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FORMULATION AND EVALUATION OF SUSTAIN RELEASE MATRIX TABLET OF STAVUDINE

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ABSTRACT

The sustained release matrix tablet of Stavudine was prepared by direct compression method using hydrophilic HPMC K4M, carbopol 934P and hydrophobic Eudragit RSPO polymers. The release of Stavudine from matrix tablet can be controlled by changing type of polymer or by its concentration. As the concentration of hydrophilic polymers increased the drug release rate from matrix tablet were decreased. By increasing concentration of Eudragit RSPO in formulation, the drug release rate also increased. In vitro release data fitted into Hixson-Crowell kinetic model suggest that the highest correlation coefficient was showed by F5 and F6 formulation batches, but present cumulative drug release for F5 was found to be 95.64% and percent cumulative drug release for F6 was found to be 92.67% as the percent cumulative drug release of F5 was higher than F6. Hence, F5 selected as an optimized batch. Optimized batch F5 were stable at the selected temperature and humidity in storage for 28 days. The best fit model was Hixson-Crowell model followed by Korsmeyer peppas, Higuchi model and first order. The value of correlation coefficient was found to be 0.998 for F5 formulation. finally it concluded that the prepared sustained release matrix tablet of Stavudine may prove to be potential candidate for safe and effective drug livery over an extended period of time.

KEYWORDS: Stavudine, Eudragit RSPO, Sustained release, Matrix tablets, Hixson-Crowell model.

INTRODUCTION

Sustained-release oral delivery systems are designed to achieve therapeutically effective concentrations of drug in the systemic circulation over an extended period of time, thus achieving better patient compliance and allowing a reduction of both the total dose of drug administered and the incidence of adverse side effects.[1] Sustained drug delivery system was aimed to release the medication in a prolonged rate to maintain plasma drug levels. The drugs having shorter half-life are suitable for the sustained drug delivery system. The main objective in designing sustained delivery system is to reduce dosing frequency and thereby increasing the action. The drug molecules shows better sustained drug release profile in matrix systems by different mechanisms. The introduction of matrix tablet as a sustained release had made a new phase for the novel drug delivery system. Hydroxypropyl methylcellulose was the mostly used hydrophilic polymer to prolong the drug release pattern due to its gelling property, rapid hydration, and robust mechanism, choice in viscosity grades, nonionic nature, reproducible release profile, cost effectiveness and good compressibility property. Sustained release system implies to the pharmaceutical dosage form formulated for retardation of release of therapeutic agent such that its appearance in the systemic circulation was delayed or prolonged and its plasma profile was sustained in duration. The onset of pharmacologic action was delayed and duration of therapeutic effect also delayed.[2,3]

Stavudine is a white to off-white crystalline solid with the molecular formula $C_{10}H_{12}N_2O_4$ and a molecular weight of 224.2. The solubility of stavudine at 23° C is approximately 83 mg/mL in water and 30 mg/mL in propylene glycol. The n-octanol/water partition coefficient of stavudine at 23°C is 0.144. Stavudine, 2',3'-didehydro-3'-deoxythymidine (D4T) is a thymidine analog approved for the treatment of HIV infection[4] like other member of this class of antiretroviral, its purported active metabolite, D4T-5'-triphosphate, is an inhibitor of the HIV reverse transcriptase and act as Chain terminator during DNA synthesis.[5] It is also a thymidine analogue which acts in same way as AZT. The anti + - HIV efficacy of stavudine is comparable to AZT, and it is used in combination regimens. It is the Food and Drug Administration approved drug for clinical use in the treatment of HIV infection, acquired immune deficiency syndrome (AIDS) either alone or in combination with other antiviral agents. The drug has a very short half-life (1.30 hrs.). However, patients receiving Stavudine develop neuropathy and lactic acidosis. The side effects of Stavudine are dose dependent and a reduction of the total administered dose reduced the severity of the toxicity.[6]

Hence in the present study attempts has been made to formulate Stavudine sustained release matrix tablet by using polymers materials hydrophilic HPMC K4M, carbopol 934P and hydrophobic Eudragit RSPO polymers.

MATERIALS AND METHODS

Stavudine was received as a gift sample from Cipla Ltd. Mumbai, Hydroxypropyl Methylcellulose K4M, Carbopol 934P, Magnesium Stearate, Microcrystalline Cellulose, talc and lactose find from S.D. Fine Chemicals Pvt. Ltd. Mumbai.

