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Research Article

SUSTAINED RELEASE OF STAVUDINE FROM DIFFERENT POLYMER MATRICES

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Abstract:

AIDS is considered to be an epidemic and according to recent estimates 40 million adults and 2.5 million children are living with the human immunodeficiency virus (HIV). India is the second largest burden of HIV infected persons. The major drawbacks of antiretroviral drugs for the treatment of AIDS are their adverse side effects during long-term therapy, poor patient compliance, and their huge cost. Sustained release formulations are preferred for such therapy because they maintain uniform drug levels, reduce dose and side effects, better patient compliance, and increase safety margin for high potency drugs. The present study was proposed to evaluate the suitability of Guargum & SCMC as polymeric materials for matrix tablets able to adequately extend drug release. The effect of polymer concentration and its type on various physicochemical properties and the drug release behavior from the matrices was also examined. A non-aqueous granulation process was adopted to prepare Stavudine tablets utilizing Guar gum and SCMC as polymers. Drug content was found to be uniform among different formulations of the tablets and ranged from 98.95±0.184% to 99.15±0.121 %. The regression coefficients obtained for first order kinetics were found to be $R^{2 =}$ 0.9705 to 0.9895, indicating that drug released from all the formulations followed first order kinetics. The study suggests that a controlled release matrix tablet of Stavudine with a natural polymer matrix would be promising for therapy of AIDS by minimizing the side effects of the synthetic polymers.

Keywords: Sustained release, Stavudine, guargum, non-aqueous granulation.

Introduction

AIDS is considered to be an epidemic and according to estimates from the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) AIDS Epidemic Update 2005, 40 million adults and 2.5 million children are living with the human immunodeficiency virus (HIV). India is the second largest burden of HIV infected persons. One of every six persons is affected with HIV infections in India[1].HIV is human immunodeficiency virus. It is the virus that can lead to acquired immune deficiency syndrome (AIDS).

Among various dosage forms, matrix tablets are widely accepted for oral sustained release (SR) as they are simple and easy to formulate. Matrix system is the release system, which prolongs and controls the release of drug that is dissolved or dispersed. Sustained release formulations are preferred for such therapy because they maintain uniform drug levels, reduce dose and side effects, better patient compliance, and increase safety margin for high potency drugs.

The objective of the present work was to develop sustained release matrix tablets of Stavudine using natural & semi-synthetic polymers. It was also proposed to evaluate the suitability of Guargum & SCMC as polymeric materials for matrix tablets able to adequately extend drug release. The effect of polymer concentration and its type on various physicochemical properties and the drug release behavior from the matrices was also examined.

Materials and methods:

The materials used like Poly Vinyl Pyrollidine, Magnesium stearate, Talc, Poly Vinyl Alcohol, Micro crystalline cellulose were of pharma & laboratory grade.

Standard curve for Stavudine:

Standard curve for Stavudine was plotted both in 0.1N Hcl as well as in Phosphate buffer pH-7.4 and estimated under UV spectrophometer at 266nm.

Pre-compression studies

Angle of repose: The angle of repose was determined by the funnel method. The accurately weighed powder blend was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the

apex of the heap of the powder blend. The blends were allowed to flow freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.[2]

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

Where 'h' and 'r' are the height and radius of the powder cone respectively.

Compressibility index: To calculate the Carr's compressibility both loose bulk density (LBD) and tapped bulk density (TBD) was determined. A quantity of 2 g of powder from each formula, previously lightly shaken to break any agglomerate formed, was introduced into a 10ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2-second intervals. The tapping was continued until no further change in volume was noted. LBD and TBD was calculated and used to calculate the Carr's index and hausner's ratio.

LBD= weight of the powder / volume of the packing.

TBD = weight of the powder / tapped volume of the packing.

