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Design, formulations and *invitro evaluation* of matrix tablets of ethambutol by using sintering technique

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ABSTRACT

Tuberculosis rampant infectious disease is considered to be the foremost cause of death caused by Mycobacterium tuberculi. Ethambutol (400 m g) is a one of the most important "first line" drug recommended by World Health Organization (WHO) for the treatment of tuberculosis. Ethambutol and different proportions of additives were mixed. Tablets containing 400 mg equivalent to Ethambutol were compressed on sixteen punch tableting compression machine. From the invitro dissolution data, it can be concluded that Eudragit RL 100 had retarding capacity of drug from being released. This retardant capacity was more in M**E4 sintered at 5.5 hr** as compared to all other formulations and release kinetics model follows Higuchi diffusion model. The drug release from ME_4 11 hr was found 84.50±0.04 slow as compared with all formulations at all sintering times.

Keywords: Ethambutol, Higuchi diffusion model, Eudragit RL 100.

INTRODUCTION

Drug delivery systems are becoming increasingly sophisticated as pharmaceutical scientist acquires a better understanding of the physicochemical and biological parameters pertinent to their performance. Despite tremendous advancements in drug delivery, the oral route remains the preferred route for administration lead to high levels of patient compliance. Matrix system made of swel lable or non swellable polymers. Slowly eroding devices and osmatically controlled devices. Conventional tablet formulations are still popular in the design of single unit, matrix type controlled release dosage forms. Matrix devices made with cellulose or acrylic acid derivatives, which release the homogeneously dispersed drug based on the penetration of water through the matrix, have gained steady popularity because of their simplicity in design. Tuberculosis (TB) is an infectious disease, caused by several species of Mycobacteria, collectively termed the tubercle bacilli. Tuberculosis is a systemic disease, the commonest form in man being the chronic pulmonary variety; acute fulminating forms such as tuberculosis pneumonia or generalized military tuberculosis can also occur. Tuberculosis can also involve other organs.

MATERIALS

Ethambutol, Eudragit RL 100, Dibasic calcium phosphate , Aerosil, Magnesium stearate, Hydrochloric acid, Sodium hydroxide, Potassium

dihydrogen phosphate, Isopropyl alcohol, Acetone, Calcium chloride.

Equipments

Electronic balance, Bulk density apparatus, Standard sieve (20# and 40#), Sixteen punch tablet compression, Friability apparatus, Hardness tester, Vernier calliper Humidity chamber, USP Tablet dissolution apparatus ,UV-Visible Spectrophotometer, FTIR Spectroscopy, Differential scanning calorimeter.

Approaches for preparation of matrix dosage forms

There are many approaches for preparing matrices for controlled drug delivery.

Sintering

Sintering is defined as the bonding of adjacent particles surface in a mass of powder, or in a compact, by the application of heat. Conventional sintering involves the heating of a compact at a temperature below the melting point of the solid constituents in a controlled environment under atmospheric pressure. Exploration of the sintering concept in the pharmaceutical sciences is relatively recent and research interests relating to this process have been growing. The concept of sintering was applied in the investigation of the effect of heating on the mechanical properties of pharmaceutical powders. The formation of solid bonds with in a powder bed during tablet compression was also studied in terms of sintering. The changes in the hardness and dissolution time of tablet at elevated temperature were described as a result of sintering. Furthermore, the sintering process has been used for the fabrication of sustained release matrix tablet for the stabilization and retardation of drug release.

THEORY OF SINTERING

The principle driving force for sintering is the reduction of total free energy in the system as a result of bonding of particles, void spaces shrinkage and the consequent decrease in total surface area of the compact. Therefore, from the thermodynamic point of view, sintering is a spontaneous process.

SINTERING MECHANISM

Single solid phase

Sintering in solid phase is likely the result of a combination of two or three of these mechanisms.

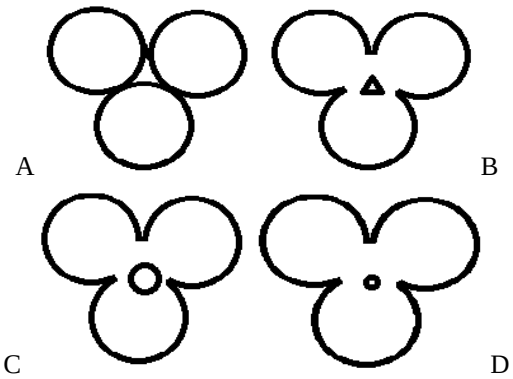
Sintering in the presence of a liquid phase

If the melting point of the components of a system is different, sintering may be facilitated at temperature with the lowest melting point of constituents. The presence of a liquid phase considerably increases the rate of diffusion. The major material transport mechanism is called the heavy alloy mechanism and it can be divided in to three stages.

1) The rearrangement 2) Accommodation and 3) The solid state sintering

Sintering of pharmaceutical compacts

The structural changes within a compact during sintering can be broken down into several stages, some of which may occur virtually simultaneously.