Eudragit RSPO had obtained from Evonic Pvt. Ltd. Mumbai. UV spectrophotometer model Shimadzu 1800, FTIR-Spectrophotometer model Bruker Japan, Eight Stage Dissolution Apparatus model TDT-08L ELECTROLAB, Roche Friabilator Indian Equipment Corporation, Mumbai, Monsanto Hardness Tester Shiv scientific stores Delhi, India.

Preformulation studies

Stavudine was a white crystalline powder. The melting point of Stavudine drug sample was found to be 293-294^{0}C, which is within the reported range of 290-292^{0}C.it complies with the purity of the drug sample. Spectrophotometric method for the estimation of stavudine.

The standard stock solution and further dilutions were prepared. 100 mg of standard Stavudine drug is weighed, transferred to a 100 ml volumetric flask and dissolved in distilled water. The flask was shaken and volume was made up to the mark with distilled water to give a solution containing 1000 µg/ml. From this stock solution, 10 ml solution was pipetted out and transferred into 100 ml volumetric flask. After scanning 10µg/ml solution, only one peak at 250 nm was observed and considered as λ_{max}.

Screening of polymer

The various hydrophilic polymers such as HPMC K4M, HPMC K15M, and Carbopol934 P are used along with the hydrophobic polymers such as Eudragit RSPO, ethyl cellulose.

From these, HPMC K4M, Carbopol 934 P, Eudragit RSPO are selected and was continued further studied. Tablets were prepared by direct compression method.

Formulation study

A successful attempt was made to formulate sustained release matrix tablet of stavudine. The different drug polymer concentrations were used and sustained release matrix tablet of

stavudine were prepared by direct compression method and effect of polymer concentrations on formulation development was studied. In the present work, total eight formulations were prepared on the basis of parameter optimized in preliminary trials.

Evaluation of sustained release matrix tablet

Angle of repose (*θ*)

The values of angle of repose for the formulations F1 to F8 showed below 30^0 which indicated good flow property.

Bulk density

The bulk densities of all formulation batches were studied. The bulk density was found in range of 0.364 ± 0.03 to 0.440 ± 0.02 for all the formulations batches F1 to F8.

Tapped density

The tapped densities of all formulation batches were studied. The tapped densities were found in range of 0.419 ± 0.03 to 0.531 ± 0.03 for all the formulations batches F1 to F8.

Carr′s compressibility index

The % compressibility index was found to be in the range of 13.12 03 to 21.56 ± 0.3 for all the formulations indicating good flow property.

Weight variation

The weight variation of all formulation batches were studies. The results are shown in table 8 The weight variation was found in range of 250 ± 1.572 to 252.4±1.654 for all formulations batches F1 to F8

Hardness

The hardness of all formulation batches were studied. The results are shown in table 8 the hardness was found in range of 5.8±0.03 to 6.5 ±0.03 for all the formulations batches F1 to F8.

Thickness

The thickness of all formulation batches were studied. The thickness was found in range of 3.10±0.002 to 3.12±0.005 for all the formulations batches F1 to F8.

Friability

The friability of all formulation batches were studied. The friability was found in range of 1.581±0.0225 to 2.223±0.0354 for all the formulations batches F1 to F8.

***In-Vitro* drug release study**

Dissolution studies on all seven formulations of Stavudine sustained release matrix tablet were carried our using a USP type II (i.e. paddle type apparatus). The values were compared with other for model and as shown in table 9, based on the highest regression values (r), fitting of the release rate data to the various models revealed that all formulation batches follows Hixson Crowell model. In vitro release data fitted into Hixson Crowell kinetic model suggest that the highest correlation coefficient was showed by F5 and F6 formulation batches; but, percent cumulative drug release for F6 was found to be 95.64 % and percent cumulative drug release of F5 was higher than F6 hence, F5 selected as an optimized batch.

The best fit model was Hixson Crowell model followed by Korsmeyer peppas, Higuchi model and first order. The value of correlation coefficient was found to be 0.998 for F5 formulation.

The stability study of optimum formulation related *In-vitro* drug release was observed over period of 28 days. The results are shown in table No.10.