The compressibility index of the powder blend was determined by Carr's compressibility index.[3]

Carr's index (%) = [(TBD-LBD) x 100]/TBD

Hausner's ratio: This value was calculated by making use of bulk and tap densities of powder samples.[4]

Hausner's ratio = TBD/LBD

Drug content: An accurately weighed amount of powder blend (100 mg) was extracted with water and the solution was filtered through 0.45-µ membrane. The absorbance was measured at 266 nm after suitable dilution.[4]

Preparation of matrix tablets: [2]

A non-aqueous granulation process was adopted to prepare Stavudine tablets. Granules were prepared as follows. Suitable proportion of excipients with drug was taken as given in Table 2. All ingredients were sifted through sieve no: 40. Guar gum was mixed with Stavudine manually and the obtained blend was mixed with Micro crystalline cellulose to form final blend. PVP K-30 was dissolved in PVA (5% w/v) and used for wet granulation of the final blend. The wet mass was passed through sieve no. 20 and wet granules dried at 50°C in an oven for 30 minutes.

Dried granules were sized by passing it through sieve no. 40 and mixed with Magnesium stearate and talc for 1 minute and compressed into tablets. Tablet weight was (300mg) kept constant as shown in Table 1.

Table-1: Total weight of the tablet - 220mg

Ingredients (mg/tablet)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Stavudine	80	80	80	80	80	80
P.V.P	06	06	06	06	06	06
Guar gum	40	80	120	--	--	--
SCMC	--	--	--	40	80	120
Micro crystalline cellulose	88	48	08	88	48	08
Magnesium Stearate	03	03	03	03	03	03
Talc	03	03	03	03	03	03

Table-2: Pre-Compression Parameters.

F. code	Angle of Repose (q)	Bulk Density	Tap Density	Compressibility index (%)	Hausner's ratio	% Drug Content
F1	24.29 ±1.29	0.2762 ±0.008	0.3250 ±0.008	15.02±0.81	1.177±0.011	99.36±0.304
F2	24.38 ±1.52	0.2738 ±0.011	0.3220 ±0.017	14.92±1.12	1.175±0.015	99.19±0.069
F3	29.20 ±1.86	0.2622 ±0.015	0.3145 ±0.021	16.59±0.97	1.199±0.014	99.21±0.185

F4	26.36 ±1.73	0.2287 ±0.009	0.2591 ±0.014	11.71±1.56	1.133±0.020	99.27±0.121
F5	27.35 ±1.32	0.2154 ±0.006	0.2467 ±0.007	12.67±0.58	1.145±0.008	99.15±0.209
F6	28.64 ±1.58	0.2119 ±0.006	0.2407 ±0.005	11.98±1.58	1.136±0.021	99.36±0.304

Evaluation of tablets:

All prepared matrix tablets were evaluated for its uniformity of weight, hardness, friability and thickness according to official methods. The weight variation was determined by taking 20 tablets using an electronic balance. Tablet hardness was determined for 10 tablets using a Monsanto tablet hardness tester. Friability was determined by testing 10 tablets in a friability tester for 4 minutes at 25 rpm.

Drug content:

Five tablets were powdered in a mortar. An accurately weighed quantity of powdered tablets (100 mg) was extracted with pH 7.4 buffer and the solution was filtered through 0.45 μ membranes. The absorbance was measured at 266 nm after suitable dilution.[4]

In vitro release study:

The in vitro dissolution studies were carried out using USP XXVII Dissolution apparatus at 50 rpm. For the first 2 hr the dissolution medium was 0.1 N hydrochloric acid and phosphate buffer pH 7.4 from 3-24 hr (900 ml), maintained at 37˚C±0.50˚C. At each time point 5 ml of sample was withdrawn and it was replaced with 5 ml of fresh medium. The drug release at different time interval was measured by UV-visible spectrophotometer. The release studies were conducted in triplicate, and the mean values were plotted versus time.[5]

Stability Studies:

The formulations were subjected to stability studies at 40 ± 2^0C and 75 ± 5 % RH for period of three months. After each month tablet samples were analyzed for physical characteristics and drug release profile.

