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FORMULATION AND EVALUATION OF STAVUDINEAS MUCOADHESIVE VAGINAL TABLETS

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ABSTRACT: Mucoadhesive drug delivery system has occupied an important place in the field of pharmaceutical research. Mucoadhesive tablets prolong the residence time of the drug at the site of application and provide extended therapeutic effect. Mucoadhesive tablets have been prepared for various sites thus offering localization as swell as systemic control of drug release. The present review focuses on concept of formulation of Stavudine as mucoadhesive vaginal tablets, their applications and various evaluation techniques. A new strategy preferably once daily is proposed for improving the sustained release of drug and localized action of stavudine, the antiretroviral. The design of the delivery system was based on the sustained release formulation with swelling and mucoadhesion of the drug delivery systems. Different polymers, such as, HPMCK100M, HPMCK15M, CARBOPOL934P and binders were used with different concentrations were tried in order to get the desired sustained release profile over a period of 8-10hrs. All the formulations were evaluated for, dimensional stability, drug content and *in vitro* drug release profile. It was found that dimensional stability and controlled release rate of the formulation increases with the increasing polymer concentration. Based on the *in vitro* studies carried out for the optimized formulation the performance of the developed formulation promises to be efficient in controlling the drug release rate throughout10hrs with the HPMCK 100M and HPMCK 15M.

INTRODUCTION: The compressed tablet is the most popular dosage form in use today. Mucoadhesive tablets, in general, have the potential to be used for controlled release drug delivery, but coupling of mucoadhesive properties to tablet has additional advantages, e.g. efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer etc.

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Mucoadhesive dosage forms can be adhered to mucosa of tissues for localized and sustained release of drugs. The vagina provides a promising site for local as well as systemic drug delivery because of its unique features of large surface area, rich blood supply and avoidance of the hepatic first-pass effect, reduction in GI and hepatic side-effects, relatively high permeability to a wide range of compounds including peptides and proteins and self-insertion.

These all make the vaginal route an alternative to the parenteral route for drugs such as various hormones like oxytocin, calcitonin, human growth hormone, drugs like bromocriptine and steroids used for replacement therapy or contraception. Vaginal mucoadhesive tablets are stable and less

messy to handle than creams or ointments. The tablets are intended to disintegrate within the vagina, releasing their contents. Moreover they offer advantages of ease of manufacture and insertion. Vaginal tablet omit the problems of leaking or slipping out of solution or semisolid formulation and expulsion of suppositories after insertion.[1-4]

MATERIALS:

Stavudine (Gift sample of M/s. Strides Acro Lab, Bangalore), HPMCK100M and HPMCK15M (NP Chemicals, Mumbai), Magnesium stearate (Sigma Labs, Hyderabad), PVPK30 (Loba Chem. Pvt. Ltd., Mumbai.), Carbopol 934P (Ozone International, Mumbai.), MCC (Otto Chem., Mumbai).

The all other reagents used were of analytical grade.

Pre-Formulation Studies:

The angle of repose, compressibility index, bulk density and hausner ratio values of Stavudine and the powder blends were determined.

Drug excipient compatibility studies are done by FT-IR spectroscopy. It is employed to ascertain the compatibility between drug and selected polymers. The pure drug and drug with excipients were scanned separately. Drug and the polymer were taken in 1:1 ratio. In the present study, the potassium bromide disc (pellet) method was employed and the spectra were taken. FT-IR spectrum of pure drug was compared with FT-IR spectrum of drug with polymer. Disappearance of pure drug peaks or shifting of peaks in any of the spectra was studied.

Standard Curve:

A stock solution of Stavudine (100µg/ml) was prepared in Distilled water. The UV Spectrum was recorded in the range of 200-400nm. The λ max of Stavudine was found to be 267nm. The solutions of 5µg/ml to 30µg/ml were prepared from stock solution by appropriate dilution with distilled water. The absorbance of each of solution was recorded using T60 UV-Visible spectrophotometer at wavelength of maximum absorption.

Formulation:

All the ingredients sufficient for a batch of 20 tablets according to formula was passed through sieve in order to enhance the flow and compaction properties and drug was triturated with polymer in a glass mortor and pestle to achieve a homogenous blend. Filler and other excipients sufficient for a batch of 20 tablets according to the formulae were passed through the mesh and thoroughly blended and mixed with lubricate magnesium stearate to ensure complete mixing. Tablets containing Stavudine equivalent to 150mg were compressed by using 10.0 mm diameter, spherical tablet punches on a 16 station rotary compression machine (M/s. Rimek mini press machinery Co. Pvt. ltd., India) at the hardness of 3 to 4kg/cm² (**Table 1**).

