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DEVELOPMENT AND CHARACTERIZATION OF SUSTAINED RELEASE MATRIX PELLETS OF STAVUDINE

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Abstract: The purpose of this study is to formulate and evaluate sustained release matrix pellets of Stavudine by using pH independent polymer i.e. Eudragit RS PO and Eudragit RL PO by using extrusion – Spheronization technique. To achieve a predetermined *in vitro* drug release for HIV infection. The sustained release matrix pellets containing Stavudine were prepared by wet granulation method by using extrusion – Spheronization technique with Ratio of Eudragit RS PO and Eudragit RL PO. The effect of ratio of polymer on *in vitro* drug release was investigated using 3^2 full factorial design. The parameters determined were pellets friability, drug content, and *in vitro* dissolution study. According to *in vitro* drug release study, Eudragit RS PO and Eudragit RL PO indicated pH independent property and no effect of pH on release. Constant release throughout GI track. Surface plots were also presented to graphically represent the effect of independent variables on the *in vitro* drug release study. The validity of generated mathematical model was tested by preparing checkpoint formulation. Formulation F5 (ratio of polymer concentration Eudragit RS PO: Eudragit RL PO - 80:48) was selected as the optimized formulation. Short term stability study (40 ± 0.5ºC and 75 ± 5% RH for 1 month) on optimized formulation indicated that there is no significance change in *in vitro* drug release.

Keywords: Matrix pellets, Eudragit RS PO, Eudragit RL PO

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INTRODUCTION

SUSTAINED RELEASE MATRIX PELLETS

Pellets are agglomerates of fine powders or granules of bulk drugs and excipients. They consist of small, free-flowing, spherical or semi-spherical solid units, typically from about 0.5 mm to 1.5 mm, and are intended usually for oral administration. Pellets can be prepared by many methods, the compaction, extrusion-spheronization and drug layering techniques being the most widely used today. Regardless of which manufacturing process is used, pellets have to meet the following requirements.

1. They should be near spherical and have a smooth surface; both considered optimum characteristics for subsequent film coating.
2. The particle size range should be as narrow as possible. The optimum size of pellets for pharmaceutical use is considered to be between 600 and 1000 μm.
3. The pellets should contain as much as possible of the active ingredient to keep the size of the final dosage form within reasonable limits.

Advantages of Pellets

- ✓ It produces spheroids with high loading capacity of active ingredient without producing extensively large particles.
- ✓ It produces particles of uniform size with narrow size distribution and good flow properties.
- ✓ Successful coating is applied to spheroid because of its spherical shape and low surface area to volume ratio.
- ✓ Dependent upon adhesive forces and surface characteristics Spheronization increases the hardness and reduces friability of granules.
- ✓ Pellets composed of different drugs can be blended and formulated in single unit dosage form that facilitates delivery of two or more chemically compatible or incompatible drug at the same or different site in GI tract.
- ✓ Pellets are frequently used in controlled release delivery system as it facilitates free dispersion of spheroids in the GI tract and offer flexibility for further modification.
- ✓ It improves the safety and efficiency of active ingredient. It helps to increase bioavailability of drugs by controlling or modifying the release rate of drugs.

- ✓ The flow characteristics of spheres make them suitable for transportation by most systems found in the pharmaceutical industry, including vacuum transfer.
- ✓ The packing of small sphere into small containers, such as hard gelatin capsules, or larger packages is much more convenient than other dry forms such as powders or granules. Eliminate quality problems with variable dosage due to packaging problems with powder.
- ✓ Spheres are a dense material and provide the lowest surface area to volume ratio and thus pharmaceutical compounds can be coated with a minimum of coating material which important for effective release of some drugs.
- ✓ Coating can provide controlled, targeted release at different locations within the body.
- ✓ Spherical particles are easily mixed. Smooth spheres are an ideal base on which to apply a coating. Minimum coating time and coating material used.
- ✓ Pellets also reduce variations in gastric emptying rates and overall transit times. Thus inter- and intra-subject variability of plasma profiles, which is common with single unit regimens, is minimized.
- ✓ High local concentration of bioactive agents, which may inherently be irritative, can be avoided.

