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Formulation and evaluation of oro dispersible tablets of Stavudine

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ABSTRACT

In this present work Orodispersible tablet of Stavudine were designed with a view to enhance the patient compliance. Oral dispersible tablet of Stavudine were prepared by direct compression method after incorporating Superdisintegrants sodium Starch glycolate, Crospovidone, Croscarmellose, and kollid on CLM. Twenty formulation having Superdisintegrants at different concentration (5, 10, 15, 20 %) level were Prepared. The prepared batches of tablets were evaluated for Tablet weight variation, content uniformity, hardness and friability. Effects of Superdisintegrants on wetting time, dispersion time, and *in vitro* release also have been studied. Tablet containing Kollidon CL M (20%) showed excellent *in vitro* dispersion time and drug release as compared to other formulations. After the color and flavor optimization study formulations F18 shows short dispersion time (18sec) with maximum drug release in 10 min. FTIR & DSC results showed no evidence of interaction between the drug and Superdisintegrants. It is concluded that Oro dispersible Stavudine tablets could be prepared by direct compression method using kollidon CL M superdisintegrants.

Key words: Stavudine, Superdisintegrants, Oro dispersible tablets, in vitro dissolution test.

1. INTRODUCTION

The oral route of administration is the most important method of administering drugs for systemic effects. Many pharmaceutical dosages are administered in the form of tablets, hard gelatin capsules, granules, powders, and liquids [1]. Many patients, particularly pediatric and geriatric and bedridden patients have difficulty in swallowing or chewing solid dosage forms [2,3]. This problem is also applicable to active working or travelling people who do not have ready access to water. Recent advances in novel drug delivery systems (NDDS) aim to develop fast dissolving / disintegrating tablets to improve patience compliance [4,5]. Oro dispersible tablets (ODTs) dissolve or disintegrate in saliva within a minute without the need of water or chewing. Advantages of oro dispersible tablets include convenience of administration, patient compliance, rapid onset of action, increased bioavailability, accurate dosing as compared to liquids, good stability, ability to provide advantages of liquid medication in the form of solid preparation, ideal for pediatric and geriatric patient and rapid dissolution/absorption of the drug [6,7].

Some drugs are absorbed from the oral cavity (mouth, pharynx and esophagus) as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form [8]. ODTs also beneficial for schizophrenic, parkinsonism or developmentally disabled patients with persistent nausea, those with conditions of motion sickness, sudden episodes of allergic attack or coughing, and patients who do not have ready access to water [9].

The various technologies used to prepare ODTs include conventional methods like direct compression, wet granulation, moulding, spray drying, freeze drying and sublimation. Direct compression represents a simple and cost effective tablet manufacturing technique [10]. The basic approach used in the development of the Oro dispersible tablets is the use of Superdisinte grants. Superdisintegrants facilitate the break up or disintegration of tablet content into smaller particles that can dissolve more rapidly than conventional dosage form [11]. The commonly used superdisintegrants are Croscarmellose sodium, Crospovidone, Kollidon CLM and sodium starch glycolate [12,13].

Stavudine is a nucleotide reverse transcri ptase inhibitors and primarily used in the treatment of AIDS [14]. Stavudine is typically administered orally as a capsule and an oral solution. The drug has a very short half-life (1.30 h). Its dose is 40 mg twice or three times a day [15]. Its solubility in water and bland taste makes it an

ideal candidate for oro dispersible tablets with regards to palatability.

The objective of the present study is to develop oro dispersible tablets of stavudine and to study the effect of different Superdisintegrants on the tablet disintegration as well as to improve the patient compliance without compromising the therapeutic efficacy.

2. MATERIALS AND METHODS

2.1. Materials

Stavudine was a gift sample from Aurobindo Pharma Ltd,Hyderabad.Croscarmellose sodium, Sodium starch glycolate, Crospovidone, Kollidon CLM was procured from Amishi drugs & chemicals Ltd, Ahmedabad. Microcrystalline cellulose was procured from Signet Chemicals. Aspartame flavours and colours (Ranbaxy, New Delhi, India) were obtained. All other ingredients used were of analytical grade.

