

EFFECT OF KOLLIDON CL ON RELEASE BEHAVIOR OF ISONIAZID AND RIFAMPICIN COMBINATION DISPERSIBLE TABLETS FOR ORAL TREATMENT OF TUBERCULOSIS

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ABSTRACT

Oral route of administration have wide acceptance up to 50-60% to total drug forms. Fast disintegrating drug delivery system has number of advantage such as faster onset of action, attractive elegance, ease of administration. In this study, an attempt has been made to study compression method, for formulation of fast disintegrating tablets of Isoniazid and Rifampicin, anti-tubercular drugs in view of enhancing bioavailability. Prior to formulation the pre-compression parameters were characterized for flow properties and prepared formulations were evaluated for physico-chemical parameters, X-ray powder crystallography, SEM. All four formulations possessed good disintegration properties with total disintegration time of 25 to 40 seconds. The effects of Kollidon CL superdisintegrant and process variables on drug release profile and disintegration property were evaluated and results revealed the better drug release with Kollidon CL. All formulations are rapidly disintegrated in oral cavity as well as all formulations possess good anti-tubercular properties. SEM Showed the mechanical strength of the formulations affected the morphological changes after compression. Hence, it is evident from this study that fast dispersible tablets could be a promising delivery system for Isoniazid and Rifampicin combination with good mouth feel and improved drug availability with better patient compliance.

Key words: Isoniazid, Rifampicin, Superdisintegrants, Bioavailability.

Introduction

Due to a society that is becoming increasingly aged, the development of an appropriate dosage form for the elderly is most desirable. because the changes in various physiological functions associated with aging including difficulty in swallowing, current dosage like capsule, are impractical.¹

Dispersible tablets are uncoated tablets that produce uniform dispersion in water. the rate of absorption of a drug from a tablet depends upon its ability to disintegrate quickly and dissolve. dispersible tablets have found wide acceptance today replace conventional suspension and dry syrap dosage form.² recently

pharmaceutical industry has become increasingly aware of the need that elderly be considered as a separate and unique medicare population. thus, oral dispersible tablets are gaining more demand and popularity from last few years.³

Isoniazid is chemically 4-pyridinecarboxylic acid hydrazine, and the usual daily dose is 300 gm daily. isoniazid is used in the treatment of primary treatment of pulmonary and extra pulmonary tuberculosis. rifampicin is chemically (12z,14e,24e)-(2s,16s, 17s, 18r, 19r, 20r, 21s, 22r, 23s)- 1,2 dihdro-5.6.9, 17, 19- heptamethyl-8-(4-methyl-peprazine-1-yliminomethyl)-1,11,13-triemino)neptho[2,1-b] furan 21-yl acetate and the usual daily dose is 450 gm daily. kollidon cl is chemically

polyvinylpyrrolidone and this is used as superdisintegrant, tablet binder, suspending or viscosity increasing agent, sweetening agent, pharmaceutical.⁴⁻⁶

Tuberculosis is an infectious disease caused by several species of *mycobacteria*. *m. tuberculosis* is a slender, or slightly curved bacillus, ranging from 1-4 μm length, they are acid-fast bacilli. oral tuberculous lesions may be either primary or secondary. primary oral tuberculous lesions are extremely rare and generally occur in younger patients associated with cervical lymphadenopathy. the primary lesion remains painless in the majority of cases. the secondary lesions, on the contrary, are more common and are seen mostly in older persons. the lesions are seen as superficial ulcers, patches indurated soft tissue lesions, or even lesions in the jaws that may be in the form of tuberculous osteomyelitis, or simple bony radiolucencies of all these oral lesions, the ulcerative form is the most common and is often painful with no associated caseation of the dependent lymph nodes.⁷⁻¹⁰

An attempt has been made, in the present work, to develop combination dispersible tablet of isoniazod and rifampicin by compression method, using a bland of kollidon cl. the objectives of the study were to investigate the performance of superdisintegrants and effect of other process variables on the characteristics of the rifampicin dispersible tablet.

Materials and Methods:

Isoniazid and rifampicin was procured from macload pharmaceuticals ltd, mumbai, india. kollidon cl sample

was obtained from fmc biopolymer, usa. all other chemicals and solvents were of analytical grade and purchased from local market in india.

Drug Excipient Compatibilities Studies:

The compatibility of drug and polymers under experimental condition is important pre-requisite before formulation. it is therefore necessary to confirm that the drug does not react with the polymer and excipients under experimental condition and should not affect the shelf life of product. this is confirmed by fourier transform infrared spectroscopy (ftir). it is a powerful technique for functional group identification of the drug molecules hence the chemical interaction of drug with the other excipients.

In the present study, the potassium bromide disc (pellet) of drug and excipients were prepared for recording the ftir spectra. the spectra were taken in the transmittance range of 4000-450 cm^{-1} . the pure drugs such as rifampicin formulations were subjected to ir studies.

Preparation of isoniazid and rifampicin dispersible tablet:^{11,12}

Different isoniazid and rifampicin dispersible tablet formulations were prepared by compression technique according to the formula given in table no. 1. the concentration of disintegrants was developed as optimal concentration under experimental formula and conditions of preparation. a total of 2 formulations were prepared. all the ingredients were passed through 60 mesh sieve separately and collected. the drug and avicel

ph 101 were mixed in a small portion of both and each time blended to get a uniform mixture in a geometrical order. the tablets were then compressed using 10 mm size punches to get a tablet of 100 mg using hydraulic press with suitable standard punches and stored in a well-closed container till use. in the first set 2 batches of isoniazid and rifampicin combination fast dispersible tablets were prepared using different concentration of kollidon cl superdisintegrants.