Characterization of Release Kinetics:

To study the release kinetics, data obtained from in vitro drug release studies were plotted in various kinetic models: zero order as cumulative amount of drug release Vs Time, First order as log cumulative percentage of drug remaining Vs time, and Higuchi's model as cumulative percentage of drug released vs. square root of time.

$$C=K_o\ t \quad \text{..... (1)}$$

Where K_0 is the zero order rate constant expressed in units of concentration/time and t is the time in hours. A graph of concentration vs. time would yield a straight line with a slope equal to K_0 and intercept the origin of the axes.

$$\text{Log } C = \log C_o - Kt/2.303 \quad \text{..... (2)}$$

Where C_0 is the initial concentration of drug, *k* is the first order constant, and t is the time.

$$Q = kt^{1/2} \quad \text{..... (3)}$$

Where *K* is the constant reflecting the design variables of the system and *t* is the time in hours. Hence, drug release rate is proportional to the reciprocal of the square root of time.

Kinetic analysis: 6,7

The results of in vitro release profile obtained for all the formulations were plotted in models of data treatment as follows:-

1. Zero- order kinetic model- cumulative % drug released versus time.
2. First- order kinetic model-Log cumulative percent drug remaining versus time.
3. Higuchi's model- cumulative percent drug released versus square root of time.
4. Korsmeyer equation / Peppa's model- Log cumulative percent drug released versus log time.

Zero order kinetics:

Zero order release would be predicted by the following equation

$$A_t=A_o-K_o$$

Where,

A_t= Drug release at time‘t’

A_o=Initial drug concentration.

$K_{O=}$Zero-order rate constant (hr^{-1})

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys Zero-order release kinetics, with a slope equal to k^o.

First order kinetics:

First-order release would be predicted by the following equation

$$\textbf{Log C= log } C_o\textbf{-}k_t\textbf{/2.303}$$

Where,

C = Amount of drug remained at time‘t’.

C_o= Initial amount of drug.

K = first- order rate constant (hr^{-1}) X

When the data is plotted as lo cumulative percent drug remaining versus time yields a straight line, indicating that the release follow first order kinetics. The constant ‘K’ can be obtained by multiplying 2.303 with the slope values.

Higuchi’s model:

Drug release from the matrix devices by diffusion has been described by following Higuchi’s classical diffusion equation.

$$\textbf{Q = [D□/□ (2A-□Cs)Cst]}^{1/2}$$

Where,

Q = Amount of drug release ant time‘t’

D = Diffusion coefficient of the drug in the matrix.

A = Total amount of drug in unit volume of matrix.

Cs= the solubility of the drug in the matrix.

T = Tortuosity.

P = Porosity of the matrix.

When the data is plotted according to equation i.e. cumulative drug release versus square root time yields a straight line, indication that the dru was released by diffusion mechanism. The slope is equal to 'k'.

Korsmeyer equation/ Peppa's model.

To study the mechanism of drug release from the sustained-release matrix tablets of stavudine, the release data were also fitted to the well-known exponential equation, which is often used to describe the drug release behavior from polymeric systems.

$$\mathbf{M_t/M_a=Kt^n}$$

Where,

M_t/M_a= the fraction of drug released at time't'.

K = Constant incorporating the structural and geometrical characteristic of the drug / polymer system.

n = Diffusion exponent related to the mechanism of the release.

Results & Discussion

Pre-compression Studies: The results of the various pre-compression evaluations were obtained as shown in Table-2.

The results of angle of repose and compressibility index (%) ranged from (24.29 ± 1.29 to 29.20 ± 1.86) and (11.71 ± 1.56 to 16.59 ± 0.97) respectively. The results of loose bulk density and tapped bulk density ranged from (0.2119±0.006 to 0.2762±0.008) and (0.2407±0.005 to 0.3250±.008) respectively. The results of angle of repose (< 30) indicate good flow properties of granules. This was further supported by lower compressibility index values.

