubercular drugs where attempts have been made to prevent the loss in bioavailability of rifampicin in presence of isoniazid.

During experimentation the inventors have found that the degradation of rifampicin is pH dependent in presence of isoniazid. At pH around 1 the degradation is minimum and increases abruptly as pH ranges between 2 and 3. Thereafter, above pH 3 the degradation is minimal.

The pH of the gastric contents is normally between 1 and 3 which results in significant degradation of Rifampicin when administered orally alongwith other anti-tubercular agents, in particular Isoniazid.

This problem has been solved by controlling the release or dissolution of both the drugs in such a way that the release takes place at different locations inside the gastrointestinal tract without compromising the total bioavailability of either of the drugs. It means that the two drugs i.e. rifampicin and isoniazid do not come in contact with each other in solution state in the gastrointestinal tract thereby preventing the interaction. The composition may also include other known anti-tubercular drugs like Ethambutol Hydrochloride and Pyrazinamide.

The site-specific release of active ingredients has been achieved by various techniques like

a) Controlling release of rifampicin and isoniazid at different locations in the gastrointestinal tract by use of pH sensitive materials
b) Controlling dissolution of drugs by forming barrier coat and/or matrix with pH insensitive materials such that the contact of rifampicin and isoniazid in solution state is avoided.
c) Using different crystal forms of the drugs such that there is significant difference in dissolution rate of the drugs.

d) Modifying the surfactant action of rifampicin with use of materials like Methylpolysiloxane, natural and synthetic oils. Use of such materials reduces the surfactant action with corresponding reduction in solubility of rifampicin.

Preferably the drug is modified such that the release takes place at pH of approximately 5.0. At pH 5.0 the drug release takes place very rapidly such that there is no loss of bioavailability. Whereas the other drug or drugs are released in the more acidic (pH 1.0 – 3.0) environment of stomach.

Further, the invention discloses the Fixed Dose Combination of anti-tuberculosis drugs in oral suspension form. Suspension type dosage forms are of particular importance for fixed dose combination where the total amount of active ingredients of a single dose becomes very high. Such high doses cannot be filled into hard or soft gelatin capsules. Even compressed tablets become too big and are very difficult to swallow.

It has surprisingly been found in the present invention that it is possible to conveniently administer such high dose combinations of anti-tubercular drugs wherein one or more active ingredients may be present in extended or delayed release form, in the form of oral suspension leading to no loss of bioavailability of any of the actives. This has been achieved by making molecular dispersion of Rifampicin and/or isoniazid having pH dependent delayed release characteristics even when finely powdered. Such powders can be blended with other drugs and compressed into tablets or made into suspensions alongwith the other drugs. Another advantage is minimal increase in size of tablets which is serious problem for high dose drugs.

Further, the active ingredients may be in taste masked form. Such dosage forms will be highly desirable for treatment of tuberculosis in masses and reduction in the development of drug resistance which commonly occurs due to non compliance of existing type of dosage forms.

The active ingredients may be having barrier coating' to prevent drug – drug/excipients interactions.

The suspension may be in ready–to–use form or to be reconstituted before use. Preferably the ready–to–use suspensions will have non-aqueous base/carrier. Suitable example of suspension bases include glycols and glycol derivatives; Propylene carbonate; glycerol; oils of animal, vegetable or mineral origin; medium chain triglycerides; transesterification products of natural vegetable oils with alkylene polyols; Esters of polyols with fatty acids.

Other ingredients of the suspension dosage form includes suspending agents, viscosity imparting agents, anti-caking agents, sweeteners, flavors, coloring agents and the like, known to persons skilled in the art.

The polymers used to modify the release of drugs may be natural, semi-synthetic, synthetic or man-modified. Suitable materials include cellulose and cellulose derivatives like microcrystalline cellulose, methyl cellulose, ethyl cellulose, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, cellulose acetate phthalate, cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, cellulose acetate trimellitate, cellulose carboxymethyl ethers and their salts, hydroxypropyl methylcellulose phthalate , hydroxypropyl methylcellulose acetate succinate. Polyethylene; Polyquaternium-1; Polyvinyl acetate (homopolymer); Polyvinyl acetate phthalate; Propylene glycol alginate; PVM/MA copolymer; PVP/ dimethiconylacrylate/polycarbamyl/polyglycolester; PVP/ dimethylamino ethylmethacry- late copolymer; PVP/dimethylaminoethylmethacrylate/ polycarbamyl polyglycol ester; PVP/polycarbamyl polyglycol ester; PVP/ VA copolymer Lanolin and lanolin derivatives, buffers, lipophilic materials like, fats, fatty acid glycerides, oleic acid, cholesterol, transesterification products of polyols with fatty acids, glyceryl monostearate, stearic acid, paraffins, beeswax, carnauba wax, tribehenin. Polyalkylene polyols like polyethylene glycols. Gelatin and gelatin derivatives. Alginates. Carbomers. Polycarbophils. Methacrylic acid copolymers. Carrageenans, pectins, chitosans, cyclodextrins, lecithins. Natural and synthetic gums containing galactomannans like xanthan gum, tragacanth, acacia, agar, guar gum, etc.
Ion exchange resins like polacrilin pottasium, acrylic acid copolymers, sodium polystyrene sulphonate, polystyrene copolymers and the like.

Buffers like sodium dihydrogen orthophosphate, disodium hydrogen phosphate, di-potasium hydrogen phosphate, potassium dihydrogen orthophosphate, borate buffer, phthalate buffer, oxalate buffer and the like.

In another embodiment of the invention, the active ingredient may be present in micronized form to achieve faster absorption. Micronisation may be carried out by processes like air jet milling, ball mill and the like. The average particle size should be less than 5 microns.

Further the invention also discloses use of bioavailability enhancers like piperine and its derivatives, Ayurvedic preparations like trikatu alongwith the compositions of present invention may also help in increasing bioavailability.

The invention is further described with the help of following examples which should not be construed as limiting the scope of invention :

1. Microencapsulation of Rifampicin

Cellulose Acetate Phthalate	64 g
Rifampicin	800 g
Polyethylene Glycol 4000	6.4 g
Water	1200 ml
Hydrochloric Acid	0.5 ml
Dichloromethane	200 ml
Isopropyl Alcohol	100 ml

Procedure

1. Dissolve Cellulose Acetate Phthalate and Polyethylene Glycol 4000 in Isopropyl Alcohol & Dichloromethane mixture
2. Disperse rifampicin in water containing 0.5 ml of Hydrochloric Acid to make a slurry and keep on a water bath at 50°C.
3. Add CAP solution to the slurry with constant stirring.
4. Filter off the microcapsules and dry them.

The above mentioned microcapsules of Rifampicin may be blended with other anti-tubercular drugs and suitable excipients to formulate into tablets, capsules or suspension.

2. Microencapsulation of Rifampicin

Sodium Alginate	20 g
Rifampicin	100 g
Calcium Chloride Solution	5% w/v
Water	500 ml

Procedure

1. Dissolve Sodium Alginate in Purified Water.
2. Disperse rifampicin in above solution.
3. Add the above suspension dropwise to Calcium Chloride Solution with constant stirring.
5. Filter off the microcapsules and dry them.

The above mentioned microcapsules of Rifampicin may be blended with other anti-tubercular drugs and suitable excipients to formulate into tablets, capsules or suspension.

3. Preparation of Microcapsules of Rifampicin

Rifampicin	100 g
Ethyl Cellulose M20	100 g
Water	600 ml
Dichloromethane	300 ml

Procedure

1. Dissolve Ethylcellulose in dichloromethane.
2. Disperse Rifampicin in water and keep in a water bath at 40°C.
3. Add solution of Ethylcellulose to drug slurry with constant stirring.
4. Filter off the microcapsules and wash with water and allow to air dry.