Extrusion-Spheronization

In basic terms, the extrusion and spheronization process involves four steps:

- ➢ Granulation – preparation of the wet mass;
- ➢ Extrusion – shaping the wet mass into cylinders;
- ➢ Spheronization – breaking up the extrudate and rounding off the particles intospheres;
- ➢ Drying – drying of the pellets.

MATERIAL

Stavudine was obtained from Balaji Pharma, Surat. Eudragit RS PO and Eudragit RL PO was obtained from Evonic Mumbai. Avicel pH-101 was obtained from Lincoln Pharma. Ltd. Povidone K-30 was obtained from Emcure Pharma.

METHOD

Extrusion-Spheronization All the solid powder materials except drug was weighed and transferred to a clean bowl and mixed thoroughly. Accurately weighed amount of drug was geometrically mixed with above powder blend. To the above powder blend water was added till wet mass of acceptable plasticity will be obtained. Above prepared wet mass was then extruded using a radial piston type extruder. The screen will be 1 mm thick and the apertures were 1 mm in diameter. Extrudates prepared was then spheronized at two different spheronization speeds, 700 and 900 rpm for 25 to 30 min. Prepared pellets was then dried below 60 ^{o}C for 2 hours. The dried pellets was passed through sieve size of 600 µm (30#), 710 µm (25#), and 1190 µm (16#), out % of usable yield in the size range of 710 µm - 1190 µm was calculated.

EVALUATION PARAMETER

- **Particle Size and Size Distribution:-**

The size and size distribution of the pellets produced was determined by agitation for 10 min with a sieve shaker fitted with a progression of standard sieves. From the weight retained on each sieve particle size is determined from standard sieve aperture size as per Indian Pharmacopeia.

- **Bulk Density:-**

Apparent bulk density was determined by placing prepared pellets into a graduated cylinder and measuring the volume and weight as it is. That is calculated by formula

Db = W/Vb

Where, W = Weight of Pellets taken,

Vb = bulk volume.

- **Tapped Density:-**

Tapped density was determined by USP method II. Pellets were filled in 100 ml

Dt = W/Vt

Where, W = Weight of pellets taken,

Vt= tapped volume.

- **Angle of Repose:-**

Angle of repose was determined by using funnel method. Pellets was poured from funnel, that can be raised vertically until a maximum cone height h was obtained diameter heap D was measured. The repose angle Φ was calculated by formula

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

Where, h = height of tip of funnel from horizontal ground surface and

r = the radius of base of conical pile.

- **Compressibility Index:-**

Compressibility index will be calculated by following equation.

Carr's index = (Tapped density - Bulk density / Tapped density) X 100

- **Hausner's Ratio:-**

Hausner's ratio will be calculated by following equation.

Hausner's ratio = Tapped density / Bulk density

- **% Yield:-**

It was determined by using following formula

% Yield = W2/W1 X 100

Where, W1 – Initial weight of blend

W2 – Final weight pellet

- **Friability:-**

Friability was measured with an Electrolab TAB friabilitor apparatus for 100 revolutions at 20 rpm. For each assay, 20 gm of pellets was mixed with 30 g of glass beads. Friability was estimated as the increase in the percentage of sampling weight due to pellets or pellet fragments.

- **Drug Content:-**

Accurately weighed 4 gm of prepared pellets are transferred into mortar pestle. Pellets crush into powder, take 400mg of powder to a 100 ml volumetric flask and Volume was then made up to 100 with Phosphate buffer pH 6.8. Above solution was filtered through wahtman paper and absorbance was measured at 266 nm.