Evaluation parameters of Rifampicin Dispersible tablets

a) Pre-Compression parameters¹³:

- i) Bulk density:- both loose bulk density (lbd) and tapped bulk density (tbd) were determined. accurately weighed amount of sample (20 gm) was transferred into a 25 ml measuring cylinder. the volume of packing was recorded. the measuring cylinder was then tapped 100 times on a plane hard wooden surface and the tapped volume of packing was recorded. lbd and tbd were calculated by the following formula:

$$\text{LBD (loose bulk density)} = \frac{\text{weight of granules}}{\text{volume of packing}}$$

$$\text{TBD (tapped bulk density)} = \frac{\text{weight of granules}}{\text{tapped volume of packing}}$$

- ii) compressibility index:- percent compressibility of granules as determined by carr's compressibility index was calculated by the following formula:

$$\text{Carr's Index} = \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \times 100$$

- iii) Angle of repose (θ):- the frictional forces in a loose powder or granules can be measured by angle of repose. this is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane.

The granules were allowed to flow through the funnel fixed to a stand at definite height (h). the angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

$$\tan \theta = h/r$$

$$\theta = \tan^{-1} (h/r)$$

where θ = angle of repose

h = height

r = radius

values of angle of repose $\leq 30^\circ$ indicate free flowing granules and $\geq 40^\circ$ suggest poorly flowing material.

b) Post-compression parameters: ¹⁴⁻¹⁷

- 1) thickness and diameter:- the tablet dimensions were measured using a calibrated dial caliper. 5 tablets of each batch were picked randomly and its thickness and hardness were measured individually. tablet thickness should be controlled within $\pm 5\%$ variation of a standard value⁴⁷.
- 2) Weight variation:- the procedure described in ip 1996 was employed to determine the weight variation of the tablets. ten tablets were randomly selected from each batch and weighed on an electronic balance and the mean weight taken. each

tablet was then weighed individually and the standard deviation in weight was calculated for each batch⁴⁸.

- 3) Hardness:- hardness indicates the ability of a tablet to withstand mechanical shocks while handling. the hardness of the tablets was determined using Monsanto hardness tester. it is expressed in kg/cm². five tablets were randomly picked from each batch and the hardness of the tablets was determined. the mean and standard deviation values were calculated for each batch.
- 4) Friability:- friability of the tablets were determined using Roche friabilator. it is expressed in percentage (%). ten tablets were initially weighed ($w_{initial}$) and placed into the friabilator. the friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions, and then the tablets were weighed again (w_{final}). the loss in tablet weight due to abrasion or fracture was the measure of tablet friability.

% friability was then calculated by :-

$$f = \frac{w(initial) - w(final)}{w(initial)} \times 100$$

% friability of less than 1% is considered acceptable.

- 5) Disintegration Test: - introduced one tablet in to each tube. the disc was added to each tube. the assembly was suspended in beaker containing buffer and operated the apparatus for 3 min. water is used as medium at temperature of 26°C.

- 6) Uniformity of Dispersion: - this test is applicable only for dispersible tablets. placed 1 tablet in 100 ml of water and stirred gently until completely dispersed. a smooth dispersion was obtained which passes through a sieve screen with a nominal mesh aperture of 710 µm (sieve no. 22).

- 7) *In-Vitro* Dissolution Study: ¹⁸⁻²⁰ *in-vitro* dissolution study were carried out on USP XXIII tablet dissolution apparatus using pH 6.8 buffer 900 ml at 100 rpm for 20 min at 37°C, employing paddle method. single tablet from each formulation was used for the studies. a 1ml sample from dissolution medium was withdrawn at different time intervals and diluted approximately so as to get a concentration of 10 µg/ml. the withdrawn sample was replaced by same amount of fresh dissolution medium to maintain sink conditions. the absorbance was measured on UV spectrophotometer at 333 nm and dissolution of rifampicin was compared with conventional marketed formulation.

- 8) Scanning Electron Microscopy: ²¹ SEM has been used to determine particle size distribution, surface topography, texture and to examine the morphology of fractured or sectioned surfaces. the SEM is most commonly used for generating three dimensional surface relief images derived from secondary electrons. the examination of the surface of polymeric drug delivery systems can provide

important information about the porosity and microstructure of the device.

9) Powder x-Ray Diffraction:^{22,23} the powder x-ray diffraction measurement were conducted over a 5-40° 2θ range on a siemens model d5000 diffractometer, equipped with monochromatic copper (α1= 1.54060 Å, α2=1.54438Å) x-ray. the step width was 0.020° 2θ/min with a time constant of 0-5 sec. the integration of the crystalline reflections was achieved using the diffrac^{plus} diffraction software (eva, version 2.0, siemens energy and automation, inc. madison, wi). the degree of crystallinity of samples was expressed as the percentage ratio of the integrated intensity of the sample to that of hydrocellulose, a crystalline standard prepared from cellulose by treating with 2.5 N HCL at boiling temperature.