TABLE1: FORMULAE OF STAVUDINE MDDS PREPARED WITH HPMCK100M, HPMCK15M AND CARBOPOL 934P

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Stavudine	30	30	30	30	30	30	30	30	30	30	30	30
CARBOPOL934	30	45	60	-	-	-	-	-	-	30	-	30
HPMCK100M	-	-	-	30	45	60	-	-	-	-	30	30
HPMCK15M	-	-	-	-	-	-	30	45	60	30	30	-
Magnesium	3	3	3	3	3	3	3	3	3	3	3	3
PVPK30	3	3	3	3	3	3	3	3	3	3	3	3
MCC	84	69	54	84	69	54	84	69	54	54	54	54
Total(mg)	150	150	150	150	150	150	150	150	150	150	150	150

Evaluation: Tablets are evaluated for its parameters like various quality control tests such as tablet thickness and diameter, Hardness, Friability, uniformity of weight and content uniformity of drug and other specific valuation tests for MDDS like adhesive strength, swelling index, and Release rate of drug.

Tablet thickness and diameter: Thickness and diameter of tablets were important for uniformity

of tablet size. Thickness and diameter were measured using Verniercalipers.

Hardness:
This test is used to check the hardness of a tablet which may undergo chipping or breakage during storage, transportation and handling. In this five tablets were selected at random and the hardness of each tablet was measured with Monsanto hardness tester. The hardness is usually measured in terms of kg/cm^2.

Friability:
The friability test was carried out to evaluate the hardness and stability instantly. In Roche friabilator in which twenty tablets were weighed (Wo) initially and put in a tumbling and rotating apparatus drum. Then, they are subjected to fall from 6 inches height. After completion of 100 rotations, the tablets were again weighed (w). The percent loss in weight or friability (f) was calculated.

Uniformity of Weight:
This test is performed to maintain the uniformity of weight of each tablet which should be in the prescribed range, this is done by sampling and weighing 20 tablets at random and average weight is calculated. Not more than two of the individual weights deviate from the average weight by more than the percentage as mentioned in IP.

Content Uniformity:
This test is performed to maintain the uniformity of weight of each tablet which should be in the prescribed range according to the Indian Pharmacopoeia. The content uniformity test is mandatory for tablets whose average weight is below 50mg. This test is performed by taking twenty tablets were selected randomly, weighed and powdered. A quantity of powdered tablet equal to 200mg of Stavudine was dissolved in distilled water in 100ml volumetric flask. This formed sample was diluted and the absorbance was measured at 267nm using distilled water as blank and the % drug content was estimated.

***In vitro* Dissolution Studies:**

Swelling Index (SI) = (Wt-Wo)/WoX100

Wt=Weight of tablets after time at‘t’.

Wo = Weight of tablet before replacing in the beaker.

Stability Studies:
The accelerated stability studies were carried out according to ICH guidelines. Optimized formulation F11 is packed in amber color bottle and aluminum foil laminated on the upper part of the bottle and this packed formulation is stored in stability chambers maintained at $40^{\circ}C \pm 2^{\circ}C$ and 75% RH ± 5% for 4 weeks. The tablets were evaluated before and after 4weeks for change in appearance, the drug content and *in vitro* release.

***Ex-Vivo* Mucoadhesive Strength:**
Bioadhesive strength of the vaginal tablets was measured on modified physical balance used for determining the *ex vivo* mucoadhesive strength of prepared vaginal tablets. The defatted mucosal membrane was obtained from sheep and it was washed with distilled water. Sheep mucosa was tied to the glass petridish, which was filled with distilled water so that it just touched the mucosal surface. The vaginal tablet was stuck to the lower side of a thread with cyanoacrylate adhesive. The two sides of the balance were made equal by keeping a 5g weight on the right hand pan. Next, weight of 5g was removed from the right hand pan, which lowered the pan along with the tablet over the mucosa. The balance was kept in this position for 5m contact time. Then weight was added slowly to the right hand pan until the tablet detached from the mucosal surface [7]. Dissolution test was carried out using (DBK dissolution test apparatus) rotating basket method (**apparatus 1**).