❑ ***In-vitro* Drug Release Study**:-

The dissolution test was performed using Apparatus - I (basket type) at 100 rpm in 900 ml HCl buffer solution pH 1.2 for 2 hr. (Gastric resistant test) and in 900 ml Phosphate buffer pH 6.8 for 22 hrs. At 37 ± 0.5 ^{0}C. 5 ml samples was withdrawn at time intervals of hrs. Replaced with 10 ml of fresh dissolution media each time. Collected samples was then analyzed by UV-visible spectro-photometer at 266 nm.

FACTORIAL DESIGN FORMULATIONS

On the basis of the preliminary trials in the present study a 3^2 full factorial design was employed to study the effect of independent variables, i.e. Ratio of concentration of Sustain Release polymer (Eudragit RS PO: X_1) and (Eudragit RL PO: X_2) on dependent variables, i.e. cumulative % drug release at Q1 value and Q20 value.

Table 1 Composition of factorial batches

Batch	Drug	Eudragit RS PO	Eudragit PL PO	Povidone K-30	Mg. Stearate	Avicel PH-101	Total
F1	80	68	36	12	1.2	202.8	400
F2	80	68	48	12	1.2	190.8	400
F3	80	68	60	12	1.2	178.8	400
F4	80	80	36	12	1.2	190.8	400
F5	80	80	48	12	1.2	178.8	400
F6	80	80	60	12	1.2	166.8	400
F7	80	92	36	12	1.2	178.8	400
F8	80	92	48	12	1.2	166.8	400
F9	80	92	60	12	1.2	154.8	400

All Value are in "mg"

EVALUATION OF 3^2 FACTORIAL DESIGN FORMULATIONS (F1 TO F9)

Table 2 Micromeritics properties factorial batches

Batch	Angle of repose(θ)*	Tapped Density (gm/cm3)*	Carr's index	Hausner's Ratio	Friability*
F1	23.55 ± 0.45	0.9058 ± 0.14	6.98 ± 0.03	1.07 ± 0.06	0.23 ± 0.02
F2	24.95 ± 0.37	0.9056 ± 0.17	6.75 ± 0.09	1.06 ± 0.04	0.22 ± 0.05
F3	23.42 ± 0.62	0.9139 ± 0.12	8.48 ± 0.06	1.09 ± 0.02	0.25 ± 0.01
F4	23.75 ± 0.35	0.9157 ± 0.28	6.49 ± 0.05	1.06 ± 0.02	0.28 ± 0.01

F5	23.89 ± 0.67	0.9125 ± 0.21	8.10 ± 0.04	1.08 ± 0.02	0.24 ± 0.06
F6	24.85 ± 0.65	0.9056 ± 0.17	6.68 ± 0.09	1.07 ± 0.04	0.23 ± 0.05
F7	23.85 ± 0.89	0.9057 ± 0.28	6.39 ± 0.05	1.06 ± 0.02	0.28 ± 0.01
F8	24.82 ± 0.52	0.9115 ± 0.31	7.87 ± 0.05	1.08 ± 0.08	0.26 ± 0.05
F9	24.66 ± 0.96	0.9139 ± 0.12	8.48 ± 0.06	1.09 ± 0.02	0.25 ± 0.01

Values are means ± SD (n=3)

Upon pelletization flow properties Stavudine increase significantly. All batches (F1-F9) showed the excellent to good flow characteristics. From above table one can conclude that as concentration of polymer increases there were minor change flow character that may due to impairment in surface prosperities as well sphericity.

Table 3 Evaluation of 3^2 full factorial batches pellet

Batch No.	Drug content (mg)	% Drug content	Capsule Fill Weight (mg)	% Practical Yield
F1	84.28 ± 0.84	105.35 ± 0.35	378.6 ± 0.58	83.52 ± 0.98
F2	76.0 ± 0.14	96.25 ± 0.12	415 ± 0.52	87.72 ± 0.57
F3	79.2 ± 0.71	99.36 ± 0.25	402.56 ± 0.66	88.24 ± 0.61
F4	76.96 ± 0.75	96.21 ± 0.24	415.16 ± 0.36	85.68 ± 0.36
F5	79.2 ± 0.33	94.52 ± 0.35	421.92 ± 0.74	83.96 ± 0.98
F6	78.28 ± 0.25	97.85 ± 0.25	408.6 ± 0.52	87.35 ± 0.52
F7	78.6 ± 0.85	98.25 ± 0.96	407.0 ± 0.85	86.25 ± 1.52
F8	80.96 ± 0.45	101.12 ± 0.85	395.52 ± 0.24	88.89 ± 1.15
F9	83.2 ± 0.22	106.85 ± 0.54	372.6 ± 0.14	85.12 ± 1.52