10) Stability Study^{24,25}:- the purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, and enables recommended storage conditions and shelf-lives to be established.

ICH specifies the length of study and storage conditions:-

accelerated testing 40⁰c±2⁰c/75% rh ±5% for 6 months

11) microbiological screening²⁶⁻²⁸

anti-tubercular activity:

a 10 mg equivalent formulation sample was dissolved in 10 ml of dmsO to get a concentration of 1000 µg/ml. further dilutions were made with dmsO to get different concentration such as 100 µg/ml, 10 µg/ml, 1 µg/ml. 0.8 ml of each concentration was pipette out into different mac carney bottles. to this, 7.2 ml of lawenstain-jensen's medium (l.j. medium) was added. these bottles were incubated at 75°-85°c for 2 hrs for two successive days for solidification and sterilization.

Procedure for inoculation:

A sweep from h37rv strain culture was discharge with the help of 22 s.w. nichrome wire loop with a 3 mm external diameter, into a sterile distilled bijou bottle containing six 3 mm glass beads and 4 ml of sterile distilled water. each loopful of growth was supposed to deliver 4 mg moist weight of bacilli. the bottle was shaken with the help of a mechanical shaker for 2 min. this constitutes the suspension. using s.w.g. nichrome wire loop, 3mm external diameter, a loopful of suspension was inoculated on the surface of each of lawenstain-jensen's medium (l.j. medium) containing test formulations.

Lawenstain-Jensen's medium (l.j. medium) containing standard drug as well as control l.j. medium was also inoculated with *mycobacterium tuberculosis* of l.j. h37rv strain. the medium inoculated for 37°c for 6 weeks reading were taken and tabulated.

Results and Discussion

The FTIR spectra of pure isoniazid indicated the characteristic absorption stretch for strong c=O stretch band (amide II) at 1560 cm^{-1} and broad bands between 3300 and 3000 cm^{-1} for bonded n-h and c-h, stretch are obtained. The fingerprint region FTIR spectra showed a characteristic sharp peak at 1670 and 1610 , 1500 cm^{-1} for c=O, ring c=c and c=n. In comparison with the pure isoniazid, the absorption peak of the spectra for isoniazid in its formulations showed no shift and no disappearance of characteristic peaks suggest that there is no interaction between isoniazid and other additives. No degradation of isoniazid molecule was observed during its formulation development. Hence, the drug-excipient combinations used in the formulation development were compatible under given set of experiments. The FTIR spectra of pure rifampicin indicated the characteristic absorption stretch for c=O group at 1572 cm^{-1} and broad bands for n-h stretch was obtained between 2800 and 2300 cm^{-1} . The fingerprint region of FTIR spectra showed a characteristic sharp peak at 1281 and 1040 cm^{-1} for c-o-c acetyl group. In comparison with the pure rifampicin, the absorption peak of the spectra for rifampicin in its formulations showed no shift and no disappearance of characteristic peaks suggest that there was no interaction between rifampicin and other additives or no degradation in rifampicin molecule during formulation development. (Figure no.1)

The result of angle of repose was found to be in the range of $27^{\circ}.2'$ to $29^{\circ}.64'$. All formulations showed angle of repose within 30° which indicates good flow of

powder mixture. Angle of repose little higher above 30° is indicative of fair flow behavior of powder. The loose bulk density and tapped bulk density for all the formulations varied from 0.53 gm/cm^3 to 0.55 gm/cm^3 and 0.66 gm/cm^3 to 0.75 gm/cm^3 respectively. The values obtained lies within the acceptable range and not large differences found between loose bulk density and tapped bulk density. The percent compressibility for all the four formulations lies within the range of 16.66 to 16.92 . All formulations showed good compressibility hence can be directly compressed. (Table no. 2).

Table 3 depicts the physical parameters (hardness, weight variation, thickness, drug content and friability) and drug content of all fabricated tablets. Table 4 reflects the wetting time and uniformity of dispersion of these tablets. All the tablet formulation showed acceptable pharmaco-technical properties and complied with pharmacopoeial specification for weight variation, drug content (%), friability, disintegration and uniformity of dispersion (uod). Hardness was maintained to be within 4 kg/cm^2 to 5 kg/cm^2 . Since fast disintegrating tablets are less hard than conventional ones, due to a lower compression employed (hardness is usually 3 kpa), these tablets can therefore be fragile and need individual packaging. The lower standard deviation values indicated that the hardness of all the formulations were almost uniform in specific method and possess good mechanical strength with sufficient hardness. To obviate the difference in the hardness, superdisintegrants

are added in the formulations. in fact, a fast disaggregating tablet must disintegrate in the

TABLE NO. 1. COMPOSITION OF RIFAMPICIN DISPERSIBLE FORMULATIONS

| Sr. No. | Ingredients | F1 | F2 |
|---------|--------------------|------|------|
| 1. | Isoniazid | 50 | 50 |
| 2. | Rifampicin | 50 | 50 |
| 3. | Avicel Ph102 | 108 | 108 |
| 6. | Kallidon CL | 10 | 12.5 |
| 7. | Mannitol | 17.5 | 17.5 |
| 8. | Sodium Saccharine | 7 | 7 |
| 9. | Magnesium Stearate | 7 | 7 |

Blank space (dace) indicate that those components not present in the formulations