The above mentioned microcapsules of Rifampicin may be blended with other anti-tubercular drugs and suitable excipients to formulate into tablets, capsules or suspension.

4. Microspheres of Rifampicin

Chitosan	500	mg
Pluronic F68	2	g
Rifampicin	10	mg
Sodium Tripolyphosphate (as 10% w/v solution in water)	10	g
Water	200	ml

Procedure

1. Dissolve Chitosan in acetic acid containing Pluronic F-68 as surfactant.
2. Add 10 mg drug into Chitosan solution. Then add Sodium Tripolyphosphate dropwise with vigorous shaking. A cloudy suspension is formed as a result of crosslinking and precipitation of Chitosan microspheres.
3. Centrifuge the microspheres at 3000 rpm for 10 minutes and wash the pellets twice with deionized distilled water and dry them.

The above mentioned microspheres of Rifampicin may be blended with other anti-tubercular drugs and suitable excipients to formulate into tablets, capsules or suspension.

5. Microspheres of Rifampicin

Rifampicin	10	g
Agar Agar	4	g
Citric Acid	2	g
Water	50	ml
Polyvinyl Alcohol	15	g
Ethanol	100	ml

Procedure

1. Dissolve Citric Acid in Water and disperse Rifampicin, and Agar Agar in it with constant stirring.

2. Meanwhile, dissolve Polyvinyl Alcohol in Ethanol.
3. Add the aqueous solution to the alcoholic solution of Polyvinyl Alcohol with constant stirring.
4. Evaporate to dryness and separate the microspheres. Such microspheres can be formulated in suspension type dosage form as exemplified below :

Rifampicin	0.200 g
(In microspheres form as per example 5)	
Isoniazid (in taste masked form	
as per example 39)	0.300 g
Pyrazinamide	0.750 g
Ethambutol Hydrochloride(in taste masked	
form as per example 28)	0.400 g
Aspartame	0.025 g
Labrafac PG (Gattefosse, France)	5.000 g
Corn oil	3.000 g
Butylated Hydroxyanisole	0.0015 g
Flavour	0.097 g

Procedure

1. Mix Labrafac PG and Corn oil and dissolve Butylated Hydroxyanisole in it with the aid of heat (40 – 50°C).
2. Then add Rifampicin, Isoniazid, Pyrazinamide, Ethambutol Hydrochloride, Flavour and Aspartame to the bulk with stirring.

6. Bilayer tablet

Layer – I

Rifampicin	0.225 g
Hydroxypropyl methyl Cellulose Phthalate	0.050 g
Isopropyl Alcohol	2.000 g

Layer – II

Isoniazid	0.150 g
Pyrazinamide	0.750 g

Ethambutol Hydrochloride	0.400 g
Starch	0.075 g
Water	0.500 g

Procedure

1. Granulate Rifampicin with solution of Hydroxypropylmethylcellulose Phthalate in Isopropyl Alcohol and dry them.
2. Separately, granulate Isoniazid, Pyrazinamide, Ethambutol Hydrochloride with Starch Paste in water and dry them.
3. Compress the granules into Bilayered tablets on a rotapress. Isoniazid (Layer – II) is immediately released. Rifampicin layer is released in delayed form in pH 5.5 and above.

7. Enteric Coated beads of Rifampicin

Rifampicin	0.5 Kg
Non-pareil beads	1.2 Kg
Polyvinyl Pyrrolidone	0.100 Kg
Isopropyl Alcohol	7.00 L
Eudragit L100	0.40 Kg
Acetone	6.00 L
Water	1.00 L
Triethyl Citrate	0.04 Kg

Procedure

1. Prepare The enteric coated beads of Rifampicin using fluid bed coater.
2. Spray dispersion of Rifampicin and Polyvinyl Pyrrolidone in Isopropyl Alcohol onto the fluidized non pareil beads.
3. Spray dispersion of Eudragit L100 and Triethyl Citrate in water/Acetone mixture on the rifampicin beads.

Such beads may be used in conjunction with other drugs to make formulations as examplified below :

(i) Rifampicin	600	mg
(In enteric coated bead form as per example 7)		
(ii) Isoniazid	150	mg

Mix (I) and (ii) and fill in hard gelatin capsules, or mix (I) and (ii) with suitable lubricants and diluent like lactose, microcrystalline cellulose and compress into tablets or fill in hard carpsules.

8. Rifampicin Granules (delayed release)

Rifampicin	9.00	Kg
Eudragit L100 (Rohm Pharma, Germany)	1.00	Kg
Acetone	3.0	L
Water	0.5	L

Procedure

1. Dissolve Eudragit L 100 in mixture of acetone and water.
2. Granulate Rifampicin in a rapid mixer granulator with the above solution. Sift the wet mass through 10 mesh screen and dry.
3. After drying the granules, sift the granules through 30 mesh screen. Such granules may be added to a oral suspension or capsule or compressed into tablets alongwith other active agents and excipients.

The above mentioned granules of Rifampicin may be blended with other anti-tubercular drugs and suitable excipients to formulate into tablets, capsules or suspension.

9. Molecular dispersion of Rifampicin with enteric (delayed release) effect

Rifampicin	9.00	Kg
Eudragit L100 (Rohm Pharma, Germany)	0.50	Kg
Cellulose Acetate Phthalate	1.00	Kg
Isopropyl Alcohol	5.0	L
Methylene chloride	10.0	L

RECTIFIED SHEET (RULE 91)

Procedure

1. Dissolve Eudragit L 100 and Cellulose Acetate Phthlate in mixture of Isopropyl Alcohol and Methylene Chloride separately. Mix both the solutions.
2. Dissolve Rifampicin in Methylene Chloride and add to the above solution and mix for one hour.
3. Evaporate the solvents on a water bath and pass the residue through a sieve of mesh size 100.

The above mentioned powder of Rifampicin has almost no release in acid stage i.e. pH 1 – 3 for upto 2 hours. Whereas above pH 5.5 more than 85% of drug is released in about 45 minutes. This powder may be blended with other anti-tubercular drugs and suitable excipients to formulate into tablets, capsules or suspension. Upon compression, there is no change in release of rifampicin during acid stage.

10. Molecular dispersion of Rifampicin with enteric (delayed release) effect

Rifampicin	8.00 Kg
Eudragit L100 (Rohm Pharma, Germany)	0.50 Kg
Polyvinyl Acetate Phthalate	0.75 Kg
Isopropyl Alcohol	4.0 L
Dichloromethane	8.0 L

Procedure

1. Dissolve Eudragit L 100 and Polyvinyl Acetate Phthalate are in mixture of Isopropyl Alcohol and Dichloromethane separately. Mix both the solutions.
2. Dissolve Rifampicin was dissolved in Dichloromethane and add to the above solution and mix for one hour.
3. Evaporate the solvents on a water bath and pass the through a sieve of mesh size 100.

The above mentioned powder of Rifampicin may be blended with other anti-tubercular drugs and suitable excipients to formulate into tablets, capsules or suspension.

11. Molecular dispersion of Rifampicin with enteric (delayed release) effect

Rifampicin	2.00 Kg
Shellac	0.10 Kg

Isopropyl Alcohol	1.0 L
Methylene Chloride	2.0 L

Procedure

1. Dissolve Shellac in a mixture of Isopropyl Alcohol and Methylene Chloride separately.
2. Dissolve Rifampicin in Methylene chloride and add to the above solution and mix for two hours.
3. Evaporate the solvents on a water bath and pass the residue through a sieve of mesh size 100.