RESULT AND DISCUSSION

formulation study were done by calculating angle of repose, bulk density, tapped density, Carr′s index and Hausners ratio along with identification of drug was carried out from characterization of drug and FT-IR. Therefore formulating sustained release matrix tablet, screening of polymer were done. In this, two hydrophilic polymers HPMC K4M, and carbopol 934P and hydrophobic Eudragit RSPO were studied. These polymers were individually studied and fail to provide required hardness. Then HPMC K4M, carbopol 934P and eudragit RSPO, Carbopol 934P were studied in combination and results into increase in hardness than individual study. These polymers were studied in combination and prepare G1 to G8 batches. From these G4, G5 and G6 retained for 12 hrs. And drug lease for G4, G5 and G6 was found to be 93.86%, 82.19% and 76.84% respectively. From that G4 was used for further formulation of sustained release matrix tablet. On the basis of the preliminary trials in the present study a 2^3 full factorial design was employed to study the effect of independent variables, i.e. concentration of HPMC K4m (X^2) and concentration of carbopol 934P (X^3) on dependent variables like % CDR and % swelling index. Formulations of F-1 to F-8 batches

with different concentrations of polymers were formulated by direct compression method and compositions as shown in the table. Formulation batches evaluated for weight variation, hardness, thickness, friability, percent drug content uniformity, swelling index and in vitro drug release study. Formulation batches also evaluated for best fit model from the study of drug release kinetics. To see if there is any possible interaction between the drug and other polymers, the samples of pure drug, drug with HPMV K4M , drug with eudragit RSPO , drug with carbopol 934P , drug with mixture of all polymers were analyzed by the FTIR study confers that there is no interaction between the drug and polymers. The stability studies of optimum formulation revealed that there is no significant reduction in percent cumulative drug release and its color was observed over the period of 28 days.

Table No. 1: Screening of HPMC K4M for batch A1 to A6.

Sr. No.	Ingredient (in mg)	A1	A2	A3	A4	A5	A6
1	Drug	25	25	25	25	25	25
2	HPMC K4M	12.5	37.5	62.5	87.5	112.5	137.5
3	Magnesium Stearate	7	7	7	7	7	7
4	Talc	7	7	7	7	7	7
5	Microcrystalline cellulose	25	25	25	25	25	25
6	Lactose	173.5	148.5	123.5	88.5	73.5	48.5
	TOTAL	250	250	250	250	250	250

Table No. 2: Screening of Eudragit RSPO for batch B1 to B6.

Sr. No.	Ingredient (in mg)	B1	B2	B3	B4	B5	B6
1	Drug	25	25	25	25	25	25
2	Eudragit RSPO	12.5	37.5	62.5	87.5	112.5	137.5
3	Magnesium Stearate	7	7	7	7	7	7
4	Talc	7	7	7	7	7	7
5	Microcrystalline Cellulose	25	25	25	25	25	25
6	Lactose	173.5	148.5	123.5	88.5	73.5	48.5
	TOTAL	250	250	250	250	250	250

Table No. 3: Screening of Carbopol 934 P for batch C1 to C6.

Sr. No.	Ingredient (in mg)	C1	C2	C3	C4	C5	C6
1	Drug	25	25	25	25	25	25
2	Carbopol 934 P	2.5	5.7.5	10	12.5	15	17.5
3	Magnesium stearate	7	7	7	7	7	7
4	Talc	7	7	7	7	7	7
5	Microcrystalline cellulose	25	25	25	25	25	25
6	Lactose	183.5	181	178.5	176	173.5	171.5
	Total	250	250	250	250	250	250

Table No. 4: Screening of HPMC K4 M with carbopol 934 P for batch D1 to D6.

Sr. No.	Ingredient (in mg)	D1	D2	D3	D4	D5	D6
1	Drug	25	25	25	25	25	25
2	HPMC K4M	12.5	37.5	62.5	87.5	112.5	137.5
3	Carbopol 934 P	2.5	5	7.5	10	12.5	15
4	Magnesium stearate	7	7	7	7	7	7
5	Talc	7	7	7	7	7	7
6	Microcrystalline cellulose	25	25	25	25	25	25
7	Lactose	171	145.5	116	88.5	61	33.5
	TOTAL	250	250	250	250	250	250

Table No. 5: Screening of Eudragit RSPO with Carbopol 934 P for batch E1 to E6.