Post – compression studies: The physical appearance, tablet hardness, friability, weight variation, and drug content uniformity of all tablet formulations were found to be satisfactory and reproducible as observed from the data in Table. Tablet hardness was found to be good (between 6.82 ± 0.12 to 7.34 ± 0.32 kg/cm$^{2)}$ depending on the compression force applied.

The percentage friability of the tablets of all the formulations ranged from (0.079 to 0.139 %), which is less than 0.5% (wt/wt) indicating that the friability is within the prescribed limits.

Weight variation results of matrix tablets ranged from to 220.04 to 220.94mg.For weight variation test, the pharmacopoeial deviation for tablets of more than 220 mg is ± 5%.The average percentage deviation of all tablet formulation was found to be within the above limit, incompliance with official standards.

Drug content was found to be uniform among different formulations of the tablets and ranged from 98.95±0.184 to 99.15±0.121 % indicating that the compression method utilized is an acceptable method for preparing good-quality matrix tablets of Stavudine.

In-vitro Dissolution Studies:

The cumulative percentage drug release from the formulations F1, F2, F3, F4, F5, and F6 were found to be 97.91±0.65%, 98.61±0.80%, 87.34±0.65%, 91.02±0.10%, 92.91 ±0.53%, 94.02±0.10% respectively. It was observed that all the formulation had been showing sustained release of the drug. In general, it can be observed that better release of the drug was seen from all the formulations. From results of *in vitro* dissolution studies, it can be concluded that the formulation F-2 (with Guargum) & F-6 (with SCMC) had better-sustained release than the other formulations with the same polymers.

Among all the formulation, F2 shows highest drug release (98.61%) in 16 hrs; whereas the drug release from other formulations was slow. This shows that Guargum is less permeable. The release rate of the drug could be extended by varying the polymer concentration. The data clearly indicate the drug release can be effectively controlled by varying the polymer and its ratio.

Kinetic studies:

The kinetic data for all the formulations is shown in Table-4. The regression coefficients obtained for first order kinetics were found to be $R^{2\,=}$ 0.9705 to 0.9895, indicating that drug released from all the formulations followed first order kinetics. Based on these release exponent values we can say that the formulations exhibited non-fickian transport. The linearity of the plots indicates that the release process is diffusion-controlled.

Stability studies:

The stability studies were performed according to ICH guidelines for 3 months and the results of the various physicochemical evaluations & dissolution studies were found to be stable in the storage period.

Table-3: Post Compression Studies.

Formulation Code	Hardness Kg\cm^2	Friability (%)	Tablet weight(mg)	% Drug Content
F1	7.02 ± 0.13	0.120	220.94	99.11±0.185
F2	6.82 ± 0.12	0.039	220.21	99.15±0.121
F3	6.88 ± 0.20	0.080	220.45	99.07±0.304
F4	7.34 ± 0.32	0.079	220.81	99.19±0.185
F5	7.22 ± 0.18	0.099	220.04	98.95±0.184
F6	7.16 ± 0.14	0.139	220.05	99.19±0.304

Table-4: Kinetic data obtained from different formulations.

Formulation	Zero order	First order	Higuchi	koresmeyer
F1	0.9439	0.9747	0.9596	0.9260
F2	0.9260	0.9705	0.9883	0.9899
F3	0.9134	0.9817	0.9816	0.9661
F4	0.8656	0.9804	0.9842	0.9874
F5	0.8978	0.9895	0.9922	0.9875
F6	0.977	0.9865	0.9917	0.7176

Conclusion

From the observations of the said work it could be concluded that both the polymers (guar gum and sodium carboxy methyl cellulose) were successful in the formation of matrix and at the same time effective in retarding the drug release. The drug release follows first-order kinetics. The mechanism of drug release was diffusion coupled with erosion. In conclusion it could be suggested that a controlled release matrix tablet of Stavudine with a natural polymer matrix would be promising for therapy of AIDS by minimizing the side effects of the synthetic polymers. A further detailed study in human subjects will through more light on their efficacy and compliance.

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