The above mentioned powder of Rifampicin may be blended with other anti-tubercular drugs and suitable excipients to formulate into tablets, capsules or suspension.

12. .Rifampicin Granules (delayed release)

Rifampicin	2.00 Kg
Eudragit L 30D	0.20 Kg
Purified Water	0.50 L

Procedure

1. Dilute Eudragit L 30 D with Purified Water.
2. Granulate Rifampicin with the above solution in a mass mixer for 1.5 – 2.0 h.
3. Pass the wet mass through multimill and dry the granules.

An oral suspension using such granules is described below :

Oral Suspension

Rifampicin	225 mg
(In delayed release granule form as per example 12)	
Isoniazid	150 mg
(In taste masked form for taste masking as per example 39)	
Ethambutol Hydrochloride (in ion-exchange complexed form for taste masking as per example 28)	400 mg

Pyrazinamide	750 mg
Colloidal Silicon Dioxide	100 mg
Aspartame	20 mg
Flavour	q.s
Medium Chain Triglyceride	q.s to 10 ml

Procedure

Disperse Colloidal Silicon Dioxide, Aspartame in Medium chain triglyceride. Add rifampicin granules, Isoniazid, Ethambutol Hydrochloride and Pyrazinamide and flavour with stirring.

13. FDC Formulation containing piperine as absorption enhancer

Rifampicin	225 mg
(In delayed release granule form as per example 12)	
Piperine	60 mg
Isoniazid	150 mg
(In taste masked form for taste masking as per example 39)	
Ethambutol Hydrochloride	400 mg
(in ion-exchange complexed form for taste masking as per example 28)	
Pyrazinamide	750 mg
Colloidal Silicon Dioxide	100 mg
Aspartame	20 mg
Flavour	q.s
Medium Chain Triglyceride	q.s to 10 ml

Procedure

Disperse Colloidal Silicon Dioxide, Aspartame in Medium chain triglyceride. Add rifampicin granules, Piperine, Isoniazid, Ethambutol and Pyrazinamide and flavour with stirring.

14. pH sensitive fast release granules of Rifampicin

Core	
Rifampicin	20 parts
Low substituted Hydroxypropyl Cellulose	52 parts
Lactose	13 parts
Hydroxypropyl Cellulose	5 parts
Alcohol (Ethanol 95 % v/v)	20 parts
Film	
Eudragit L 100	5.5 parts
Isopropyl Alcohol	60.2 parts
Acetone	33.5 parts
Dibutyl Phthalate	0.8 parts

Procedure

1. Mix Rifampicin, Low substituted Hydroxypropyl Cellulose, Lactose.
2. Granulate the above bulk with alcoholic solution of Hydroxypropyl Cellulose.
3. Dry the granules and sift through mesh 60.
4. Coat the granules with enteric film forming solution of Eudragit L 100 and Dibutyl Phthalate in Isopropyl Alcohol and Acetone using fluid bed coater.

Such granules may be used to make capsules, tablets or oral suspension.

15. Millispheres of Rifampicin

Phase - I	
Rifampicin	10 g
Sodium Alginate	20 g
Water	90 g
Phase – II	
Chitosan	5 g
Calcium Chloride	5 g
Water	200 ml

Prepare Phase – I solution by dispersing Rifampicin and Sodium Alginate in Water. Dissolve Chitosan, Calcium Chloride in water to prepare Phase – II. Add Phase – I dropwise with stirring to Phase – II. Soft millispheres of rifampicin are formed. Separate by filteration and dry under vacuum.

Such millispheres may be used to formulate oral suspension dosage form alongwith other anti – tubercular agents.

16. Rifampicin in Lipophilic Matrix

Rifampicin	5.0 Kg
Glyceryl Monostearate	2.0 Kg
Poloxamer 188	0.1 Kg
Lactose	2 Kg
Ethyl Cellulose	0.5 Kg
Alcohol (Ethanol 95 % v/v)	2.0 L

Procedure

1. Dissolve Glyceryl Monostearate and Poloxamer in Alcohol and heat up to 70°C so as to obtain a clear solution.
2. Add drug to the bulk and cool.
3. Evaporate the alcohol and granulate the residue with Lactose as diluents and Ethyl Cellulose as binder.

Such granules may be used to formulate a tablet, capsule, dosage form or oral suspension dosage form alongwith other anti – tubercular agents.

17. Rifampicin in Carbomer Matrix

Rifampicin	5.0 Kg
Carbomer (Carbopol 934P, BF Goodrich)	1.0 Kg
Lactose	5.0 Kg
Ethyl Cellulose	0.5 Kg
Acetone	2.0 L
Alcohol (Ethanol 95 % v/v)	10.0 L
Water	5.0 L

Procedure

1. Dissolve the drug in alcohol and Carbopol in water. Mix both the solution and keep aside for one hour.
2. Evaporate the solvents and pulverised the mass into powder and granulate with Lactose as diluent and Ethyl Cellulose in Acetone as binder.

Such granules may be used to formulate a tablet, capsule, dosage form or oral suspension dosage form alongwith other anti – tubercular agents.

18. Mesosomes of Rifampicin

Rifampicin	2.0 Kg
Glyceryl Monostearate	1.0 Kg
Palmitic Acid	0.5 Kg
Tween 60	0.1 Kg
Water	5.0 L

Melt Glyceryl Monostearate and Palmitic Acid in a water bath and disperse drug in it. Pour the molten mass to hot purified water containing Tween 60 under stirring. Then add this to ice chilled water with continuous stirring. Filter the mesosomes and air dry them.

The above mentioned mesosomes of rifampicin may be blended with anti tubercular drugs and suitable excipients to formulate into tablets, capsules or suspensions

19. Tablet- in-tablet formulation (rifampicin in delayed release form)

Core tablet	**Per tablet**
Rifampicin	225 mg
Starch	20 mg
Lactose	28 mg
Water	——
Magnesium Stearate	10 mg
Sodium Lauryl sulphate	10 mg
Sodium Starch Glycollate	30 mg

Pass Rifampicin and Lactose through sieve and granulate with Starch Paste and pass through multimill. Dry the granules at 50° to 60°C and pass through sieve of mesh size 18. Pass Sodium Starch Glycollate, Sodium Lauryl Sulphate and Magnesium Stearate through sieve of mesh size 40 and mix with the dried granules and compress.

Enteric Coating of Rifampicin Tablets (Batch Size 2.0 Kg)

Eudragit L 100	88.00 g
Purified Talc	20.00 g
Triethyl Citrate	18.00 g
Dichloromethane	1.30 L
Isopropyl Alcohol	0.60 L

Dissolve Eudragit L 100 in Isopropyl Alcohol and dichloromethane mixture. Add Triethyl Citrate and Talc to the above bulk and mix for 45 minutes. Coat the tablets to a weight build up of 6 – 8% w/w.

Outer Tablet

Pyrazinamide	750 mg
Ethambutol Hydrochloride	400 mg
Isoniazid	150 mg
Magnesium Stearate	10 mg
Sodium Starch Glycollate	30 mg
Lactose	65 mg
Povidone	50 mg
Purified Water	------

Pass Pyrazinamide, Ethambutol Hydrochloride, Isoniazid and lactose through a sieve and granulate with Povidone solution in water. Pass the wet mass through multimill and dry the granules 50 – 60° C. Pass dried granules through sieve of mesh size 16. Pass Magnesium Stearate and Sodium Starch Glycollate through sieve of mesh size 60 and mix with dried granules. Compress into tablets alongwith the Rifampicin enteric coated tablets in between.