Values are means ± SD (n=3)

All the prepared pellets showed acceptable Pharmaco-technical properties. Assay results of pellets of F1-F9 batches were found to be in the Pharmacopoeial limits of 90-100%.

- **Comparison of Release Profile of factorial Batches**:-

Table 4 Comparison of release profile of factorial batches

Time (hrs)	Drug release (%)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	9.0±1.25	14.32±1.47	18.25±1.44	7.89±0.55	12.08±0.36	15.78±0.33	9.87±1.52	10.12±0.87	13.89±0.66
2	14.32±0.66	20.45±1.25	22.78±0.31	12.54±1.25	15.98±0.85	20.84±0.44	12.45±0.98	14.35±0.33	17.54±0.74
4	20.04±1.22	25.87±0.25	29.89±0.17	18.52±0.45	23.66±0.83	28.14±1.85	18.24±0.34	20.87±0.87	25.99±1.47
6	28.44±1.87	35.89±0.87	37.87±0.85	26.98±1.54	31.86±1.14	35.24±1.69	27.65±1.85	29.78±1.85	33.65±0.25
8	36.12±0.33	41.21±0.54	45.78±0.71	32.15±0.74	38.99±1.65	42.57±1.96	36.47±1.09	37.14±1.02	40.87±0.36
10	42.87±0.78	47.89±1.54	54.04±1.46	40.78±1.24	46.87±0.52	50.78±0.94	42.74±0.47	44.32±0.35	47.21±1.25
12	51.98±1.44	58.16±1.74	61.87±1.29	49.32±1.36	54.45±1.87	59.68±0.24	50.34±1.06	52.17±0.14	55.13±1.81
16	65.87±0.34	75.29±1.36	84.65±0.59	64.78±1.63	69.79±0.95	75.89±0.43	63.48±1.34	63.72±1.34	72.85±1.06

20	79.66±0.21	88.79±0.89	98.23±0.53	76.78±0.36	85.09±0.43	90.87±1.24	78.54±0.58	78.54±1.57	88.76±1.47
24	94.87±1.61	97.95±0.88	99.12±0.93	95.25±0.74	99.08±0.41	100.78±1.2	94.21±0.36	96.87±1.54	101.2±0.9

Values are means ± SD (n=3)

