INTERNATIONAL RESEARCH JOURNAL OF PHARMACY

www.irjponline.com ISSN 2230 – 8407

Research Article

STABILITY STUDY OF STAVUDINE SINTERED MATRIX TABLET

Vaibhav Bhamre*[1], Dipika Sherkar[1], Dilip Derle[2], Minal Narkhede[1]

[1]Department of Pharmaceutics, M.G.V's Pharmacy College, Panchavati, Nasik, India

[2]Department of Pharmaceutics, M.V.P's College of Pharmacy, Nasik, India

Article Received on: 03/11/12 Revised on: 11/12/12 Approved for publication: 23/12/12

*Email: vaibhav.bhamre@gmail.com

ABSTRACT

Stavudine has half life ($t_{1/2}$) 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 40^0 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 60^0C 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 analogue[3-5] approved for treatment of HIV infection[6-8]. 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 it[9]. 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 heat[10]. 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[11]. The sintering process has been used for the fabrication of sustained release matrix tablets for the stabilization and retardation of the drug release[12]. 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 factors [13].

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 hydrolysis[14,15]. 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 form[16].

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 Compression[17,18]

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/cm^2.

Sintering[19,20]

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° for 4 hr in hot air oven. The directly compressed tablets so prepared after sintering are termed as Sintered Matrix Tablet.

Stability Study[21,22]

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 60^0c for 12 months. Tablets were withdrawn in four stages i.e. pre exposure, after 3 months, after 6 months and after 12 months. Withdrawed tablets were then evaluated for organoleptic evaluation, drug content, drug release; percent water uptake and percent matrix erosion.

Evaluation[23-28]

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 following formula as,

% water uptake = [(wet wt – remaining dry wt.) / remaining dry wt.] X 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

% erosion = [(original wt – remaining dry wet) / original wt] X 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.

Table 1: Organoleptic property of unsintered and sintered tablet

Storage Condition	Formulation Code	Period (Month)			
		0	3	6	12
Refrigerator Temp	Unsintered	White	White	White	Dull
	Sintered	White	White	Dull	Blackish
Room Temp.	Unsintered	White	White	White	White
	Sintered	White	White	White	Yellowish
Elevated Temp	Unsintered	White	Yellowish	Yellow	Blackish
	Sintered	White	Yellow	Blackish	Blackish

Table 2: Drug content in unsintered and sintered tablet

Storage Condition	Formulation Code	Drug content (%) for Period (Month)			
		0	3	6	12
Refrigerator Temp	Unsintered	98.9	98.9	87	71
	Sintered	98.6	96.3	81	68
Room Temp.	Unsintered	98.9	98.7	95.6	87.4
	Sintered	98.6	98.3	94.7	82.6
Elevated Temp	Unsintered	98.9	85	63.5	43.1
	Sintered	98.6	81	61.8	41.8

