STABILITY STUDY OF STAVUDINE SINTERED MATRIX TABLET

Vaibhav Bhamre*1, Dipika Sherkar1, Dilip Derle2, Minal Narkhede1

1Department of Pharmaceutics, M.G.V’s Pharmacy College, Panchavati, Nasik, India
2Department of Pharmaceutics, M.V.P’s College of Pharmacy, Nasik, India

ABSTRACT
Stavudine has half life (t1/2) 1.5 hours; therefore it needs to be frequently administered during therapy which gives patient incompliance. In this study attempt has been done to study effect of three different storage conditions on stability of Stavudine sintered matrix tablet. Tablets were prepared using combination of Eudragit RS 100 (22 - 33 %w/w) and Compritol 888 ATO (9-13 %w/w) by direct compression. The prepared tablets were sintered using 40°C temperature for time period of 4 hrs. Prepared Stavudine sintered matrix tablets are then exposed to refrigerated condition, room temperature and elevated temperature of 60°C for stability study. The unsintered and sintered tablets were evaluated by organoleptic evaluation, drug content, drug release; percent water uptake and percent matrix erosion. Comparison is made in between results of evaluation parameters of unsintered and sintered formulations. It was evident that different storage conditions for identical formulation significantly impact the release profile of drug.

Key words: Stavudine Sintered Matrix Tablet, Refrigerated Temperature, Room Temperature, Elevated Temperature

INTRODUCTION
Stavudine, 2',3'-Didehydro-3',deoxythimidine(d4T)1-2 is a thymidine analogue3-4 approved for treatment of HIV infection6-8. Stavudine triphosphate, an active metabolite inhibits the HIV reverse transcriptase by competing with natural substrate, thymidine triphosphate. It also causes termination of DNA synthesis by incorporating into it9. Converting twice daily into once daily improves adherence and therefore enhances effectiveness of antiretroviral therapy. Sintering is defined as the bonding of adjacent particle surfaces in a mass of powder or in a compact by application of heat10. 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 pressure11. The sintering process has been used for the fabrication of sustained release matrix tablets for the stabilization and retardation of the drug release12. However, the actual sintering kinetics of particulate body is determined not only by the properties of the particles themselves and the nature of their local interaction with each other, but also by macroscopic factors13.

It is evident that there is a moisture dependant amorphous to-crystalline transformation is possible for the solid state. In the presence of a relative humidity of greater than 30%, the amorphous form transforms to the hydrate of Stavudine, whereas during exposure to only temperature, it transforms to form II (anhydrous). This is a significant observation, since it implies that the presence of traces of amorphous Stavudine in commercial products can lead to possible instability due to the formation of the hydrate of Stavudine, which could lead to increased degradation by hydrolysis14,15. It is thus imperative to prevent the possible accidental formation of amorphous Stavudine during the various stages of large-scale manufacturing, as this could adversely affect the shelf life of the dosage form16.

In this study we studied the preparation and stability of Stavudine Sintered Matrix Tablet at different conditions of storage.

MATERIAL AND METHOD
Material
Stavudine (215.5mg), Eudragit RS 100 (22 - 33 %w/w) and Compritol 888 ATO (9-13 %w/w) were used for formulation. Stavudine (STV) was obtained as a gift sample from Matrix Laboratories Ltd, Sinner. Compritol 888 ATO and Eudragit RS 100 were obtained as a gift sample from Glenmark Pharmaceutical Ltd, Sinner. All the other reagents were used are of laboratory grade.

Method
Direct Compression17,18
STV was mixed with excipient (except lubricant) by geometric mixing in a polyethylene bag for 10 min in proportion. Then lubricant was added and mixed for an additional 5 min and the final blend of 440 mg was directly compressed using 12 mm punches on a rotary tablet compression machine Hardness of tablets was kept to 5-6 kg/cm².

Sintering19,20
Prepared tablets were then proceeds for sintering by Heat treatment subjecting to thermal treatment by placing on aluminum foil and sintering is carried out at 40°C for 4 hr in hot air oven. The directly compressed tablets so prepared after sintering are termed as Sintered Matrix Tablet.

Stability Study21,22
Stability study has been carried out by packing tablets in aluminum foil and exposing unsintered (Unsint) and sintered tablets (Sint) to refrigerator temperature (RF), room temperature (RT) and elevated temperature (ET) of 60°C for 12 months. Tablets were withdrawn in four stages i.e. pre exposure, after 3 months, after 6 months and after 12 months. Withdrawal tablets were then evaluated for organoleptic evaluation, drug content, drug release; percent water uptake and percent matrix erosion.

Evaluation23-28
Organoleptic Properties
Organoleptic properties of tablet like color, was evaluated for unsintered and sintered tablet at four stages as mentioned above for each storage condition.

Drug Content
Five tablets were weighed and powdered, dissolved in pH 7.4 phosphate buffer and volume adjusted upto 200 ml, filtered. 1
ml was withdrawn and diluted to 25 ml with solvent. Absorbance was recorded at 266 nm.