Film Coating of outer tablets (Batch Size 2.0 Kg)	
Hypromellose	40.00 g
Purified Talc	2.00 g
Polyethylene Glycol 400	8.00 g
Titanium Dioxide	2.00 g
Colour	q.s.
Dichloromethane	0.66 L
Isopropyl Alcohol	0.33 L

Dissolve Hypromellose in Isopropyl Alcohol and Dichloromethane mixture. Add Polyethylene Glycol 400, Titanium Dioxide, Purified Talc and colour to the above bulk and mix for 45 minutes. Coat the tablets to a weight build up of 3 – 4% w/w.

20. Tablet- in-tablet formulation (Isoniazid in delayed release form)

Core tablet	**Per tablet**
Isoniazid	150 mg
Lactose	30 mg
Starch	5 mg
Water	-----
Magnesium Stearate	3 mg
Purified Talc	3 mg

Pass Isoniazid and Lactose through sieve and granulate with Starch paste and pass through multimill. Dry the granules at 50° to 60°C and pass through sieve of mesh size 18. Pass Magnesium Stearate and Talc through sieve of mesh size 60 and mix with the dried granules and compress.

Enteric Coating of Isoniazid Tablets (Batch Size 2.0 Kg)	
Hydroxypropylmethyl Cellulose Phthlate	80.00 g
Purified Talc	25.00 g
Dibutyl Sebacate	15.00 g
Dichloromethane	1.30 L
Isopropyl Alcohol	0.60 L

Dissolve Hydroxypropylmethyl Cellulose Phthlate in Isopropyl Alcohol and Dichloromethane mixture. Add Dibutyl Sebacate and Talc to the above bulk and mix for 45 minutes. Coat the tablets to a weight build up of 4 – 6% w/w.

Outer Tablet

Pyrazinamide	750 mg
Ethambutol Hydrochloride	400 mg
Rifampicin	225 mg
Lactose	70 mg
Magnesium Stearate	10 mg
Sodium Starch Glycollate	15 mg
Povidone	30 mg
Purified Water	------

Pass Pyrazinamide, Ethambutol Hydrochloride, Rifampicin and Lactose through a sieve and granulate with Povidone solution in water. Pass the wet mass through multimill and dry the granules at 50 – 60° C. Pass the dried granules through sieve of mesh size 16. Pass Magnesium Stearate and Sodium Starch Glycollate through sieve of mesh size 60 and mix with dried granules. Compress the tablets alongwith the Isoniazid enteric coated tablets in between.

Film Coating of outer tablets (Batch Size 2.0 Kg)

Hypromellose	40.00 g
Purified Talc	2.00 g
Polyethylene Glycol 400	8.00 g
Titanium Dioxide	2.00 g
Colour	q.s.
Dichloromethane	0.66 L
Isopropyl Alcohol	0.33 L

Dissolve Hypromellose in Isopropyl Alcohol and Dichloromethane mixture. Add Polyethylene Glycol 400, Titanium Dioxide, Purified Talc and colour to the above bulk and mix for 45 minutes. Coat the tablets to a weight build up of 3 – 4% w/w.

21. Tablet formulation containing Isoniazid in Delayed Release form

Core tablet	**Per tablet**
Isoniazid	150 mg
Lactose	30 mg
Eudragit L 30 D (Rohm Pharma, Germany)	50 mg
Purified Water	------

Pass Isoniazid and Lactose through sieve and granulate with aqueous dispersion of diluted Eudragit L 30 D in a mass mixer for atleast 2 hours. Pass the granules through sieve and dry them.

Outer Tablet	
Isoniazid Enteric Coated equivalent to Isoniazid 150 mg	230 mg
Ethambutol Hydrochloride	400 mg
Pyrazinamide	750 mg
Rifampicin	225 mg
Lactose	20 mg
Magnesium Stearate	10 mg
Sodium Starch Glycollate	35 mg
Povidone	30 mg
Purified Water	------

Pass Pyrazinamide, Ethambutol Hydrochloride, Rifampicin and Lactose through a sieve and granulate with Povidone solution in water. Pass the wet mass through multimill and dry the granules at 50 – 60° C. Pass the dried granules through sieve of mesh size 16. Mix Magnesium Stearate , Sodium Starch Glycollate and Isoniazid granules with above granules and compress.

Film Coating of tablets (Batch Size 2.0 Kg)	
Hypromellose	40.00 g
Purified Talc	2.00 g
Polyethylene Glycol 400	8.00 g

PAN/ANTI-T/D

Titanium Dioxide	2.00	g
Colour	q.s.	
Dichloromethane	0.66	L
Isopropyl Alcohol	0.33	L

Dissolve Hypromellose in Isopropyl Alcohol and Dichloromethane mixture. Add Polyethylene Glycol 400, Titanium Dioxide, Purified Talc and colour to the above bulk and mix for 45 minutes. Coat the tablets to a weight build up of 3 – 4% w/w.

22. Molecular dispersion of Isoniazid with enteric (delayed release) effect

Isoniazid	10.00	Kg
Eudragit L100 (Rohm Pharma, Germany)	2.00	Kg
Isopropyl Alcohol	5.0	L
Alcohol (Ethanol 95 % v/v)	15.0	L

Dissolve Eudragit L 100 in Isopropyl Alcohol. Dissolve Isoniazid in Alcohol and add to the above solution and mix for one hour. Evaporate the solvents on a water bath and pass the residue through a sieve of mesh size 100.

The above powder may be used to make capsules, tablets or oral suspension.

23. Molecular dispersion of Isoniazid with enteric (delayed release) effect

Isoniazid	8.00	Kg
Eudragit L100 (Rohm Pharma, Germany)	1.00	Kg
Polyvinyl Acetate Phthalate	0.75	Kg
Isopropyl Alcohol	4.0	L
Alcohol (Ethanol 95 % v/v)	15.0	L

Dissolve Eudragit L 100 and Polyvinyl Acetate Phthalate in Isopropyl Alcohol separately. Mix both the solutions and dissolve Isoniazid in Alcohol and add to the above solution and mix for one hour. Evaporate the solvents on a water bath and pass the residue through a sieve of mesh size 100.

The above powder may be used to make capsules, tablets or oral suspension.

RECTIFIED SHEET (RULE 91)

24. Molecular dispersion of Isoniazid with enteric (delayed release) effect

Isoniazid	2.00 Kg
Shellac	0.10 Kg
Isopropyl Alcohol	1.0 L
Alcohol (Ethanol 95 % v/v)	5.0 L

Dissolve Shellac in a Isopropyl Alcohol. Dissolve Isoniazid in Alcohol and add to the above solution and mix for two hours. Evaporate the solvents on a water bath and pass the residue through a sieve of mesh size 100.

An oral suspension using above molecular dispersion is described below :

Oral Suspension

Isoniazid (In delayed release molecular dispersion form as per example 23)	150 mg
Rifampicin	225 mg
Ethambutol Hydrochloride (in ion-exchange complexed form for taste masking as per example 28)	400 mg
Pyrazinamide	750 mg
Colloidal Silicon Dioxide	100 mg
Aspartame	20 mg
Flavour	q.s
Medium Chain Triglyceride	q.s to 10 ml

Disperse Colloidal Silicon Dioxide, Aspartame in Medium chain Triglyceride. Add Isoniazid powder, Rifampicin, Ethambutol Hydrochloride and Pyrazinamide and flavour with stirring.