2.2. Preparation of tablets

Oro dispersible tablets containing 40 mg of Stavudine were prepared by direct compression method and the various formula compositions used in the study are shown in [Table 1 & 1a]. All the powders passed through a 60 mesh sieve. All the ingredients without magnesium stearate and talc were mixed uniformly followed by addition of magnesium stearate and talc. The prepared powder blends were compressed (6 mm diameter, round flat faced punches) using multiple punch tablet compression machine (Cad mach Machinery Ltd., Ahmedabad, India). All the tablets were stored in airtight containers for further study.

2.3. Evaluation of Stavudine oro dispersible tablets

2.3.1. Tablet Hardness

The Stavudine oro dispersible tablets hardness was measured by using Monsanto hardness tester. From each batch the crushing strength of ten tablets with known weights were recorded in kg/cm^2 and average was calculated and presented with standard deviation [16].

2.3.2. Friability

Previously weighed 10 tablets from each batch were taken in Roche friabilator (Roche friabilator, Pharma labs, Ahmedabad, India). After100 revolutions of friabilator tablets were recovered. The tablets were then made free from dust and the total remaining weight was recorded .Friability was calculated from the following formula [8].

$$\text{Percentage friability} = \frac{(\text{Initial weight} - \text{Final weight}) \times 100}{\text{Initial weight}}$$

2.3.3. Weight Variation Test

To study weight variation individual weights (W_I) of 20 tablets from each formulation were noted using electronic balance. The average weight (W_A) was calculated and Percent weight variation of each tablet was calculated as follows [17].

$$\% \text{ weight variation} = (\text{Individual weight} - \text{Average weight} / \text{Average weight}) \times 100$$

Table 1. Composition of Stavudine ODT tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16
Stavudine	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40
MCC	47.5	47.5	47.5	47.5	42.5	42.5	42.5	42.5	37.5	37.5	37.5	37.5	32.5	32.5	32.5	32.5
SSG	5	-	-	-	10	-	-	-	15	-	-	-	20	-	-	-
Crospovidone	-	5	-	-	-	10	-	-	-	15	-	-	-	20	-	-
CCS	-	-	5	-	-	-	10	-	-	-	15	-	-	-	20	-
Kollidon CLM	-	-	-	5	-	-	-	10	-	-	-	15	-	-	-	20
Aerosil	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mg.stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Talc	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Total weight	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100

Table 1a. Composition of ODTs tablets with flavor and Coloring agents

Ingredients(mg)	F17	F18	F19	F20
Stavudine	40	40	40	40
MCC	35	35	35	35
Kollidan CL M	20	20	20	20
Citric acid	10	10	10	10
Menthol	10	10	10	10
Aspartame	20	20	20	20
Banana	-	-	5	5
Orange	5	5	-	-
Sunset Yellow	2		2	-
FDC red 40	-	2		2
Aerosil	5	5	5	5
Mg stearate	1	1	1	1
Talc	2	2	2	2
Total	150	150	150	150

2.3.4. Thickness

Ten randomly selected Stavudine oro dispersible tablets from each formulation were used for thickness determination. Thickness of each tablet was measured by using digital Vernier Caliper (Mitutoyo Dial Thickness Gauge, Mitutoyo, Japan) and the results were expressed as mean values of 10 determinations, with standard deviations [18].

2.3.5. Drug content

Twenty tablets were taken and powdered ; powder equivalent to one tablet was taken and dissolved in 100 ml of 0.01N HCl buffer. The solution was filtered, suitably diluted and the drug content was measured by using UV-Visible Spectrophotometer (Elico, India) at 266 nm. Each measurement was carried out in triplicate and the average drug content in the oro dispersible tablet was calculated [19].

2.3.6. Wetting Time

Five circular tissue papers of 10cm diameter were placed in a Petridish containing 10.0 ml of water containing Eosin blue. A tablet was carefully placed on the surface of tissue paper. The time required for develop blue color on the upper surface of the tablet was noted as the wetting time [20,21].

2.3.7. In -Vitro Disintegration time

Disintegration time of Stavudine oro dispersible tablets was measured using USP tablet disintegration test apparatus (Electrolab, India) using 900 ml of distilled water without disk at room temperature [22].

2.3.8. In -Vitro Drug Release

In vitro drug release studies were carried out using USP dissolution apparatus type II (Electrolab, Mumbai, India) at 37 ± 0.5ºC .The study were performed with rotation speed of 50 rpm using 900ml dissolution medium of 0.01N HCl buffer as dissolution medium. The samples were withdrawn at predetermined intervals (5min) and replaced with an equal volume of buffer. The drug release at different time intervals was measured using an UV spectrophotometer (Elico, Ahemadabad, India) at 266 nm after suitable dilution. The study was performed in triplicate [23,24].