**In vitro Drug release**

Unsintered and sintered tablet drug release study was carried for 12 hrs in 0.1 N HCl for first two hrs and then placed in phosphate buffer pH 7.4 at 37°C at 100 rpm. At regular interval sample were withdrawn for 1 hour and the same volume of fresh dissolution medium was replaced to maintain the volume constant. The withdrawn samples were filtered and concentration of drug present in the samples was calculated with the help of calibration curve constructed. It is expected that there should be sustain release of drug from tablet on storage for varying time period.

**Percent Water uptake**

Previously weighed 20 tabs were kept in pH 7.3 phosphate buffer for 24 hrs. After 24 hrs these tabs were again weighed and kept for drying. Percent water uptake was calculated using these weights in the following formula as,

\[
\% \text{ water uptake} = \left(\frac{\text{wet wt} - \text{remaining dry wt.}}{\text{remaining dry wt.}}\right) \times 100
\]

Percent water uptake is a test that verifies drug release i.e. more the percent water uptake more will be the drug release.

**Percent matrix erosion**

Same procedure was carried as for the % water uptake and following formula was used to calculate % erosion

\[
\% \text{ erosion} = \left(\frac{\text{original wt} - \text{remaining dry wt.}}{\text{original wt}}\right) \times 100
\]

Percent matrix erosion is directly proportional to drug release. In case of matrix tablet drug release takes place by erosion or diffusion of matrix so retardation in matrix erosion will lead to retardation in drug release.

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<th>Table 1: Organoleptic property of unsintered and sintered tablet</th>
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<th>Table 2: Drug content in unsintered and sintered tablet</th>
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Fig 1: Drug release profile for Tablet stored at refrigerated temperature

Fig 2: Drug release profile for Tablet stored at room temperature

Fig 3: Drug release profile for Tablet stored at elevated temperature

Fig 4: Percent water uptake of Stavudine sintered Matrix Tablet at different storage condition
RESULT AND DISCUSSION

Organoleptic Property (Color)

From table 1 it is observed that unsintered and sintered tablet shows no color change for maximum period of 6 months at room temperature and 3 months in refrigerator condition. It means that Stavudine remains stable for maximum period of 6 months in both formulations at room temperature and 3 months in refrigerator condition but unstable on storage for 12 months and 6 months respectively i.e. degradation of drug takes place in case of Stavudine in sintered matrix tablet stored for 12 months at room temperature and 6 months at refrigerator condition. Color change occur in other two conditions indicate that Stavudine in Sintered Matrix Tablet is stable for 3 months only at refrigerator condition but storage of same at elevated temperature shows instability within 3 months.

Drug content

From table 2 it is observed that drug content is 98.7% in unsintered formulation and remains equivalently same i.e. 98.6% in sintered formulation. When both these formulation are exposed to different storage conditions for different time period then drug content remains with change in acceptable limit of 5% in case of storage at room temperature for 6 months and storage at refrigerated condition for 3 months.

That is maximum bioavailability can be obtained in Stavudine Sintered Matrix Tablet stored at room temperature for 6 months and 3 months in refrigerated condition for 3 months.

Drug Release

Drug release study was carried using USP dissolution apparatus II for 12 h unsintered and sintered formulation stored at different conditions for varying time period. Diagrammatic representation of percent drug release Vs Time has been shown in following figures from 1 to 3. From fig 1 to 3 it is observed that unsintered and sintered tablet at pre exposure condition shows sustain release of drug. On storage of prepared tablet to various conditions for varying time period drug release was found to be decreased except in case of storage at refrigerated condition for 3 months and at room temperature for 6 months i.e. stability of Stavudine Sintered Matrix Tablet remain unaffected during this period of storage.

Percent Water Uptake

From fig 4 it is observed that in case of unsintered tablet percent water uptake is more and comparatively less in sintered tablet; this is due to sintering of a tablet by heat treatment. Sintering is responsible for retardation in drug release i.e. retardation in percent water uptake.

As shown in fig 4 proper correlation lies for storage at room temperature for 6 months and storage at refrigerated condition for 3 months between percent water uptake of unsintered and sintered formulation. On storage at higher temperature bonding between drug – polymer disturbs and thus result in quick absorption of water and rapid drug release and inverse in refrigerated condition that the bonding shrinks and extra retardation in drug release.

Percent Matrix Erosion

From fig 5 it is observed that retardation or increase in rate of matrix erosion equalizes the results in percent water uptake i.e. higher the percent water uptake, higher will be the matrix erosion thus more will be the drug release and visa versa.

CONCLUSION

From all above study and its evaluation with mentioned parameter it is concluded that storage condition and period of storage profoundly influences on stability of prepared Stavudine Sintered matrix Tablet. Prepared Stavudine Sintered matrix tablet passes stability test on storage for 3 months at refrigerated condition and 6 months for room temperature. Stability of Prepared Stavudine Sintered matrix tablet is confirmed by feeding drug release data to data analysis and it is observed that tablet possesses Matrix as a release model and diffusion is the mechanism of drug release.

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