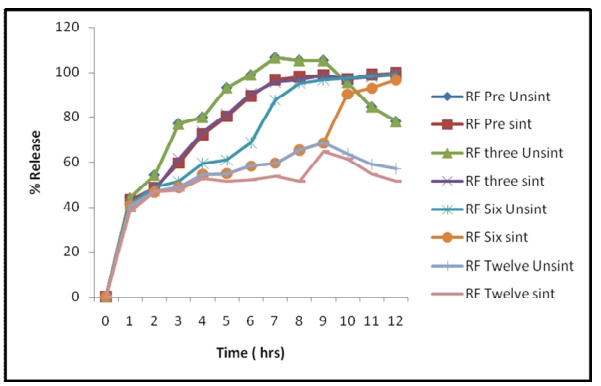

Fig 1: Drug release profile for Tablet stored at refrigerated temperature

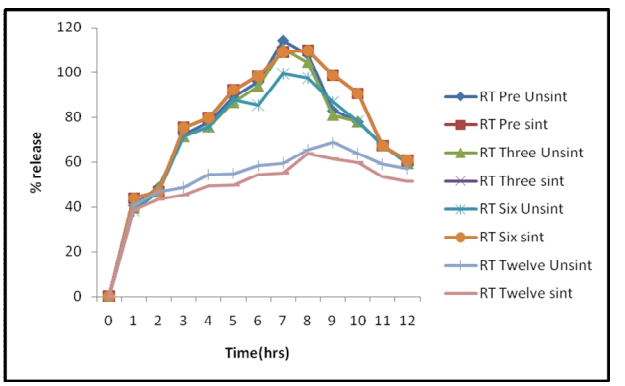

Fig 2: Drug release profile for Tablet stored at room temperature

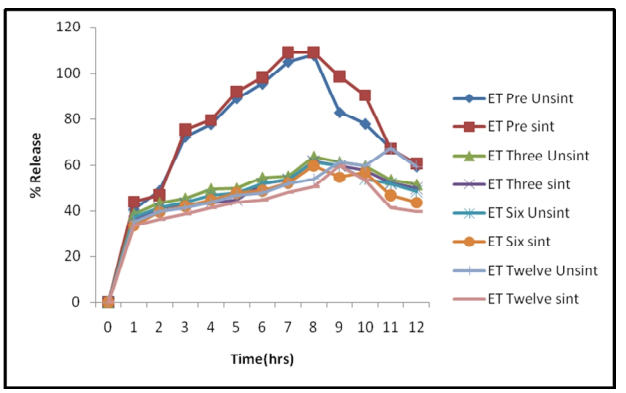

Fig 3: Drug release profile for Tablet stored at elevated temperature

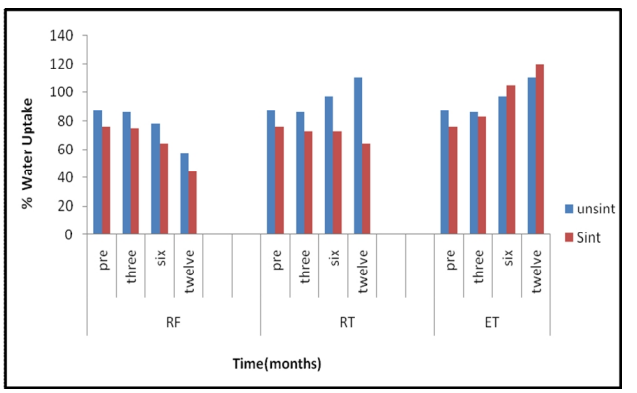

Fig 4: Percent water uptake of Stavudine sintered Matrix Tablet at different storage condition

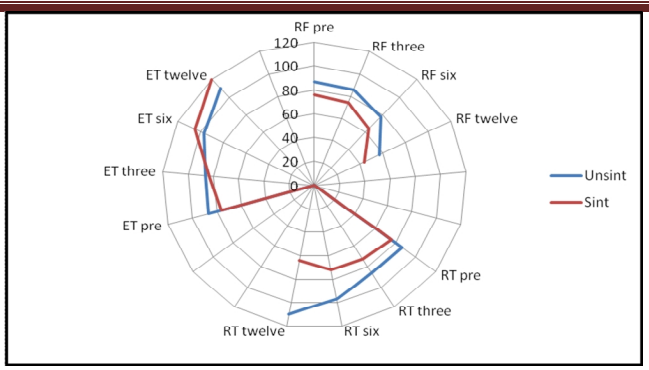

Fig 5: Radar diagram for percent matrix release of unsintered and sintered matrix tablet.

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 equalize 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 vice 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.

ACKNOWLEDGEMENT

Author greatly acknowledge to Dr. R. S. Bhambar, Principal M.G.V's Pharmacy College Panchavati Nasik for his kind help and support and also to Matrix Lab India, Sinner and Glenmark Pharmaceuticals for providing drug and polymers.

REFERENCES

1. The Merck index- An encyclopedia of chemicals, drugs and biological. 13th edition. Published by Merck Research Laboratories. Merck Index No 8881.
2. Anthony C Moffat, M. David Osselton, Pvian Widdop. Clarke Analysis of Drug and Poison. Pharmaceutical Press Publication.3rd edition. Pg 1569-1570.
3. J.P. Horwitz et al. Cyclic saligenyl phosphotriesters of 2', 3'-dideoxy-2', 3'-didehydrothymidine (d4T)--a new pro-nucleotide approach 1. Eur J Org Chem 1996; 31: 205
4. Stavudine: From Wikipedia, the free encyclopedia.
5. The Indian Pharmacopoeia. Government of India Ministry of Health and Family Welfare. 3rd vol. Published By the Indian Pharmacopoeia Commission Ghaziabad, 2007:1745-1747.
6. Oral account of the history of AZT, d4T and ddC by Jerome Horwitz and Hiroaki Mitsuya in the documentary film I am alive today - History of an AIDS drug.
7. Richard Finkel, Luigi X. Cubeddu, Michelle A. Clarke. Pharmacology. 4th edition. Lippincotts Illustrated Reviews. Lippincott Williams and Wilkins Publication. 447 – 448.
8. Riddler SA, Anderson RE, Mellors JW. Antiretroviral activity of Stavudine. Antiviral Res. 1995; 27:189-203.
9. KD Tripathi. Essentials of Medical Pharmacology. 5th edition. Jaypee Brothers Medical Publishers (P) Ltd, New Delhi.2004:729.
10. Luk C.L., Jane H.L., Swarbrick J., Boylan J. C. Sintering in pharmaceutics. Vol 2. Encyclopedia of Pharmaceutical Technology. Marcel Dekker Publication, New York. 2002: 87–101.