2.3.9.Flavor, color and mouth feel optimization

To assess the color, flavor, taste and mouth feeling of prepared Stavudine Orodispersible tablets, different age group healthy volunteers were employed. The human test was performed according to the guidelines and the reports of the volunteers were recorded [25].

2.3.10. Drug excipients compatibility study

The pure drug, Stavudine and formulations with the Croscarmellose sodium, Sodium starch glycolate, Crospovidone, Kollidon CLM powders was mixed separately with IR grade KBr and pellets were prepared by applying a pressure of 10 tons in a hydraulic press. The pellets were scanned over a wavelength range of 400 to 4,000 cm^{-1} [26].

DSC studies also performed to investigate the physical state of the drug in the tablets and to know the interactions of drug with Superdisinte grants in the formulation. Thermal properties of pure drug and the formulation were evaluated by Differential scanning calorimetry (DSC) using a Diamond DSC (Mettler Star SW 8.10). The analysis was performed at a rate 5 ^{0}C min-1 from 500 ^{0}C to 2000 ^{0}C temperature range under nitrogen flow of 25 ml min [27].

3. RESULTS AND DISCUSSION

The physicochemical characterizations of different batches of Stavudine oro dispersible tablets are given in (Table 2-3). The thickness of the ODTs tablets were ranged between 2.42± 0.08 to 2.69 ± 0.03 mm. All the batches showed uniform thickness. Weight variations for different formulations were found to be 98.2 ± 1.37 to 102 ± 1.8 mg. All the tablets passed weight variation test as the percentage weight variation was within the pharmacopoeial limits (10%).

Table 2: Physico chemical properties of Stavudine ODT tablets

Formulation code	Hardness (kg/cm²)	Thickness (mm)	Friability	Weight variation
F1	3.5±0.5	2.69± 0.03	0.54	99.4±1.5
F2	3.0±0.5	2.44±0.03	0.54	101±1.8
F3	4.0±0.5	2.50±0.09	0.68	102.3±1.6
F4	3.5±0.5	2.48±0.50	0.64	102±1.8
F5	3.5±0.5	2.65 ±0.02	0.45	101.1±1.1
F6	4.0±0.5	2.55 ±0.09	0.53	101.2±1.6
F7	3.5±0.5	2.45±0.09	0.63	99.2±1.5
F8	3.0±0.5	2.45±0.50	0.55	102.2±1.5
F9	3.5±0.5	2.60 ± 0.09	0.54	102.1±1.8
F10	4.0±0.5	2.48 ±0.06	0.65	98.2 ± 1.37
F11	3.5±0.5	2.50±0.09	0.55	100.3 ± 1.36
F12	4.0±0.5	2.52±0.40	0.64	101.5±1.8
F13	3.5±0.5	2.50 ± 0.09	0.65	99.3±1.8
F14	3.5±0.5	2.45 ± 0.08	0.55	102.3±1.6
F15	3.9±0.5	2.42± 0.08	0.65	100.2 ± 1.39
F16	3.5±0.5	2.53± 0.08	0.68	101.3 ± 1.3

Table 3: Physico chemical properties of Stavudine ODT tablets

Formulation code	% Drug content	Disintegration time	Wetting Time
F1	98.14 ± 1.1	65±1.1	37±1.6
F2	100.19 ± 0.5	47±2.1	35±2.8
F3	99.58 ±0.52	41±1.5	33±2.2
F4	101.26 ± 0.96	42±1.1	31±1.9
F5	98.58 ± 0.99	40±0.8	30±2.5
F6	99.40± 0.97	30±0.8	33±3.2
F7	100.58 ± 0.99	25±0.8	35±1.7
F8	98.26 ± 0.8	25±0.8	31±1.8
F9	100.17 ± 1.24	28±0.9	27±1.5
F10	101.6±1.9	25±0.9	29±2.4
F11	101.6±1.8	24±0.9	33±1.9
F12	101.1±1.5	20±0.9	28±1.7
F13	98.6 ± 0.98	25±1.1	33±1.8
F14	101.1 ± 0.9	20±1.5	32±2.8
F15	100.7 ± 1.1	22±1.5	28±1.6
F16	99.26 ± 0.97	18±1.1	33±1.9