The stirring rate was 50rpm. Distilled water was used as dissolution medium 900ml and was maintained at 37+2°C. Samples of 5ml were withdrawn at predetermined time intervals, filtered and replaced with 5ml of fresh dissolution medium. The collected samples were suitably diluted with dissolution fluid, where ever necessary and were analyzed for the Stavudine at 267 nm by using a double beam UV spectrophotometer (T60 UV-Visible spectrophotometer). [5-6]

Swelling Index:

The degree of swelling of bio-adhesive polymers is an important factor affecting adhesive. For conducting the study, a tablet was weighed and placed in a petri-dish containing 5ml of distilled water for 12hrs. The tablets were taken out from the petri-dish and excess water was removed carefully by using filter paper. The swelling Index was calculated using the above formula.

RESULTS AND DISCUSSION:

Pre-Formulation Parameters:

The preformulation studies were performed. The tests done are Angle of Repose, Bulk Density, Carr's index, Hausner ratio, FT-IR studies for drug polymer compatibility studies. The angle of repose varied from $23^o20\pm0.01$ to $27^o20\pm0.07$, Bulk density varied from 0.34±0.004 to 0.39±0.008g/ml, Carrs index ranged from 9.22 to14.23%, Hausner ratio ranged from 1.1 to 1.18. (**Table 2**)

The FTIR graphs of the pure drug and the optimized formula showing the compatibility of drug with the polymers. As described in the methodology section the FT-IR studies were carried out for pure drug alone and along with polymers and other excipients. The results were summarized as follows. An FT-IR spectrum of pure Stavudine and of with polymers (HPMCK 100M and HPMCK15M were in optimized formula). These peaks were not affected in the formulations and were equally prominent. This indicates. That there is no interaction between Stavudine and other excipients used.

TABLE 2: PRE-FORMULATIONPARAMETERS

Formulation	*Angleof Repose(°)	*Bulk Density(g/ml)	*Tapped Density(g/ml)	*Carr's Index (%)	*Hausner Ratio
F1	25º20±0.02	0.39±0.007	0.68±0.008	11.23±0.02	1.18±0.05
F2	26º20±0.01	0.38±0.008	0.59±0.001	14.23±0.03	1.17±0.04
F3	24º20±0.04	0.38±0.009	0.76±0.006	10.23±0.01	1.14±0.02
F4	27º20±0.06	0.37±0.003	0.45±0.002	9.23±0.02	1.13±0.01
F5	26º20±0.08	0.36±0.004	0.63±0.007	11.23±0.03	1.15±0.01
F6	25º20±0.09	0.35±0.005	0.85±0.008	12.23±0.04	1.16±0.03
F7	27º20±0.07	0.34±0.002	0.56±0.002	14.23±0.05	1.11±0.02
F8	24º20±0.08	0.38±0.004	0.67±0.003	11.23±0.06	1.12±0.03
F9	23º20±0.01	0.37±0.006	0.79±0.004	12.23±0.04	1.1±0.05
F10	25º20±0.05	0.35±0.005	0.85±0.006	11.23±0.01	1.14±0.04
F11	26º20±0.08	0.34±0.008	0.69±0.008	9.23±0.02	1.13±0.03
F12	24º20±0.09	0.39±0.001	0.89±0.007	14.23±0.05	1.12±0.02

Construction of Standard graph in Distilled water:

The pure drug Stavudine was accurately weighed 10mg and was mixed with10ml of distilled water, results in the solution producing 1mg/ml conc. This is referred as primary stock solution. From this a series of concentrations of 5µg/ml, 10µg/ml, 15µg/ml, 20µg/ml, 25µg/ml, and 30µg/ml were prepared and the absorbance was checked at 267nm.

Evaluation of Prepared Tablets:

The prepared tablets were evaluated for parameters like weight variation, hardness, friability, drug content and thickness and the values are given in **Table 3**

TABLE3: EVALUATION OF PREPARED STAVUDINE MUCOADHESIVE TABLETS

Formulation	*Weight Variation (mg)	*Hardness (kg/cm^2)	*Friability (%)	*Drug Content(%)	*Thickness (mm)
F1	148.12±0.87	3.1±0.75	0.382±0.03	99.43±0.55	1.51±0.24
F2	151.75±1.67	3.0±0.77	0.312±0.06	98.60±2.52	1.66±0.30