11. Lian-Dong Hu, Yang Liu, Xing Tang, Qian Zhang. Preparation and in vitro/in vivo evaluation of sustained-release metformin hydrochloride pellets. Eur J Pharm Biopharm 2006;64: 185–192.
12. Michael M. Crowley, Britta Schroeder, Anke Fredersdorf, Sakae Obara , Mark Talarico , Shawn Kucera, James W. McGinity . Physicochemical Properties and Mechanism of Drug Release from Ethyl Cellulose Matrix Tablets Prepared by Direct Compression and Hot-melt Extrusion. Int J Pharm 2044; 26:509–522.
13. Eugene A. Olevsky. Theory of sintering: from discrete to continuum. Mater Sci Eng R23; 1998:41–100.
14. Gandhi, R.B., Bogardus, J.B., Bugay, D.E., Perrone, R.K., Kaplan, M.A.,. Pharmaceutical relationships of three solid state forms of Stavudine. Int J Pharma 2000; 201:221–237.
15. Mirmehrabi, M., Rohani, S., Murthy, K.S.K., Radatus, B. Polymorphic behavior and crystal habit of an anti-viral/HIV drug: stavudine. Crystal Growth Des 2006;6:141–149.
16. Schalk Strydom, Wilna Liebenberg, Lian Yu, Melgardt de Villiers. The effect of temperature and moisture on the amorphous-to-crystalline transformation of Stavudine. Int J Pharm 2009; 379:72–81.
17. B. Sreeneevasa Rao et al. Design and Evaluation of Ethylene Vinyl Acetate Sintered Matrix Tablet. Indian J Pharm Sci 2003; 65:496-502.
18. Monica R. P. Rao, Anuradha A. Ranpise, K. C. Thanki, S. G. Borate, and G. N. Parikh. Effect of Processing and Sintering on Controlled Release Wax Matrix Tablets of Ketorolac Tromethamine. Indian J Pharm Sci. 71(5). Pg 538–544.
19. B. Sreeneevasa Rao et al. Design and Evaluation of Ethylene Vinyl Acetate Sintered Matrix Tablet. Indian J Pharm Sci. 2003; 65: 496-502.
20. B. Sreeneevasa Rao et al. Studies on Release of Rifampicin from Sintered Matrix Tablet. Indian J Pharm Sci 2001;63(5):371-378
21. Monica Rao, Anuradha Ranpise, Sameer Borate, and Kaushik Thanki. Mechanistic Evaluation of the Effect of Sintering on Compritol® 888 ATO Matrices. AAPS Pharm Sci. 10(2): 355–360.
22. Dhirendra Kumar,Vivek Dave, Shaila Lewis, Brajesh Parmar, Kavita R. Gajbhiye,, Sarvesh Paliwal. Design and evaluation of sustained-release matrix once daily formulation of Stavudine. Int J Drug Del 2:125-134.
23. Kiran D Wagh, K Sundaramoorthy, T Vetrichelvan. Formulation and in vitro evaluation of stomach specific drug delivery system of Stavudine. Res J Pharm Biol Chem Sci 1(4):240-251
24. Hamdy Abdelkader, Ossama Youssef Abdalla and Hesham Salem. Formulation of Controlled-Release Baclofen Matrix Tablets II: Influence of Some Hydrophobic Excipients on the Release Rate and In Vitro Evaluation. AAPS Pharm Sci Tech, 9(2): 675-683
25. K. Prakash, P. Narayana Raju,K. Shanta Kumari And M. Lakshmi Narasu. Solubility and Dissolution Rate Determination of Different Antiretroviral Drugs in Different pH Media Using UV Visible Spectrophotometer. E-Journal of Chemistry. 5(S2):1159-1164.
26. D.Nagaswamy Venkatesh, S.Sangeetha, M.K.Samanta, S.Sankar, and B.Suresh. Design and Evaluation of Ethyl Cellulose Sustained Release Matrix Tablets of Theophylline. Int. J Pharm Sci Nanotech 1(1):60-63.
27. S H Lakade and M R Bhalekar. Formulation and Evaluation of Sustained Release Matrix Tablet of Anti-Anginal Drug. Influence of Combination of Hydrophobic and Hydrophlic Matrix Former. Res J Pharm Tech. 1(4):410-413.
28. Patil S. V., Kuchekar B. S., Janugade B.U., Lade P. D. In Vitro Studies of Stavudine Sustained Release from Hydrophilic Matrices. J Pharm Res. 2(12): 1855-1856.

Source of support: Nil, Conflict of interest: None Declared