TABLE NO. 2. PRE-COMPRESSSION PARAMETERS: CHARACTERIZATION OF FORMULATION

POWDER

| Formulations | Angle of Repose (θ) | Loose Bulk Density (gm/cm^3) | Tapped Bulk Density (gm/cm^3) | % Compressibility | Appearance |
|--------------|------------------------------|---|--|-------------------|---------------|
| F1 | 26.16 | 0.52 | 0.63 | 17.46 | Reddish white |
| F2 | 27.20 | 0.54 | 0.65 | 16.92 | Reddish white |

TABLE NO: 3: POST-COMPRESSSION PARAMETERS: EVALUATION OF TABLETS

| Formulation Code | Uniformity of Thickness* (mm) | Hardness* (kg/cm^3) | Weight** (mg) | Drug Content Uniformity* (mg) | Friability (%) | Test of dispersion |
|------------------|-------------------------------|--------------------------------|---------------|-------------------------------|----------------|--------------------|
| F1 | 2.251±0.050 | 4.65±0.13 | 261±3.01 | 96.44±0.55 | 0.69 | Passed |
| F2 | 2.229±0.038 | 4.67±0.13 | 261±2.75 | 97.39±0.44 | 0.71 | Passed |

* Tests performed, n=3
 * Tests performed, n=10

TABLE NO. 4. POST-COMPRESSION PARAMETERS: WETTING TIME, WATER ABSORPTION RATIO

| Formulation Code | Wetting Time (Seconds) | Water Absorption Ratio |
|------------------|------------------------|------------------------|
| F1 | 229.58± 1.47 | 25.56 ± 2.74 |
| F2 | 222.78 ± 1.71 | 27.08 ± 1.24 |

Data expressed at mean±SD, all experiments performed in triplicate

TABLE NO: 5: POST-COMPRESSION PARAMETERS: IN VITRO DISPERSION TIME, DISSOLUTION REPORT

| Formulation Code | Disintegration Time (Second) | Dispersion Time (Second) | % Drug release (INH) | % Drug release (RIFA) |
|------------------|------------------------------|--------------------------|----------------------|-----------------------|
| F1 | 31.43 ± 1.14 | 120.16± 0.86 | 97.18 | 94.11 |
| F2 | 33.24± 0.74 | 158.74 ± 0.75 | 96.28 | 96.28 |

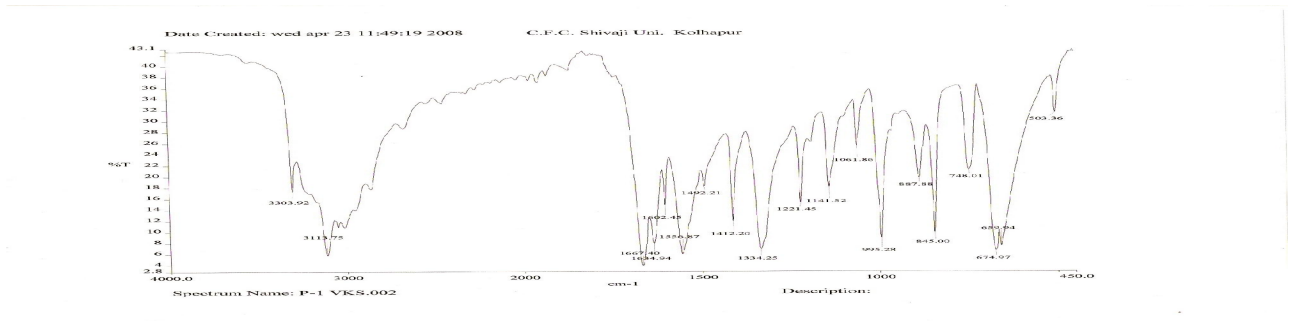
TABLE NO. 6: ANTI-TUBERCULAR ACTIVITY OF RIFAMPICIN DISPERSIBLE FORMULATIONS

| TEST COMPOUND | ZONE OF INHIBITION AT DIFFERENT DRUG CONCENTRATION | |
|---------------|--|-----------|
| | 100 µg | 300 µg |
| F1 | No growth | No growth |
| F2 | No growth | No growth |
| Control | No growth | No growth |
| Standard | No growth | No growth |

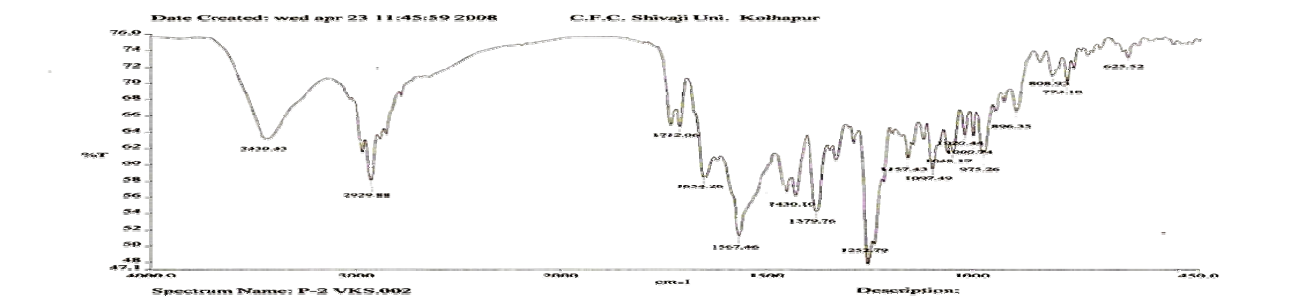
TABLE NO. 7: STABILITY STUDIES- RESIDUAL DRUG CONTENT AFTER SIX-MONTH STORAGE

| TIME (months) | FORMULATIONS | | |
|----------------|--------------|----------------|-----------------|
| | Drug Content | % Drug Content | % Residual Drug |
| 1 | 10.92 | 98.28 | 99.26 |
| 2 | 10.78 | 97.02 | 98.02 |
| 3 | 10.63 | 95.67 | 97.67 |
| 4 | 10.37 | 93.33 | 96.33 |
| 5 | 10.28 | 92.52 | 95.52 |
| 6 | 10.09 | 90.81 | 90.81 |