F3	148.26±1.41	3.8±0.73	0.372±0.03	99.43±0.83	1.44±0.25
F4	150.56±2.13	3.2±0.76	0.392±0.02	99.26±1.56	1.57±0.35
F5	149.18±1.12	3.9±0.77	0.353±0.08	97.63±0.96	1.67±0.20
F6	150.62±1.56	3.8±0.74	0.337±0.05	98.33±1.15	1.46±0.32
F7	151.23±0.87	3.2±0.75	0.353±0.07	99.43±0.83	1.41±0.26
F8	148.5±1.67	3.1±0.50	0.380±0.09	99.50±1.15	1.64±0.34
F9	149.25±1.12	3.5±0.77	0.368±0.03	99.25±0.55	1.57±0.28
F10	151.50±2.13	3.1±0.55	0.393±0.01	99.43±0.83	1.60±0.25
F11	149.25±0.50	3.8±0.45	0.332±0.05	98.63±0.96	1.71±0.30
F12	150.50±0.75	3.9±.075	0.362±0.02	98.60±2.52	1.54±0.20

TABLE4: *IN VITRO* MUCOADHESIVE STRENGTH STUDY OF MUCOADHESIVE TABLETS

Batch	*Mucoadhesive	*MucoadhesiveForce
F1	7.50±0.25	0.7
F2	11.50±0.36	1.127
F3	15.50±0.52	1.519
F4	7.20±0.35	0.705
F5	10.50±0.40	1.029
F6	15.00±0.55	1.47
F7	7.20±0.24	0.705
F8	10.45±0.26	1.0241
F9	14.60±0.81	1.43
F10	15.50±0.55	1.519
F11	15.20±0.46	1.489
F12	15.45±0.81	1.514

Mucoadhesive strength were determined (**Table 4**) and in all the formulations, as the polymer concentration increased, the mucoadhesive strength increased.

Swelling Index:

The bio adhesion and drug release profile are dependent upon swelling behaviour of the tablets. Swelling index was calculated with respect to time. The Swelling index was for all formulations F1 to F12 (After 4 hours) were in the range 38.06 to 72.71%. With increase in HPMC concentration, swelling index increased in all the batches. This may be attributed to rapid hydration and gel layer formation by HPMC around the surface of the tablet. As the proportion of the HPMC increases, proportion of the diluents decreases. The diluents MCC is very porous and weakly swellable polymer. Therefore MCC does not form gel layer around the surface. In the batches F1, F4, F7 the proportion of MCC is higher, there fore observed swelling index is much less in these cases as compared to other batches in the same series.

The accelerated stability studies of optimized formulation F11 were performed as per ICH guidelines and the results are tabulated (**Table 5**)

TABLE 5: STABILITY STUDIES

S.No	Parameter	Initial	After 4 hrs
1	Avg. Weight(mg)	149.8	149.2
2	Hardness(kg/cm)	3.5	3.1
3	Thickness(mm)	1.67	1.5
4	Friability	0.18%	0.20%
5	Drugcontent	99.10%	98.54%
6	%CDR	99.21%	98.74%

The *in vitro* dissolution study were conducted by rotating basket method using distilled water as dissolution media and absorbance were measured at 267nm. The cumulative percent release of all the formulations were tabulated. (**Table 6 & 7**)

TABLE6: PERCENT CUMULATIVE DRUG RELEASE PROFILES FOR STAVUDINE MUCOADHESIVE FORMULATIONS PREPARED BY DIRECT COMPRESSION METHOD

Time (hours)	*Cumulative% drug release					
	F1	F2	F3	F4	F5	F6
1	47±1.2	41±2.8	29±2.5	42.8±1.5	37.7±2.8	23±2.2
2	69.3±2.5	65.6±1.2	42±1.65	63.7±2.8	51.2±1.6	35±1.3
3	84±2.8	75.15±1.6	59±2.1	82.3±1.1	64±2.5	43.5±2.3
4	99.26±0.6	89.52±1.1	76±1.2	98±0.6	75.41±1.1	57±0.6
5	-	99.8±0.5	89.3±3.1	-	86.32±3.2	68±3.1
6	-	-	99.75±0.7	-	99±0.8	77.1±1.85
7	-	-	-	-	-	86±2.5
8	-	-	-	-	-	99.2±0.75
9	-	-	-	-	-	-
10	-	-	-	-	-	-

TABLE 7: PERCENT CUMULATIVE DRUG RELEASE PROFILES FOR STAVUDINE MUCOADHESIVE FORMULATIONS PREPARED BY DIRECTCOMPRESSION METHOD