Different Stages in the Sintering of Pharmaceutical Compacts

- Inter particle bonding
- Neck growth.
- Pore-channel closure.
- Pore rounding
- Pore shrinkage

FORMULATION OF SINTERED MATRIX TABLETS

Preparation of Powder Blend

All the ingredients mentioned were weighed and passed through mesh #40 separately. The drug and polymer were blended first in mortar and pestle then the remaining ingredients are added in that and blended for 20 min. Finally the blend was passed through mesh #20 and used for evaluation of flow characteristics.

Composition of Ethambutol Sintered matrix tablet

S. No	INGREDIENTS	ME1	ME2	ME3	ME4
1	Ionized	400	400	400	400
2	Eudragit RL 100	30	50	60	70
3	Sodium Starch Glycolate	15	15	15	15
4	Aerosil	1	1	1	1
5	Dibasic calcium	14	24	14	04
6	Magnesium Stearate	10	10	10	10
	Total	500	500	500	500

*All the quantities are expressed as mg per tablet.

Preparation of Matrix Tablets

Ethambutol and different proportions of additives were mixed .Quantity sufficient for a batch of 40 tablets was mixed thoroughly to ensure complete mixing. Tablets containing 300 mg equivalent to Ethambutol were compressed using 12 mm round, biconcave and plain punches (surface lubricated with magnesium sterate) on sixteen punch tableting compression machine.

Sintering method

The punched tablets were subjected to sintering process. The lower of the dessicator was filled with acetone, closed and kept aside for saturation. After saturation the compressed tablets were taken in petridishes and placed over a wire mesh which was kept above the lower chamber of the dessicator containing acetone. The dessicator was made air tight by closing the lid with the help of wax. The acetone vapors in the saturated dessicator enter the pores of tablets solubilize the surface of the polymer particles which results in fusion of particles, thus bringing about sintering. Tablets of each formulation were divided into '3' batches and exposed to '3' different duration of sintering time (1.5 hr, 3.0 hr, 5.5 hr). After sintering, the tablet were removed from the dessicator, and dried at room temperature for 24 hr to evaporate the adhering acetone and were finally dried in vacuum dessicator at 30^0C over fused calcium chloride to remove the residual acetone from the tablet for 24 hr and stored in dessicator for further studies

EVALUATION OF SINTERED MATRIX TABLETS

The release rate of Ethambutol from tablets was studied using USP Dissolution Testing Apparatus type-I (Basket method). The dissolution test was performed using 900 ml of 0.1N HCl, at 37 ± 0.5°C and 100 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus for 2 hours and the samples were replaced with fresh dissolution medium. Absorbance of these solutions was measured at 340n m using UV-visible spectrophotometer.

Release kinetics

To study the release kinetics of *In-Vitro drug* release, data was applied to kinetic models such as zero order, first order, Higuchi and Korsmeyer-Peppas.

Stability study

In present study the selected formulation M E4 5.5 hr exposure up to 3 months stability studies at accelerated condition (40˚C ±2˚C at 75% RH ±5%RH) to find out the effect of aging on hardness, drug content and *invitro* drug release. Stability studies were carried out at accelerated condition (40˚C ±2˚C at 75%RH ±5%RH) for the optimized formulation M E4 5.5 hr. The tablets were stored at 40˚C±2˚C at 75% RH ±5%RH for accelerated temperature in aluminum pack for 3 months. The samples were withdrawn after periods of 1 month, 2 month and 3 month. The samples were analyzed for its hardness, drug content and *invitro* drug release.

RESULTS AND DISCUSSION

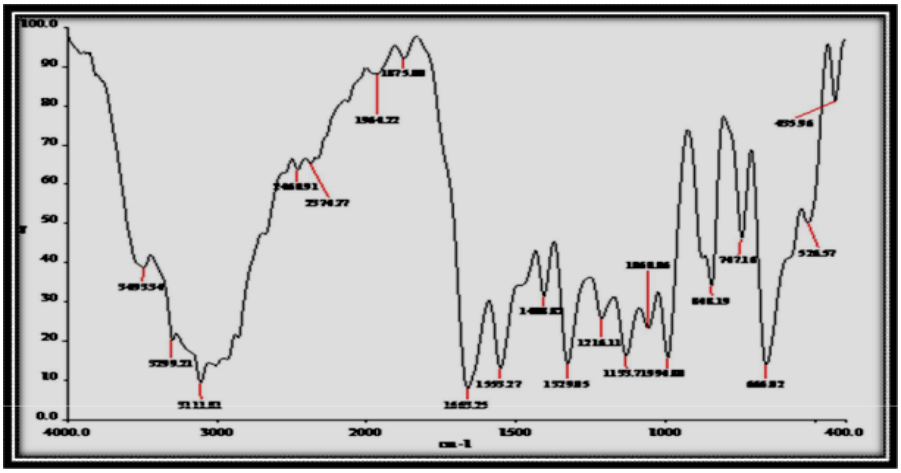
Preformulation studies

Drug-Polymer Compatibility Study

Fourier Transform Infra-Red Spectroscopy (FTIR)