Sr. No.	Ingredient (in mg)	E1	E2	E3	E4	E5	E6
1	Drug	25	25	25	25	25	25
2	Eudragit RSPO	12.5	37.5	62.5	87.5	112.5	137.5
3	Carbopol 934 P	2.5	5	7.5	10	12.5	15
4	Magnesium stearate	7	7	7	7	7	7
5	Talc	7	7	7	7	7	7
6	Microcrystalline cellulose	25	25	25	25	25	25
7	Lactose	171	143	116	88.5	61	33.5
	TOTAL	250	250	250	250	250	250

Table No. 6: Screening of HPMC K4M, Eudragit RSPO with Carbopol 934 P for batch G1 to G6.

Sr. No.	Ingredient (in mg)	G1	G2	G3	G4	G5	G6
1	Drug	25	25	25	25	25	25
2	HPMC K4M	12.5	37.5	62.5	87.5	112.5	137.5
3	Eudragit RSPO	137.5	112.5	87.5	62.5	37.5	12.5
4	Carbopol 934 P	2.5	5	7.5	10	12.5	15
5	Magnesium Stearate	7	7	7	7	7	7
6	Talc	7	7	7	7	7	7
7	Microcrystalline cellulose	25	25	25	25	25	25
8	Lactose	33.5	31	28.5	26	23.5	21
	TOTAL	250	250	250	250	250	250

Table No. 7: Compositions of different batches of sustained release matrix tablet of Stavudine.

Sr. No.	Ingredient (in mg)	F1	F2	F3	F4	F5	F6	F7	F8
1	Stavudine	25	25	25	25	25	25	25	25
2	HPMC K4M	100	100	100	100	87.5	87.5	87.5	87.5
3	Eudragit RSPO	62.5	62.5	75	75	62.5	62.5	75	75
4	Carbopol 934 P	10	15	10	15	10	15	10	15
5	Magnesium stearate	7	7	7	7	7	7	7	7
6	Talc	7	7	7	7	7	7	7	7
7	Microcrystalline cellulose	25	25	25	25	25	25	25	25
8	Lactose	13.5	8.5	11	6	26	21	13.5	8.5
	TOTAL	250	250	250	250	250	250	250	250

Table No. 8 Physical parameter of matrix table.

Sr. No.	Formulation Batch	Weight variation (mg)	Hardness (Kg/cm^2)	Thickness (mm)	% friability
1	F1	252.3±2.325	5.8±0.03	3.11±0.02	2.081±0/03
2	F2	251.6±1.25	6.2±0.007	3.12±0.51	2.213±0.02
3	F3	2524±1.652	6.0±0.06	3.10±0.051	2.213±0.021
4	F4	250.2±1.358	6.4	3.11±0.02	1.581±0.0225
5	F5	250.2±2.042	6.2±0.008	3.10±0.005	1.829±0.035
6	F6	249.5±2.36	6.1±0.01	3.12±0.01	2.152±0.01
7	F7	250±1.572	6.5±0.03	3.10±0.002	1.981±0.054
8	F8	251.1±1.168	6.3±0.05	3.11	2.223±0.0354

Table No. 9: Drug Release Kinetics.

Formulation batches	Mathematical models (Kinetics)					Best fit models
	Zero order	First order	Hignuchi Model	Korsme yen peppes	Hixson Crowell	
	r	r	r	r	r	
F1	0.94	0.993	0.985	0.985	0.993	Hixson Crowell
F2	0.957	0.994	0.985	0.989	0.996	Hixson Crowell
F3	0.953	0.983	0.986	0.993	0.997	Hixson Crowell
F4	0.949	0.996	0.983	0.988	0.997	Hixson Crowell
F5	0.950	0.969	0.987	0.993	0.998	Hixson Crowell
F6	0.953	0.987	0.979	0.991	0.998	Hixson Crowell
F7	0.950	0.978	0.981	0.991	0.996	Hixson Crowell
F8	0.954	0.978	0.977	0.992	0.996	Hixson Crowell

Table No. 10: Stability study for matrix tablet formulation.