Time (hours)	*Cumulative % drug release					
	F7	F8	F9	F10	F11	F12
1	43.4±1.2	39±2.1	26.8±1.1	15±1.3	8.8±0.4	10±2
2	65.8±2.1	53±1.3	37.0±2.3	23±2.1	15.2±1.3	17±1.9
3	83.5±2.8	66.3±2.5	49.0±1.4	35±2.6	26±1.9	28±2.0
4	99±0.65	77.8±3.2	57.2±1.9	47±3.2	37±2.5	39±1.6
5	-	89.8±1.6	69.32±2.5	60±3.6	49±2.4	48.3±2.2
6	-	99±0.5	85.0±3.1	76±2.5	57.2±1.9	59.1±1.5
7	-	-	99.68±0.3	89.3±1.2	69±3.1	71±3.2
8	-	-	-	99±0.3	77.1±1.8	86±2.1
9	-	-	-	-	86±2.1	99.35±0.4
10	-	-	-	-	98.4±0.9	-

TABLE 8: KINETICSOFDRUGRELEASE

Formulation	r^2			
	Zero Order	First Order	Higuchi	Peppas
F1	0.928	0.638	0.999	0.999
F2	0.918	0.594	0.996	0.988
F3	0.982	0.636	0.966	0.991
F4	0.953	0.657	0.994	0.999
F5	0.942	0.571	0.993	0.993
F6	0.986	0.616	0.963	0.992
F7	0.949	0.655	0.995	1
F8	0.934	0.566	0.997	0.995
F9	0.981	0.618	0.949	0.974
F10	0.996	0.726	0.898	0.986
F11	0.997	0.767	0.9	0.995
F12	0.993	0.772	0.877	0.993

From the kinetic values i.e., r^2 values obtained from different plots of optimized formulation F11, we can conclude that he optimized formulation F11 follows Zero order and Higuchi mechanism of drug release and non fickian transport. (**Table 8**)

CONCLUSION: Stavudine is an antiretroviral drug and the site of action is systemic/site specific and the drug pH ranges from 3.5 to 5.5, the present work was aimed to formulate mucoadhesive vaginal tablets of The tablets were formulated using polymers like HPMCK 100M, HPMCK 15M and CARBOPOL 934P along with suitable excipients. The pre-formulation studies and post-formulation studies were carried out. All the formulations were prepared by direct compression method.

The prepared tablets of all the formulations were evaluated for physical characters, assay, *in-vitro* drug release, swelling index, drug-polymer compatibility studies, hardness and friability. The main aim was to optimize the formulation for 8-10 hours *in-vitro* release. Optimized formulation **F11** containing HPMCK 100M and HPMCK 15M was consider as the best product with respect to *in vitro* drug release for 10 hours release action and improved site-specificaction. The results showed that the drug release rate was increased as the viscosity of the polymer was increased.

The formulation F11 prepared by direct compression containing HPMCK 100M and HPMCK 15M exhibited good swelling index and maximum rate of drug release. So, this formulation was considered to be the optimized formulation. Thus the formulated mucoadhesive vaginal tablets of Stavudine (cumulative % release is 98.8% in 10hrs) offer a superior alternative over convention a marketed dosage forms (cumulative % release of 99.2 % in 7hrs) in regards of Localized action and Sustained release of drug.

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REFERENCES:

1. Ahuja A, Khar RK, Ali J: Mucoadhesive drug delivery systems. Drug Dev Ind Pharm. 1995; 23(5):489–515.
2. Vermanik, Garg: The scope and potential of vaginal drug delivery. Pharm Sci Technol Today 2000; 3:359-364.
3. Muranshi S, Yamamoto A, Okada H: Rectal and vaginal absorption of peptides and proteins.Pharma Biotech.1993; 4:199-227.
4. Riya Das, Kazi Asraf Ali, Amal Kumar Bandyopadhyay: Mucoadhesion and mucoadhesive tablet. A review. Int. J. Pharm Sci Tech. 2011;6:65-115
5. Han RY, Fang JY, Sung KC et. al.: Mucoadhesive buccal disks for novel nalbuphineprodrug controlled delivery: effect of formulation variables on drug release and mucoadhesive performance. Int J. Pharm. 1999; 177:201-209
6. Nafee Na, Ismail FA, Boraie NA et.al. : Formulation and evaluation of buccal mucoadhesive tablet containing water soluble drugs. Drug Dev Ind Pharm.2004; 30:995-1004.
7. J. Gupta, J. Tao, S. Garget. al.: Design and development of an in vitro assay for evaluation of solid vaginal dosage forms. Pharmacology and Pharmacy.2011;2:289-298.

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