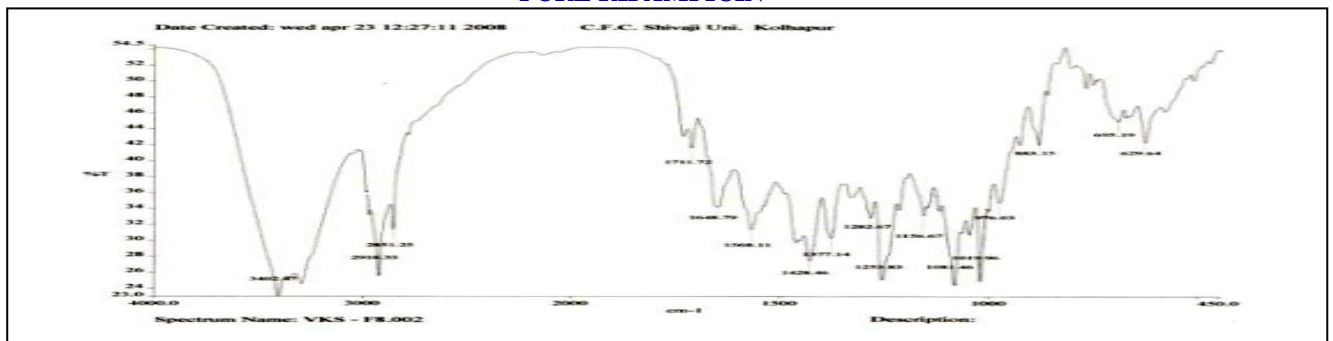
FIGURE NO. 1: FTIR STUDY OF THE PREPARED COMBINATION DISPERSIBLE FORMULATIONS



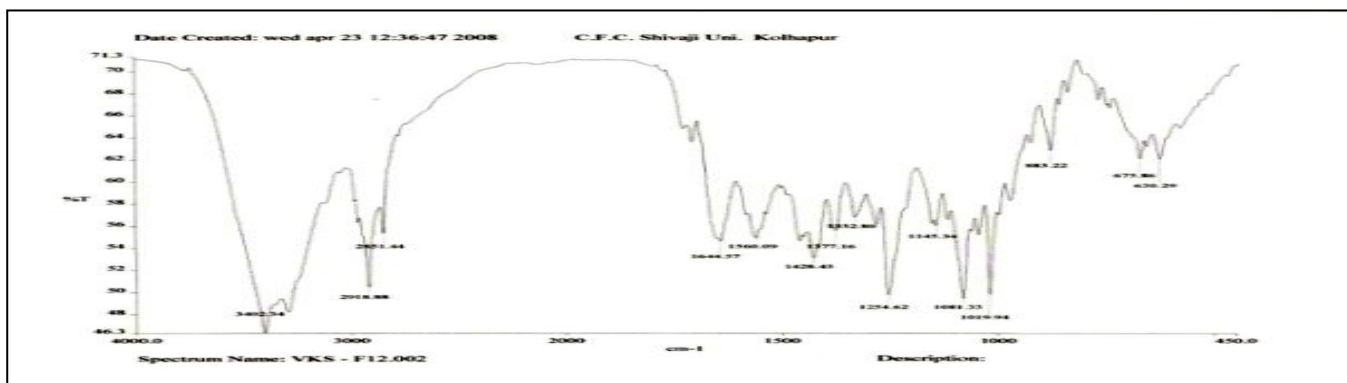
PURE ISONIAZID



PURE RIFAMPICIN



FORMULATION F-1