Sr. No.	Periods	2-8^{0}C	Room Temp.	40^{0}C RH 75%
1	Initial (% CDR)	95.64	95.64	95.64
2	7 days (% CDR)	95.32	95.46	95.38
3	14 days (% CDR)	95.13	95.25	95.14
4	21 days (% CDR)	94.67	95.09	94.91
5	28 days (% CDR)	94.28	94.93	94.80
6	Colour	No Change	No Change	No Change

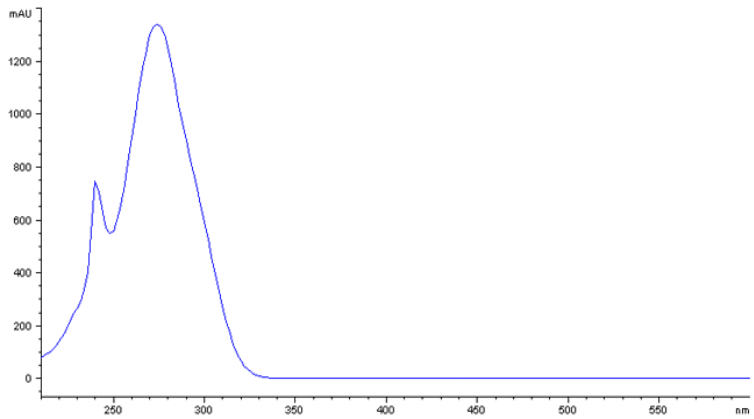

Figure 1: U.V. Spectra of Stavudine.

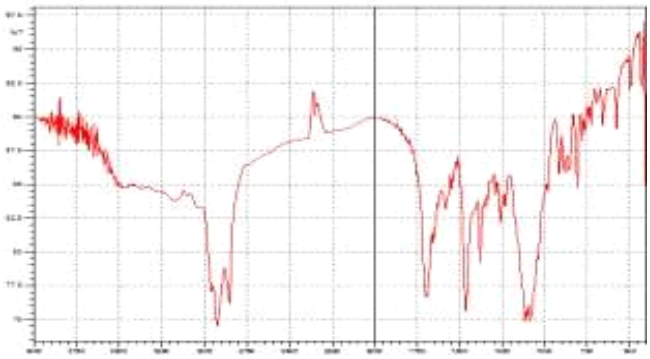

Figure 2: FT-IR spectra of Stavudine.

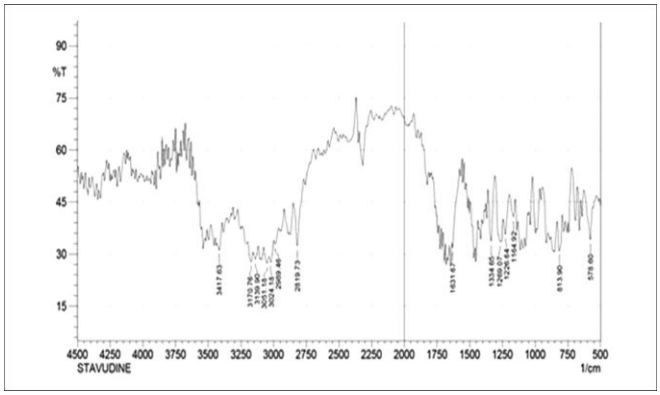

Figure 3: FT-IR spectra of Stavudine.

CONCLUSION

The sustained release matrix tablet of Stavudine was prepared by direct compression method using hydrophilic HPMC K4M, carbopol 934P and hydrophobic eudragit RSPO polymers. The release of Stavudine from matrix tablet can be controlled by changing type of polymer or by its concentration. As the concentration of hydrophilic polymers increased the drug release rate from matrix tablet were decreased. By increasing concentration of eudragit RSPO in formulation, the drug release rate also increased. Based on the highest regression values (r^2), fitting of the release rate data to the various models revealed that the all formulation batches follows Hixson-Crowell model. In vitro release data fitted into Hixson-Crowell kinetic model suggest that the highest correlation coefficient was showed by F5 and F6 formulation batches, but present cumulative drug release for F5 was found to be 95.64% and percent cumulative drug release for F6 was found to be 92.67% as the percent cumulative drug release of F5 was higher than F6. Hence, F5 selected as an optimized batch. The best fit model was Hixson-Crowell model followed by Korsmeyer peppas, Higuchi model and first order. The value of correlation coefficient was found to be 0.998 for F5 formulation, drug release mechanism was the dissolution occurs in planes that are parallel to be the drug surface. Optimized batch

F5 were stable at the selected temperature and humidity in storage for 28 days. From the stability studies it was found that there was no significant change in the percent cumulative drug release and its color. Hence, finally it concluded that the prepared sustained release matrix tablet of Stavudine may prove to be potential candidate (Hixson Crowell Model, r = 0.998) for safe and effective drug delivery over an extended period of time.

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