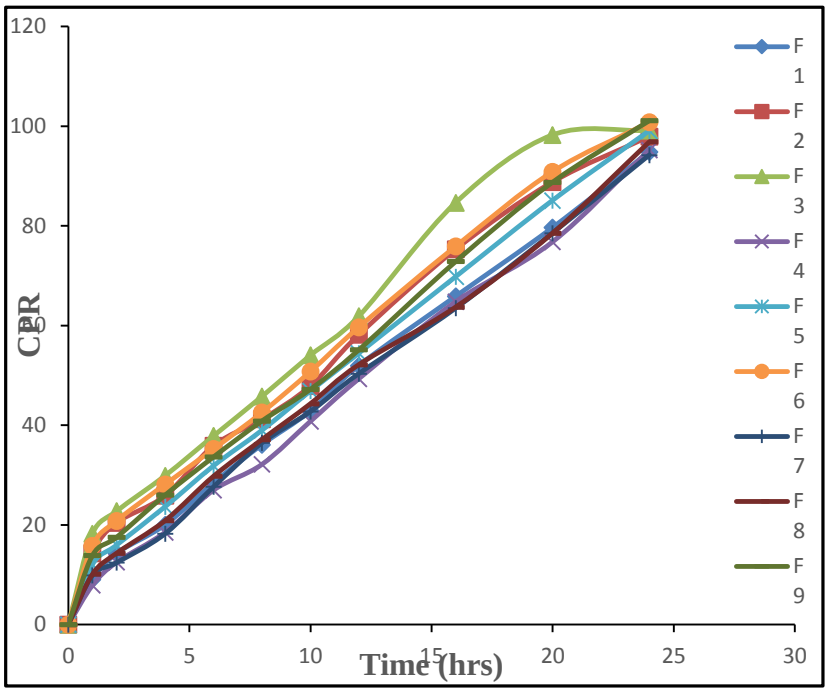

Figure 1 Comparison of release profile of factorial batches

The drug release profile of all 9 batches range is from 94.21 to 101.02 at 24 hours. From all batches Batch F5 shows drug release profile more comparable to the theoretical drug release profile. So, F5 batch is optimized.

RESULTS AND DISCUSSION

Formulation and evaluation of sustain release matrix pellets of antiretroviral drug with the objective of preparing such pellets, extrusion Spheronization method was selected. Initially process optimization was carried out by selection of process variable like, Spheronization speed and Spheronization time. Than by selecting optimized processing time and speed formulation was developed for various polymer selection and based on preliminary trail Eudragit RS PO and RL PO were selected. Ratio of Eudragit RS PO and Eudragit RL PO were optimized by factorial design.

Different Sustain release polymer was evaluated for % practical yield, flow property, hardness, friability, drug release profile. For selection of sustain release matrixing agent three polymers namely Eudragit RS PO, Eudragit RL PO and HPMC K_4M were evaluated. After that Ratio of

concentration of Eudragit RS PO and Eudragit RL PO was selected as sustain release matrix forming polymer. Optimum conc. of Povidone K-30 was checked as binding agent.

From the above study, when used HPMC K_4M as a sustain release matrixing agent. It shown that the flow parameters like angle of repose (θ), bulk density, tapped density compressibility and Hausner's ratio are suggestive of very poor flow properties of the pellets and can got rod shaped pellets which cannot be convert in spherical.

So, further preliminary work carried out with Eudragit RS PO and Eudragit RL PO. *In vitro* dissolution study was done. In this study, we could design and develop formulation, which gave sustain release of drug in throughout GIT for prolong period of time.

The concentration of the polymers could be successfully optimized by 3^2 full factorial designs. In this study, the concentration of sustain release polymer Eudragit RL PO and Eudragit RL PO were taken as independent variables whereas Q1 value, Q20 value were selected as dependent variables.

Contour plots and surface plots of all the dependent variables were prepared and the Ratio of concentrations of Eudragit RS PO and Eudragit RL PO were optimized as 20 %w/w and 12 %w/w respectively to validate the optimized batch and check point batch was prepared. The advantage of this formulation was that sustain drug release was obtained and the smaller pellets remained adhered in wrinkles of stomach and upper small intestine.

The mechanism by which this optimized batch provided the sustain drug release were initially by diffusion and then after by Swelling of polymer (Eudragit RS PO and Eudragit RL PO, a pH independent polymer).

CONCLUSION:-

The objective of the study was to prepare and evaluate Stavudine pellets by extrusion-Spheronization for sustained release. The method which was employed was simple, rapid, and economical and did not require the use of toxic solvents. The results of micromeritic properties of the pellets were well within the limit, which indicated good flow potential for the prepared pellets. From the FTIR studies, it was observed that there was no chemical interaction between the used drug and polymers indicating that drug were in stable form.

The drug content study revealed uniform distribution of the drug in the pellets. The drug release rate varied among the formulations depending on the compositions of polymers used. The obtained dissolution data indicated that the drug release follows Case II Transport. Optimized formulation F5 was an ideal formulation for a once daily administration.

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