Major peak observed in FTIR spectrum of Ethambutol and Ethambutol with Eudragit RL 100

Wave No. (cm^{-1})	Functional group
3115.77	C-H stretching
1868.98	C=O stretching
1557.41	N-H stretching
1335.42	C=O stretching
1221.28	C=N stretching
1061.77	C-N stretching
995.43	C-C stretching
845.20	C-C stretching
660.45	C-H bending



FTIR spectrum of Ethambutol with Eudragit RL 100

Differential Scanning Calorimetry (DSC) analysis

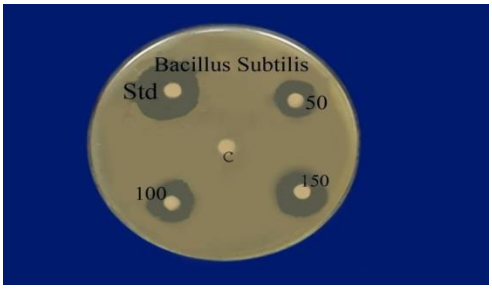
DSC thermogram parameters

S. No.	DSC thermogram of	Onset temperature (°C)	Peak temperature (°C)
1	ETH	170.16	176.80
2	ETH+ Eudragit RL 100	169.75	172.04

Anti-Microbial Assay: Microbial Activity of the Optimized Formulation

S. No.	organism	Zone of inhibition			
		Std	ME4 5.5 Hr		
		µg	50 µg	100 µg	150 µg
	Bacillus subtilis				
1		30	17	23	25

Zone of inhibition of Standard and ME4 sintered at 4.5 hr

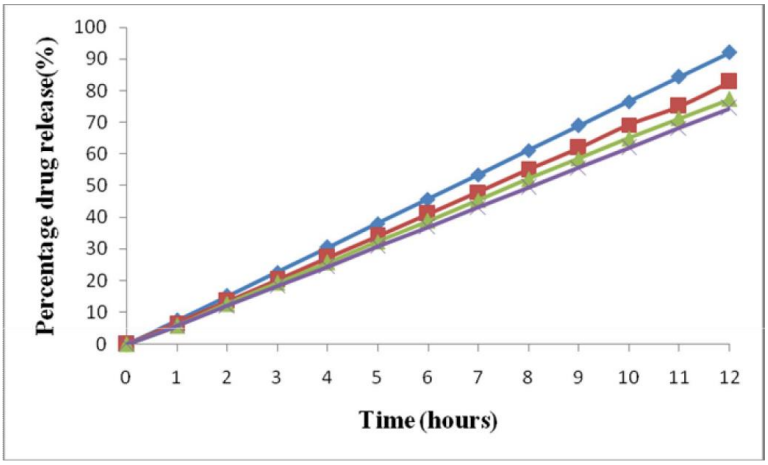


Hence by comparing the Zone of inhibition of formulation ME4 sintered at 5.5 hr with Standard, there found no basic difference in potency. This indicated that there was no degradation of formulation M E4 even sintered at 5.5 hr.

Invitro drug release study

Percentage drug Release in different formulations for different timings

S.NO.	Time (hrs)	Drug release (%)			
		ME1	ME2	ME3	ME4
1	1.5	45±0.04	35±0.09	47±0.03	43±0.06
2	3	56±0.01	49±0.04	49±0.09	48±0.09
3	5	58±0.09	56±0.06	51±0.05	45±0.07
4	6	62±0.04	66±0.04	55±0.03	59±0.04
5	7	65±0.07	76±0.08	59±0.04	62±0.01
6	8	66±0.01	78±0.03	65±0.09	66±0.06
7	9	68±0.02	79±0.07	73±0.02	75±0.05
8	10	71±0.04	81±0.02	76±0.03	79±0.04
9	11	78±0.09	82±0.07	80±0.03	84±0.07



Comparative drug release profile of ME1 ◆; E2 ▬ ; M E 3 △ ; ME4 x at 4.5 hr.

When percentage drug release plotted versus time it was observed that, as increases in polymer concentration and sintering time shows that the decreases in release rate of drug. The drug release from ME4 5.5 hr was found 84.50±0.04 slow as compared with all formulations at all sintering times. That is might be due to increases in hardness of matrix, which retard the drug release from the tablets.

CONCLUSION

Formulation M**E4 sintered 5.5 hr** showed the highest hardness. This was due to increased in sintering time. From the *invitro* dissolution data, it can be concluded that Eudragit RL 100 had capable of retardant the drug from being released. This retardant capacity was more in M**E4 sintered at 5.5 hr** as compared to all other formulations. Release kinetics model showed the drug release from M**E4 sintered at 5.5 hr** follows Higuchi diffusion model. This fact supports the conclusion that the drug was released by a diffusion process. The optimized formulation ME4 **sintered at 5.5 hr** was subjected to stability studies. From the above it was concluded that formulation M**E4 sintered at 4.5 hr** was stable in short term stability study. From the above summary it can be concluded that this type of system provides a simple, convenient and alternative method for achieving controlled release in oral dosage form.

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