25. Enteric Coated beads of Isoniazid

Isoniazid	1.0 Kg
Non-pareil beads	3.0 Kg

PAN/ANTI-T/D

Polyvinyl Pyrrolidone	0.20 Kg
Isopropyl Alcohol	14.00 L
Eudragit L100	0.80 Kg
Acetone	12.00 L
Water	2.00 L
Triethyl Citrate	0.10 Kg

Procedure

The enteric coated beads of Isoniazid are manufactured using fluid bed coater. Spray dispersion of Isoniazid and Polyvinyl Pyrrolidone in Isopropyl Alcohol onto the fluidized non pareil beads. Further coat dispersion of Eudragit L100 and Triethyl Citrate in water/Acetone mixture on the Isoniazid beads.

Such beads may be used in conjunction with other drugs to make formulation as examplified below :

(i) Isoniazid 150 mg
(In enteric coated bead form as per example 25)

(ii) Rifampicin 600 mg

Mix (I) and (ii) and fill in hard gelatin capsules, or mix (I) and (ii) with suitable lubricants and diluent like lactose, microcrystalline cellulose and compress into tablets

26. Isoniazid in Lipophilic Matrix

Isoniazid	5.0 Kg
Glyceryl Monostearate	2.0 Kg
Poloxamer 188	0.1 Kg
Lactose	2 Kg
Ethyl Cellulose	1.0 Kg
Alcohol (Ethanol 95 % v/v)	10.0 L

Dissolve Glyceryl Monostearate and Poloxamer in Alcohol and heat up to 70°C so as to obtain a clear solution. Add drug to the bulk and cool. Evaporate the Alcohol and granulate the mixture with Lactose as diluents and Ethyl Cellulose as binder.

The above mentioned granules of Isoniazid may be blended with other anti-tubercular drugs and suitable excipients to formulate into tablets, capsules or suspension.

27. Bilayer tablet containing Isoniazid in extended release form

Layer – I	
Isoniazid	0.150 g
Hydroxypropylmethyl Cellulose K4M	0.050 g
Isopropyl Alcohol	2.000 g
Layer – II	
Rifampicin	0.225 g
Ethambutol Hydrochloride	0.400 g
Pyrazinamide	0.750 g
Starch	0.075 g
Water	0.500 g

Granulate Isoniazid with solution of Hydroxypropylmethyl Cellulose K4M in Isopropyl Alcohol and dry. Granulate Rifampicin, Ethambutol Hydrochloride and Pyrazinamide with Starch paste in water and dry. Compress into bilayered tablets on a rotapress. Rifampicin (Layer – II) is immediately released. Isoniazid layer is released in delayed form.

28. Ethambutol Hydrochloride in taste masked form using complexation

Ethambutol Hydrochloride	1.0 Kg
Polystyrene Copolymer	2.0 Kg
Water	5.0 L

Disperse Polystyrene copolymer in Water and add Ethambutol Hydrochloride to it with constant stirring. Continue stirring for two hours and filter the complex and dry.

The above complex may be included in a tablet, capsule or suspension dosage form for taste masked and delayed release Isoniazid suspension containing other antitubercular drugs.

29. Tablet-in-tablet formulation (Rifapentine in delayed release form)

Core tablet :	**Per tablet**
Rifapentine	150 mg
Microcrystalline Cellulose	75 mg
Starch	10 mg
Water	-----
Disodium Edetate	3 mg
Magnesium Stearate	5 mg
Purified Talc	2 mg
Sodium Lauryl Sulphate	5 mg

Pass Rifapentine and Microcrystalline Cellulose through sieve and granulate the mass with Starch paste and pass through multimill. Dry the granules at 50° to 60°C and pass through sieve of mesh size 18. Pass Magnesium Stearate, Disodium Edetate, Sodium Lauryl Sulphate and Purified Talc through sieve of mesh size 60 and mix with the dried granules and compress.

Enteric Coating of Rifapentine Tablets (Batch Size 2.0 Kg)

Cellulose Acetate Phthlate	85.00 g
Purified Talc	20.00 g
Polyethylene Glycol 400	10.00 g
Dichloromethane	1.33 L
Isopropyl Alcohol	0.66 L

Dissolve Cellulose Acetate Phthlate in Isopropyl Alcohol and Dichloromethane mixture. Add Polyethylene Glycol 400 and Talc to the above bulk and mix for 45 minutes. Coat the tablets to a weight build up of 4 – 6% w/w.

Outer Tablet

Pyrazinamide	750 mg
Ethambutol Hydrochloride	400 mg
Isoniazid	150 mg
Lactose	60 mg

Magnesium Stearate	20 mg
Sodium Starch Glycollate	30 mg
Starch	20 mg
Purified Talc	5 mg
Purified Water	------

Pass Pyrazinamide, Ethambutol Hydrochloride, Isoniazid and Lactose through a sieve and granulate with Starch Paste prepared in Purified Water. Pass the wet mass through multimill and dry the granules at 50 – 60° C. Pass the dried granules through sieve of mesh size 16. Pass Magnesium Stearate, Purified Talc and Sodium Starch Glycollate through sieve of mesh size 60 and mix with dried granules. Compress the tablets alongwith the Rifapentine enteric coated tablets in between.

Film Coating of outer tablets (Batch Size 2.0 Kg)	
Hypromellose	40.00 g
Purified Talc	2.00 g
Polyethylene Glycol 400	8.00 g
Titanium Dioxide	2.00 g
Colour	q.s.
Dichloromethane	0.66 L
Isopropyl Alcohol	0.33 L

Dissolve Hypromellose in Isopropyl Alcohol and Dichloromethane mixture. Add Polyethylene Glycol 400, Titanium Dioxide, Purified Talc and colour to the above bulk and mix for 45 minutes. Coat the tablets to a weight build up of 3 – 4% w/w.

30. Effervescent Tablet / granules (Rifampicin in delayed release form).

	Per tablet
Rifampicin Enteric Coated Granules	
Equivalent to Rifampicin (from example no. 8)	225 mg
Pyrazinamide	750 mg
Isoniazid	150 mg
Ethambutol Hydrochloride	400 mg

Anhydrous Citric Acid	340 mg
Sodium Bicarbonate	360 mg
Anhydrous Sodium Carbonate	20 mg
Povidone	50 mg
Polyethylene Glycol 6000	25 mg
Sodium Benzoate	20 mg
Aspartame	20 mg
Magnesium Stearate	7.5 mg
Sodium Lauryl Sulphate	2.5 mg
Flavour	25 mg
Isopropyl Alcohol	-----
Dichloromethane	----

Pass Pyrazinamide, Ethambutol Hydrochloride, Isoniazid through a sieve of mesh size 40. Pass Anhydrous Citric Acid, Sodium Bicarbonate and Anhydrous Sodium Carbonate through sieve of mesh size 100 and mix with the above bulk. Dissolve Povidone in Isopropyl Alcohol and Dichloromethane mixture and granulate the bulk with binder solution and pass the wet mass through multimill and dry the granules. Pass the dried granules through sieve of mesh size 16. Pass Magnesium Stearate, Polyethylene Glycol 6000, Aspartame, Sodium Benzoate, Sodium Lauryl Sulphate and flavour through sieve and mix with dried granules.

The above effervescent granules can be dispensed in a pouch / sachets or in a tablet dosage form. All the processing is carried in dehumidified conditions at relative humidity not more than 20% and temperature not more than 25°C.