FORMULATION F-2

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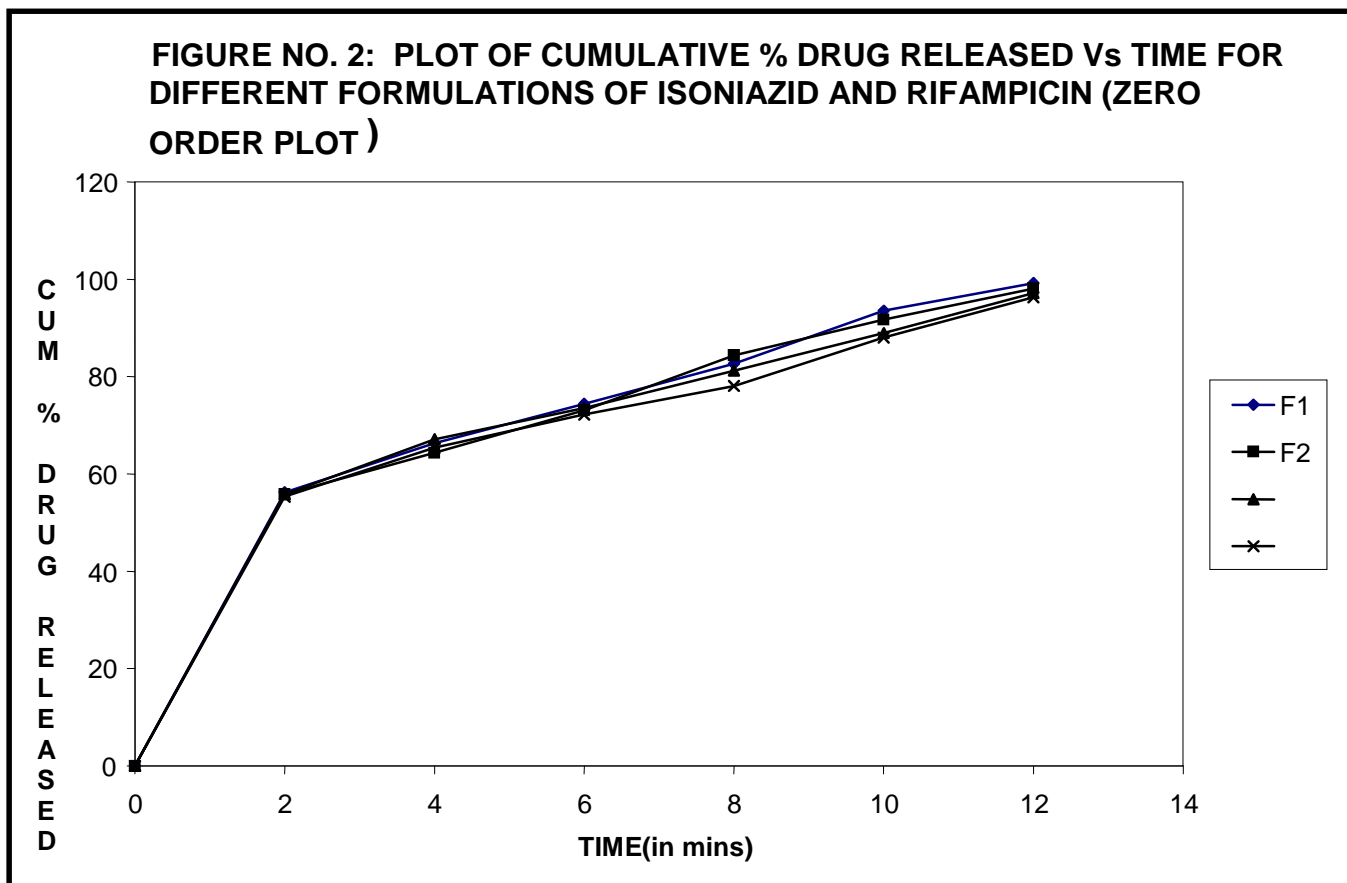


FIGURE NO. 3: SCANNING ELECTRON MICROSCOPE (SEM) STUDY OF THE PREPARED COMBINATION DISPERSIBLE FORMULATIONS.