31. Buffered tablets containing Rifampicin in delayed release form

	Per tablet
Rifampicin delayed release granules equivalent to Rifampicin (from example no. 8)	225 mg
Pyrazinamide	750 mg
Isoniazid	150 mg
Ethambutol Hydrochloride	400 mg
Lactose	22.5 mg

Starch	30 mg
Magnesium Stearate	7.5 mg
Sodium Starch Glycollate	30 mg
Sodium Carbonate	100 mg
Purified Water	-----

Pass Pyrazinamide, Ethambutol Hydrochloride, Isoniazid and Lactose through a sieve of mesh size 40. Granulate the above bulk with Starch paste containing water and pass the wet mass through multimill and dry the granules. Pass Magnesium Stearate, Sodium Starch Glycollate and Sodium Carbonate through sieve and mix with dried granules, rifampicin enteric coated granules and compress.

Film Coating of tablets (Batch Size 2.0 Kg)

Hypromellose	40.00 g
Purified Talc	2.00 g
Polyethylene Glycol 400	8.00 g
Titanium Dioxide	2.00 g
Colour	q.s.
Dichloromethane	0.66 L
Isopropyl Alcohol	0.33 L

Dissolve Hypromellose in Isopropyl Alcohol and Dichloromethane mixture. Add Polyethylene Glycol 400, Titanium Dioxide, Purified Talc and colour to the above bulk and mix for 45 minutes. Coat the tablets to a weight build up of 3 – 4% w/w.

32. Hard Gelatin Capsule Formulation Containing Isoniazid in Delayed Release form.

	Per Capsule
Isoniazid Enteric Coated tablets (example no. 20)	200 mg ≅ 1 Tab.
Rifampicin (Compacted)	225 mg

Sodium Lauryl Sulphate	3 mg

Pass Rifampicin through sieve of mesh size 22 and mix with the Sodium Lauryl Sulphate previously passed through sieve of mesh size 40. Fill 228 mg of above powder and one Isoniazid enteric coated tablet in each empty hard gelatin capsules size "0".

33. Molecular dispersion of rifabutin with enteric (delayed release) effect

Rifabutin	10.00 Kg
Eudragit L100 (Rohm Pharma, Germany)	2.50 Kg
Isopropyl Alcohol	6.0 L
Dichloromethane	17.0 L

Dissolve Eudragit L 100 in a mixture of Isopropyl Alcohol and Dichloromethane. Dissiove Rifabutin in Dichloromethane and add to the above solution and mix for one hour. Evaporate the solvents on a water bath and pass the residue through a sieve of mesh size 100.

The above mentioned powder of Rifabutin may be blended with other anti-tubercular drugs and suitable excipients to formulate into tablets, capsules or suspension.

34. Tablet formulation containing Rifabutin in Delayed Release form

	Per tablet
Rifabutin (In delayed release molecular dispersion form as per example 33)	150 mg
Isoniazid	150 mg
Ethambutol Hydrochloride	400 mg
Pyrazinamide	750 mg
Lactose	135 mg
Magnesium Stearate	20 mg
Sodium Starch Glycollate	30 mg
Starch	30 mg
Purified Talc	5 mg

Pass Pyrazinamide, Ethambutol Hydrochloride, Isoniazid and Lactose through a sieve and granulate with Starch Paste prepared in Purified Water. Pass the wet mass through multimill and dry the granules at 50 – 60° C. Pass the dried granules through sieve of mesh size 16. Mix Magnesium Stearate , Sodium Starch Glycollate, Purified Talc and Rifabutin delayed release powder with dried granules and compress.

Film Coating of tablets (Batch Size 2.0 Kg)	
Hydroxypropyl Methylcellulose	40.00 g
Purified Talc	2.00 g
Polyethylene Glycol 400	8.00 g
Titanium Dioxide	2.00 g
Colour	q.s.
Dichloromethane	0.66 L
Isopropyl Alcohol	0.33 L

Dissolve Hydrxypropylmethylcellulose in Isopropyl Alcohol and Dichloromethane mixture. Add Polyethylene Glycol 400, Titanium Dioxide, Purified Talc and colour to the above bulk and mix for 45 minutes. Coat the tablets to a weight build up of 3-4% w/w.

36. Powder for reconstitution containing Isoniazid in Delayed Release form.

Each 10 ml of reconstituted suspension contains

Isoniazid (In delayed released molecular dispersion form as per example 22)	150 mg
Rifampicin	225 mg
Ethambutol Hydrochloride (In ion exchange complexed form for taste masking as per example 28)	400 mg
Pyrazinamide	750 mg
Methyl Hydroxybenzoate	5 mg

Sodium Metabisulphite	10 mg
Sweetening Agent	q.s.
Xanthan Gum	20 mg
Flavour	q.s.

Pass Pyrazinamide, Ethambutol Hydrochloride, Isoniazid delayed release powder, Rifampicin, Methyl Hydroxybenzoate, and Sodium Metabisulphite through sieve of mesh size 60. Pass Xanthan Gum and Sweetening Agent through a sieve of mesh size 100. Mix both the bulks and fill in amber coloured glass bottles.

36. Powder for reconstitution containing Rifampicin in Delayed Release form.

Each 10 ml of reconstituted suspension contains

Rifampicin in delayed release molecular dispersion form equivalent to Rifampicin (as per example 9)	225 mg
Isoniazid (in taste masked form as per example 39)	150 mg
Ethambutol Hydrochloride (In ion exchange complexed form for taste masking as per example 28)	400 mg
Pyrazinamide	750 mg
Methyl Hydroxybenzoate	5 mg
Sodium Metabisulphite	10 mg
Sweetening Agent	q.s.
Xanthan Gum	20 mg
Flavour	q.s.

Pass Pyrazinamide, Ethambutol Hydrochloride, Isoniazid, Rifampicin delayed release powder, Methyl Hydroxybenzoate, and Sodium Metabisulphite through sieve of mesh size 60. Pass Xanthan gum and Sweetening Agent through a sieve of mesh size 100 and mix both the bulks and fill in amber coloured glass bottles.

RECTIFIED SHEET (RULE 91)

37. An Anti Tubercular formulation in kit form.

The kit contains (A) One tablet of Isoniazid 150 mg (Enteric coated)
(B) One tablet containing Rifampicin, Ethambutol Hydrochloride and Pyrazinamide (Film coated)

(A) Isoniazid Tablets 150 mg (Enteric coated)

	Per tablet
Isoniazid	150 mg
Lactose	30 mg
Starch	5 mg
Water	——
Magnesium Stearate	3 mg
Purified Talc	3 mg

Pass Isoniazid and Lactose through sieve and granulate the mass with Starch paste and pass through multimill. Dry the granules at 50° to 60°C and pass through sieve of mesh size 18. Pass Magnesium Stearate and Talc through sieve of mesh size 60 and mix with the dried granules and compress.

Enteric Coating of Isoniazid Tablets (Batch Size 2.0 Kg)

Eudragit L 100	80.00 g
Purified Talc	25.00 g
Triethyl Citrate	15.00 g
Dichloromethane	1.30 L
Isopropyl Alcohol	0.60 L

Dissolve Eudragit L 100 in Isopropyl Alcohol and Dichloromethane mixture. Add Triethyl Citrate and Talc to the above bulk and mix for 45 minutes. Coat the tablets to a weight build up of 4 – 6% w/w.

(B) Rifampicin, Ethambutol Hydrochloride and Pyrazinamide Tablets (film coated)

	Per Tablet
Pyrazinamide	750 mg

Ethambutol Hydrochloride	400 mg
Rifampicin	225 mg
Lactose	50 mg
Magnesium Stearate	15 mg
Talc	6 mg
Starch	19 mg
Crospovidone	35 mg
Purified Water	———

Pass Pyrazinamide, Ethambutol Hydrochloride, Rifampicin and Lactose through a sieve and granulate with Starch paste prepared in Purified Water. Pass the wet mass through multimill and dry the granules at 50 – 60° C. Pass dried granules through sieve of mesh size 16. Pass Magnesium Stearate, Purified Talc and Crospovidone through sieve of mesh size 60 and mix with dried granules and compress.

Film Coating of tablets (Batch Size 2.0 Kg)	
Hypromellose	40.00 g
Purified Talc	2.00 g
Polyethylene Glycol 400	8.00 g
Titanium Dioxide	2.00 g
Colour	q.s.
Dichloromethane	0.66 L
Isopropyl Alcohol	0.33 L

Dissolve Hypromellose in Isopropyl Alcohol and Dichloromethane mixture. Add Polyethylene Glycol 400, Titanium Dioxide, Purified Talc and colour to the above bulk and mix for 45 minutes. Coat the tablets to a weight build up of 3 – 4% w/w.

38. An Anti Tubercular formulation in kit form.

The kit contains (A) One tablet of Rifampicin 150 mg (Enteric coated).
(B) One tablet containing Isoniazid, Ethambutol Hydrochloride and Pyrazinamide (Film coated).

(A) Rifampicin Tablets 150 mg (Enteric coated)

	Per tablet
Rifampicin	225 mg
Microcrystalline Cellulose	55 mg
Starch	10 mg
Water	------
Magnesium Stearate	5 mg
Sodium Lauryl Sulphate	5 mg

Pass Rifampicin and Microcrystalline Cellulose through sieve and granulate the mass with Starch paste and pass through multimill. Dry the granules at 50° to 60°C and pass through sieve of mesh size 18. Pass Magnesium Stearate and Sodium Lauryl Sulphate through sieve of mesh size 60 and mix with the dried granules and compress.

Enteric Coating of Rifampicin Tablets (Batch Size 2.0 Kg)

Eudragit L 100	80.00 g
Purified Talc	25.00 g
Triethyl Citrate	15.00 g
Dichloromethane	1.30 L
Isopropyl Alcohol	0.60 L

Dissolve Eudragit L 100 in a Isopropyl Alcohol and Dichloromethane mixture. Add Triethyl Citrate and Talc to the above bulk and mix for 45 minutes. Coat the tablets to a weight build up of 4 – 6% w/w.

(B) Isoniazid, Ethambutol Hydrochloride and Pyrazinamide Tablets (film coated)

	Per Tablet
Pyrazinamide	750 mg
Ethambutol Hydrochloride	400 mg
Isoniazid	150 mg
Magnesium Stearate	15 mg
Talc	6 mg

Starch	35 mg
Sodium Starch Glycollate	35 mg
Purified Water	------

Pass Pyrazinamide, Ethambutol Hydrochloride and Isoniazid through a sieve and granulate with Starch paste prepared in Purified Water. Pass the wet mass was passed through multimill and dry the granules at 50 – 60° C. Pass the dried granules through sieve of mesh size 16. Pass Magnesium Stearate, Purified Talc and Sodium Starch Glycollate through sieve of mesh size 60 and mix with dried granules and compress.

Film Coating of tablets (Batch Size 2.0 Kg)

Hydroxypropyl Methylcellulose	40.00 g
Purified Talc	2.00 g
Polyethylene Glycol 400	8.00 g
Titanium Dioxide	2.00 g
Colour	q.s.
Dichloromethane	0.66 L
Isopropyl Alcohol	0.33 L

Dissolve Hydroxypropyl Methylcellulose in Isopropyl Alcohol and Dichloromethane mixture. Add Polyethylene Glycol 400, Titanium Dioxide, Purified Talc and colour to the above bulk and mix for 45 minutes. Coat the tablets to a weight build up of 3-4% w/w.

39. Isoniazid in taste masked form using complexation

Isoniazid	1.0 Kg
Polystyrene Copolymer	2.0 Kg
Water	5.0 L

Disperse Polystyrene copolymer in Water and add Isoniazid to it with constant stirring. Continue stirring for two hours and filter the complex and dry.

The above complex may be included in a tablet, capsule or suspension dosage form for taste masked and delayed release Isoniazid suspension containing other antitubercular drugs.

40. Microemulsion formulation of Rifampicin and other Tubercular drugs.

	Per Tablet
Rifampicin	150 mg
Pyrazinamide	250 mg
Ethambutol Hydrochloride	267 mg
Isoniazid	100 mg
Poloxamer 188	25 mg
Vitamin E Polyethylene Glycol Succinate	20 mg
Hydrogenated vegetable Oil	20 mg
Magnesium Stearate	15 mg
Talc	6 mg
Starch	35 mg
Sodium Starch Glycollate	35 mg
Purified Water	—

Pass Pyrazinamide, Ethambutol Hydrochloride, Rifampicin and Isoniazid through a sieve and granulate with Starch paste containing Poloxamer 188, Vitamin E Polyethylene Glycol Succinate and Hydrogenated vegetable oil. Pass the wet mass was passed through multimill and dry the granules at 50 – 60° C. Pass the dried granules through sieve of mesh size 16. Pass Magnesium Stearate, Purified Talc and Sodium Starch Glycollate through sieve of mesh size 60 and mix with dried granules and compress.

Such tablets on dilution with water gives a microemulsion.

41. Vesicular carriers for Rifampicin

Rifampicin	500 mg
Chloroform	q.s.
Cholesterol	49 mg
Polysorbate 80	35 mg
Distearyl Phosphatidyl Choline	7 mg

Dichloromethane	10 ml
Calcium Chloride (25mM ssolution)	10 ml

Dissolve Rifampicin in minimum volume of Chloroform and add Cholesterol, Polysorbate 80 and Distearyl Phosphatidyl Choline to it. Add Dichloromethane, 2ml of calcium Chloride solution. Sonicate for 2 hours or till a milky emulsion is formed and evaporate the solvent layer under controlled conditions of temperature and pressure on a rota evaporator till a semisolid viscous liquid is obtained. Now add remaining amount of Calcium Chloride solution and evaporate the solvents on a rota evaporator for overnight and collect the vesicular carriers.

Such carriers can be incorporated into a tablet, capsule or liquid dosage form.

42. Tablet containing Rifampicin in molecular dispersion (in delayed release) form.

	Per Tablet
Rifampicin in delayed release molecular dispersion Form equivalent to Rifampicin (as per example no. 9)	225 mg
Pyrazinamide	750 mg
Ethambutol Hydrochloride	400 mg
Isoniazid	150 mg
Lactose	60 mg
Magnesium Stearate	20 mg
Sodium Starch Glycollate	30 mg
Starch	20 mg
Purified Talc	5 mg
Purified Water	-----

Pass Pyrazinamide, Ethambutol Hydrochloride, Isoniazid and Lactose through a sieve and granulate with Starch Paste prepared in Purified Water. Pass the wet mass through multimill and dry the granules at 50 – 60° C. Pass the dried granules through sieve of mesh size 16. Pass Magnesium Stearate, Purified Talc and Sodium Starch

Glycollate through sieve of mesh size 60 and mix with dried granules and rifampicin delayed release powder. Compress the blend into tablets.

Film Coating of tablets (Batch Size 2.0 Kg)	
Hypromellose	40.00 g
Purified Talc	2.00 g
Polyethylene Glycol 400	8.00 g
Titanium Dioxide	2.00 g
Colour	q.s.
Dichloromethane	0.66 L
Isopropyl Alcohol	0.33 L

Dissolve Hypromellose in Isopropyl Alcohol and Dichloromethane mixture. Add Polyethylene Glycol 400, Titanium Dioxide, Purified Talc and colour to the above bulk and mix for 45 minutes. Coat the tablets to a weight build up of 3 – 4% w/w.