F-1 Formulation

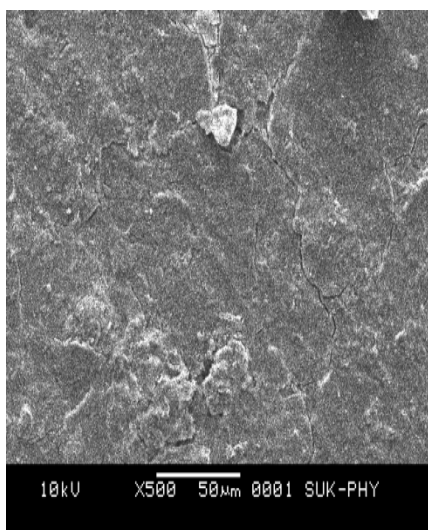


PLATE NO.1

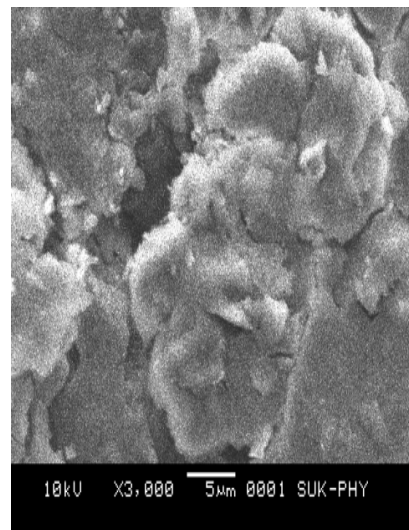


PLATE NO.2

F-2 Formulation

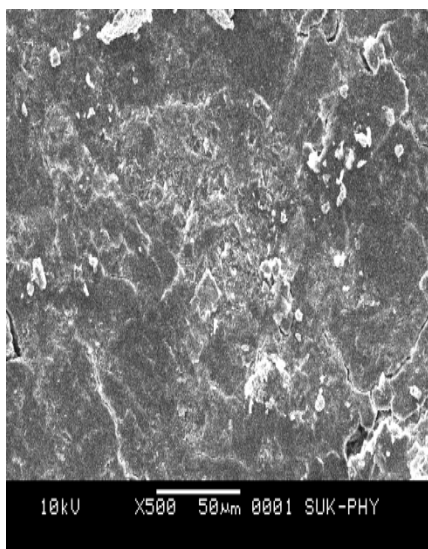


PLATE NO.1

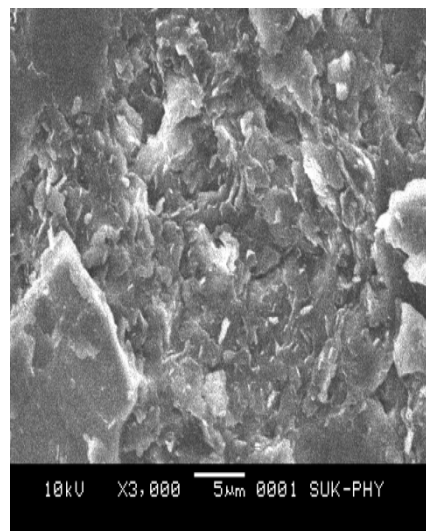
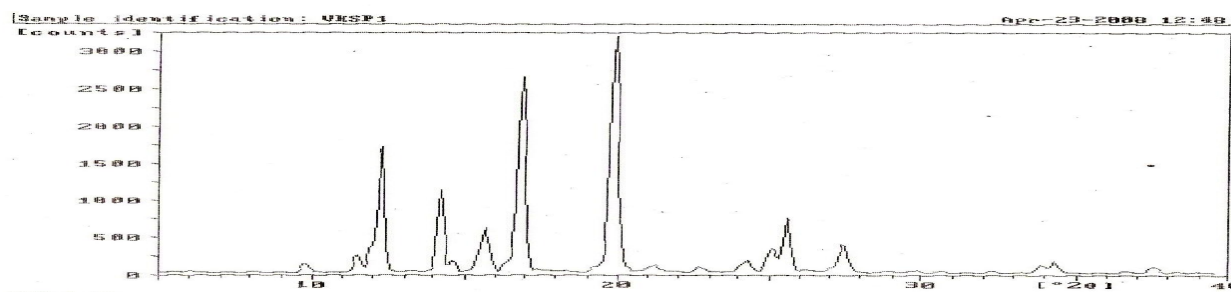
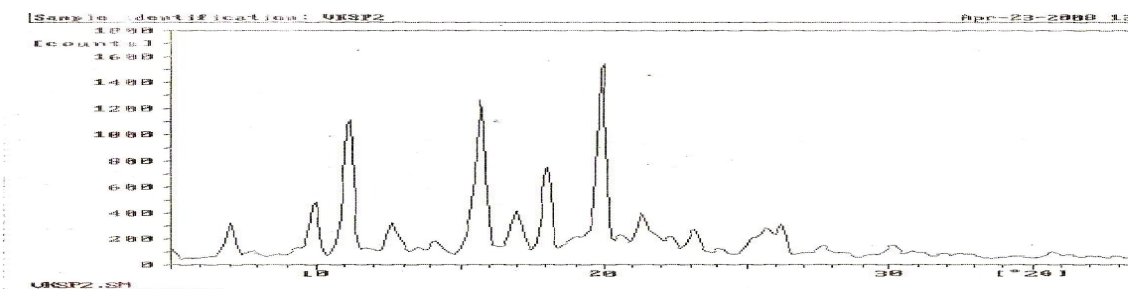