43. Tablet containing Isoniazid in molecular dispersion (in delayed release) form.

	Per Tablet
Isoniazid in delayed release molecular dispersion form equivalent to Isoniazid (as per example no. 23)	150 mg
Pyrazinamide	750 mg
Ethambutol Hydrochloride	400 mg
Rifampicin	225 mg
Lactose	60 mg
Magnesium Stearate	20 mg
Sodium Starch Glycollate	30 mg
Starch	20 mg
Purified Talc	5 mg
Purified Water	——

Pass Pyrazinamide, Ethambutol Hydrochloride, Rifampicin and Lactose through a sieve and granulate with Starch Paste prepared in Purified Water. Pass the wet mass through multimill and dry the granules at 50 – 60° C. Pass the dried granules through sieve of mesh size 16. Pass Magnesium Stearate, Purified Talc and Sodium Starch Glycollate through sieve of mesh size 60 and mix with dried granules and isoniazid delayed release powder. Compress the blend into tablets.

Film Coating of tablets (Batch Size 2.0 Kg)

Hypromellose	40.00	g
Purified Talc	2.00	g
Polyethylene Glycol 400	8.00	g
Titanium Dioxide	2.00	g
Colour	q.s.	
Dichloromethane	0.66	L
Isopropyl Alcohol	0.33	L

Dissolve Hypromellose in Isopropyl Alcohol and Dichloromethane mixture. Add Polyethylene Glycol 400, Titanium Dioxide, Purified Talc and colour to the above bulk and mix for 45 minutes. Coat the tablets to a weight build up of 3 – 4% w/w.

Claims

1. A pharmaceutical composition of anti tubercular drugs for oral use comprising Rifampicin and/or Isoniazid, wherein the bioavailability of Rifampicin and/or other drugs is enhanced.
2. A pharmaceutical composition of anti tubercular drugs for oral use comprising Rifampicin and/or Isoniazid wherein, more preferably, the bioavailability of Rifampicin is enhanced by preventing its degradation caused by presence of Isoniazid.
3. A composition as claimed in claim 1 wherein Rifampicin and Isoniazid do not come in contact with each other in solution state.
4. A composition as claimed in claim 1 wherein Rifampicin and Isoniazid do not come in contact with each other in solution state at pH between 1 and 4.
5. A composition as claimed in claim 1 wherein Rifampicin is present in delayed release and/or extended release form such that minimal amount of Rifampicin is dissolved between pH 1 and 4.
6. A composition as claimed in claim 1 wherein Isoniazid is present in delayed release and/or extended release form such that minimal amount of drug is dissolved between pH 1 and 4.
7. A composition as claimed in any of the preceding claims wherein delayed release of Rifampicin and/or Isoniazid is achieved by treating the drugs with pH sensitive polymers comprising Cellulose Acetate Phthalate, Hydroxypropyl Methylcellulose Phthalate, Polyvinyl Acetate Phthalate, Hydroxypropyl Methycellulose Acid Succinate, Alginic Acid, Methacrylic Acid Polymers, Carbomers, Polacrillin Potassium and Chitosan.
8. A composition as claimed in claim 1 to 7 wherein Rifampicin and/or Isoniazid is present in form of molecular dispersion along with a pH sensitive polymer resulting in delayed release of drug.
9. A composition as claimed in any of the preceding claims wherein extended release of Rifampicin and/or Isoniazid is achieved by treating the drugs with pH independent polymers comprising Cellulose, Hydroxypropyl Methylcellulose, Hydroxypropyl Cellulose, Hydroxyethyl Cellulose, Ethyl Cellulose ; Natural Gums like Xanthan gum, Karaya Gum, Guar gum, Tragacanth and Acacia.



10. A composition as claimed in any of the preceding claims which is dispensed in kit form wherein the drugs are present in individual unit dosage forms.
11. A composition as claimed in any of the preceding claims wherein Rifampicin and/or Isoniazid is present in micronized form.
12. A composition as claimed in any of the preceding claims comprising crystal or polymorphic forms of Rifampicin and/or Isoniazid having reduced solubility between pH 1 and 4.
13. A composition as claimed in any of the preceding claims which comprises buffers to raise the pH of gastric contents beyond 3.
14. A composition as claimed in any of the preceding claims which comprises bioavailability enhancing agents like Piperine and Ayurvedic formulation like Trikatu.
15. A composition as claimed in any of the preceding claims which is amenable to high speed, low cost manufacturing and also easy to administer such as in the form of tablets, capsules, suspension, pastilles, jellies and powder for reconstitution.
16. A composition as claimed in claim 15 wherein the tablets may be film coated tablets, compression coated tablets or bilayer tablets.
17. A composition as claimed in claim 1 wherein the anti-tubercular drugs are present in taste neutralized form.
18. A process for the preparation of a pharmaceutical composition as claimed in claim 1 which comprises enhancing the bioavailability of Rifampicin and/or Isoniazid.
19. A process as claimed in claim 18 wherein, more preferably, the bioavailability of Rifampicin is enhanced by preventing its degradation caused by presence of Isoniazid.
20. A process as claimed in claim 18 wherein Rifampicin and Isoniazid do not come in contact with each other in solution state.
21. A process as claimed in claim 18 wherein the drugs Rifampicin and/or Isoniazid are made into 'delayed release form' or extended release form'.
22. A process as claimed in claim 21 wherein the drugs Rifampicin and/or Isoniazid are made into 'delayed release form' or extended release form' by

* C L M S *

microsphere formation by conventional polymers by the conventional techniques.

23. A process as claimed in claims 18 to 22 wherein delayed release of Rifampicin and/or Isoniazid is achieved by treating the drugs with pH sensitive polymers comprising cellulose acetate phthalate, Hydroxypropyl methylcellulose phthalate, Polyvinyl acetate phthlate, Hydroxypropyl methyl cellulose acid succinate, alginic acid, Methacrylic acid polymers, Carbomers, Polacrillin and Chitosan.
24. A process as claimed in claims 18 to 23 wherein extended release of Rifampicin and/or Isoniazid is achieved by treating the said drugs with pH independent polymers comprising Cellulose, Hydroxypropyl methyl cellulose, Hydroxyethyl cellulose, Ethyl cellulose, Natural gums like Xanthan gum, Karaya gum, Guar gum, Tragacanth and Acacia.
25. A process as claimed in claims 18 to 24 wherein the drugs Rifampicin and/or Isoniazid are present in micronized form.
26. A process as claimed in claims 18 to 25 wherein the drugs Rifampicin and/or Isoniazid are present in taste neutralized form.
27. A process as claimed in claims 18 to 26 wherein crystal or polymorphic forms of Rifampicin and/or Isoniazid having reduced solubility between pH 1 and 4 are used.
28. A process as claimed in claims 18 to 27 wherein conventional buffers are added to the composition to raise the pH of gastric contents beyond 3.
29. A process as claimed in any of the preceeding claims wherein bioavailability enhancing agents like Piperine and Ayurvedic formulation like Trikatu are added to the composition.
30. A process as claimed in any of the preceeding claims wherein the composition prepared is formed into tablets, capsules, suspensions, pastilles, jellies or powder for reconstitution by known methods.
31. A process for the preparation of anti tubercular drugs composition for oral use substantially as herein described and illustrated by the examples herein.
32. A pharmaceutical composition of anti tubercular drugs for oral use substantially as herein described and illustrated by the examples herein.

* C L M S *