PLATE NO.2

FIGURE NO.4: XRD STUDY OF THE PREPARED RIFAMPICIN DISPERSIBLE FORMULATIONS

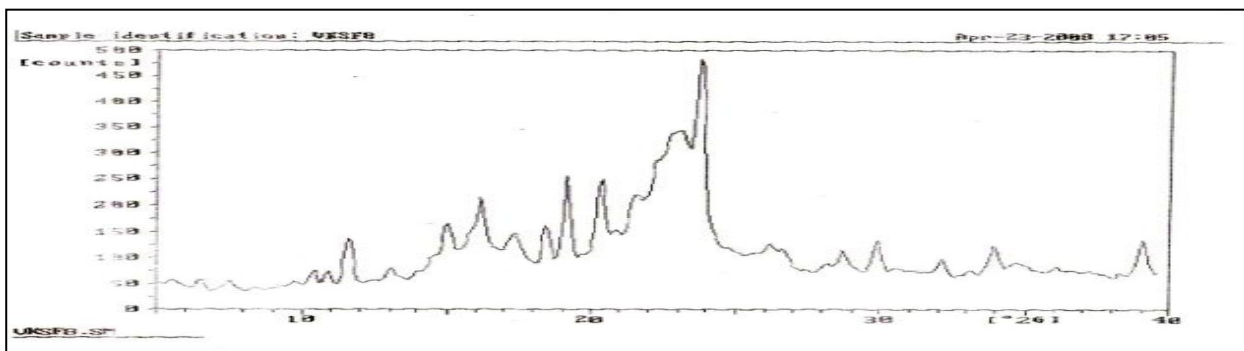


PURE ISONIAZID

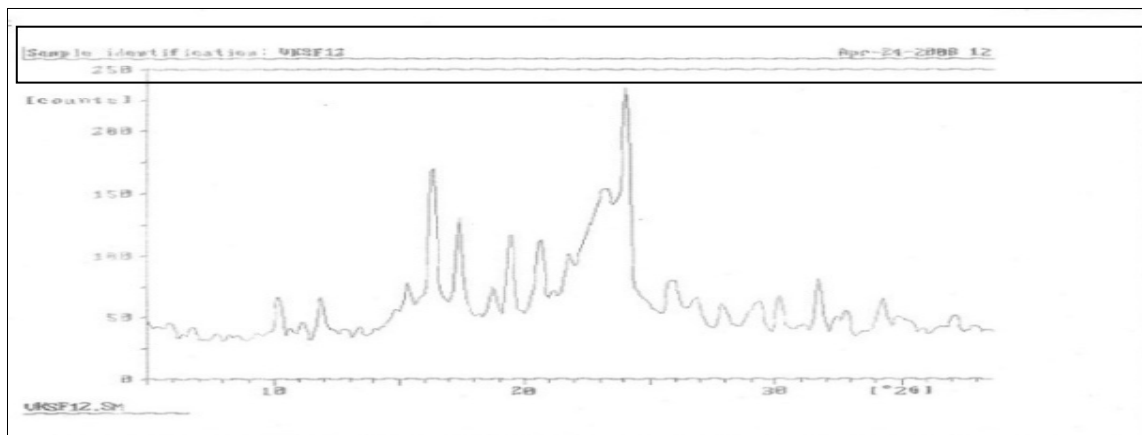


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FORMULATION F-1



FORMULATION F2

saliva; harder tablets need a de-aggregating agent of a superior ability, in this case kollidon cl, was employed. tablet disintegration was affected by the wicking and swelling of the disintegrant, and the wicking property would be closely related to the porosity. both the porosity and average pore size of tablets in all formulation decreased with increase of the tablet hardness. the wicking property may also correlate to the wetting behavior of the tablet. rapid dispersion within seconds has been observed in all the formulations, on the basis of the de-aggregation time of the tablets, almost all the formulations developed can be defined "fast dispersible": the limit for de-aggregation is in fact suggested as within 3 min. the

direct compressed tablets consumes less wetting time and all formulation passes test for dispersion.

The high ratio of water absorption was found in tablet containing kollidon cl, which is due to hydrophilicity and swelling capacity. all formulated dispersible tablets gave faster and rapid dissolution of isoniazid and rifampicin. the results are reported in table 5 and formulations follow mixed order release kinetics. the graphs were plotted as time vs percentage (figure no.2) drug release for all the formulations.

All formulations were subjected to scanning electron microscopy (sem) to examine the surface topography, texture of the formulations, morphology of fractured or sectioned surfaces, that can provide important

information about the porosity of the device in the matrix of the formulations by subjecting the formulations to SEM in dry state at the different magnifications, x500, x1000 using a jeol jsm-t330a. SEM images are shown in figure no.3. after examination the photographic results obtained from SEM, it was observed that formulation f2, contained particles of similar microscopic geometric which reflects the particles sizes of the parent potato starches of the range of 10-100 μm . additionally, examination at higher magnification suggested that the surfaces of the particles contained small, micron size, features. However, in case of Kollidon Cl formulations no cracks were observed, suggesting that the formulations had good mechanical properties. The small increase in drug release may not necessarily be attributed to surface rupturing or creak formation. the particles on the tablet surface were more compressed then those inside, there existed many empty spaces between the particles throughout the tablet where water could be absorbed by capillary forces. at higher magnification, a detailed distribution of pores can be observed. upon contact with water or saliva, the particles could easily dissociate, and the whole tablet disintegrated to form a paste, which is easy to swallow. as the compression pressure increased, the pores become smaller. the porous structure of the tablet was especially hard to observe.

X-ray powder diffractometry (xrpd) is a powerful technique for the identification of the

crystalline solid phases. every crystalline solid phase has a unique xrpd pattern, which can form the basis for its identification. the x-ray powder diffraction (xrd) spectra of rifampicin showed characteristic diffraction peaks in the 8.84° , 7.30° , 5.25° , 2θ characteristic peaks of rifampicin were detectable in the formulations (f-1 to f4). it is very difficult to identify the presence of avicel ph 102 or superdisintegrants in the xrpd spectra as they are polymers with amorphous structure and no sharp peaks are apparent at particular 2θ , due to the very low crystallinity of these components. x-ray powder diffraction spectras are shown in xrd figure no.4.

The anti-tubercular activity of the formulations is investigated in the lawenstain- jensen's medium (l.j. medium). h37rv strain is used for the anti-tubercular activity and formulations are evaluated in two concentrations i.e. 100 μl and 300 μl . the result indicates that all formulation active against the h37rv strain, and possess the anti-tubercular activity. the result of screening is tabulated in table no. 7. the formulations f1 was selected for stability studies on the basis of their high cumulative % drug release studies. the stability studies were carried out at $25^\circ\text{c}/60\% \text{rh}$ and $40^\circ\text{c}/75\% \text{rh}$ for all the selected formulations up to 6 months. for every 1 months time interval the tablets were analyzed for *in vitro* disintegration time. these formulations showed not much variation in any parameter. the accelerated stability study shows no degradation in the tablet formulations during study (table no.8). thus, it can be concluded that dispersible

table of rifampicin can be formulated by employing disintegration agents containing disintegrants such as crosscarmellose sodium (ac-di-sol), explotab (ssg), polyplasdone xl. further, long term stability studies and *in-vivo* studies need to be carried out for establishing the existing products.

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