Table 4: Physico chemical properties of Stavudine ODT tablets for color & flavor optimization

Parameter	F17	F18	F19	F20
Weight Variation (mg)	150.2±1.5	151.1±1.5	151.3±1.5	152±1.8
Friability (%)	0.65	0.69	0.68	0.69
Hardness (Kg/cm^2)	4±0.5	3.5±0.5	3.5±0.5	4±0.5
Thickness (mm)	3.55±0.5	4.52±0.4	3.57±0.2	4.58±0.5
Disintegration time (Sec)	25±0.8	20±0.9	22±1.1	18±1.1
Wetting time (sec)	36±1.8	38±1.7	37±1.9	39±1.9
Taste/mouth feel	Average	Excellent	Average	Good
Assay (%)	98	99	100	101

Table 5: Color identification data

S.No.	Age	Sunset yellow	FDC Red no.40	S.No.	Age	Sunset yellow	FDC Red no.40
1	11	--	--	16	33	Excellent	--
2	12	--	Poor	17	35	Excellent	Average
3	15	--	--	18	29	Excellent	--
4	10	--	Average	19	25	Excellent	--
5	15	--	--	20	30	Excellent	Good
6	14	--	--	21	50	--	Excellent
7	12	--	--	22	55	--	Excellent
8	13	--	--	23	54	--	Excellent
9	14	--	--	24	62	Good	Good
10	16	Good	--	25	64	--	Good
11	26	Excellent	--	26	60	Good	--
12	28	Excellent	--	27	57	--	Excellent
13	30	Good	--	28	56	--	Excellent
14	32	Excellent	--	29	57	--	Excellent
15	35	Good	Average	30	63	--	--

Hardness of all the prepared ODTs tablets was found to be satisfactory .The hardness were ranged from 3.0±0.5 to 4.0±0.5 kg/ cm^2. The percentage friability of all the formulations was ranged from 0.45 % to 0.68 %. In the present study, the percentage friability for all the formulations was within the prescribed limits, indicates the tablets possess good mechanical strength. The percentage of drug content for F1 to F16 was found to be in between 98.14 ± 1.1 to 101.6±1.9 of Stavudine it complies with official specification. Wetting time of the tablets were ranged 27±1.5 to 37±1.6 sec and disintegration time were 65±1.1 to 18±1.1 sec which indicated fast wetting and disintegration of tablet formulations in mouth. The cumulative percentage of the drug release determined by dissolution was ranging from 96.43±0.5 to 100±0.9 % after 15min as shown in figure 1.1-1.5. Superdisintegrants at different concentration level (5, 10, 15 and 20% w/w) were used to assist disintegration. The formulation prepared with lower concentration of Crospovidone, Kollidan, Sodium starch glycolate, Croscarmellose sodium yields rapid disintegration and dissolutions. However DT was a little more in the lower

concentrations of Superdisintegrant formulations. To improve the disintegration time, the formulations were prepared with higher concentrations of superdisintegrants such as 15 and 20%. Higher concentrations of superdisinte grants improved the disintegration time without any changes in the physico-chemical properties. All formulations had disintegration time of less than 65 second. Among the four Superdisintegrant we have used, Kollidon CLM showed maximum efficiency. The mouth feel of the formulations prepared with Kollidan CLM, Sodium starch glycolate, croscarmellose sodium is resulted smooth and fine particles where as the formulations prepared with crospovidone, yields particulate matter on the tongue. Formulation F16 containing 20% w/w Kollidon CLM showed the least disintegration time of 18 sec. Formulation F16 was selected for further color and flavor optimization study. Sweetener aspartame was used along with citric acid and menthol.

Different flavoring agents such as banana, orange, were incorporated into the formulations prepared with Kollidan CL M (20%) and aspartame as sweetener. There is no significant change was observed in the physico-chemical properties (Table 4). In-vivo taste and flavor evaluation was performed on the prepared tablets at different time intervals. The formulations prepared with Kollidan CL M-Aspartame-Orange flavor scored excellent during in-vivo evaluation. Based on the above results the formulation (F17) was selected as optimized formulation for further color optimization. The tablets were incorporated with different coloring agents.

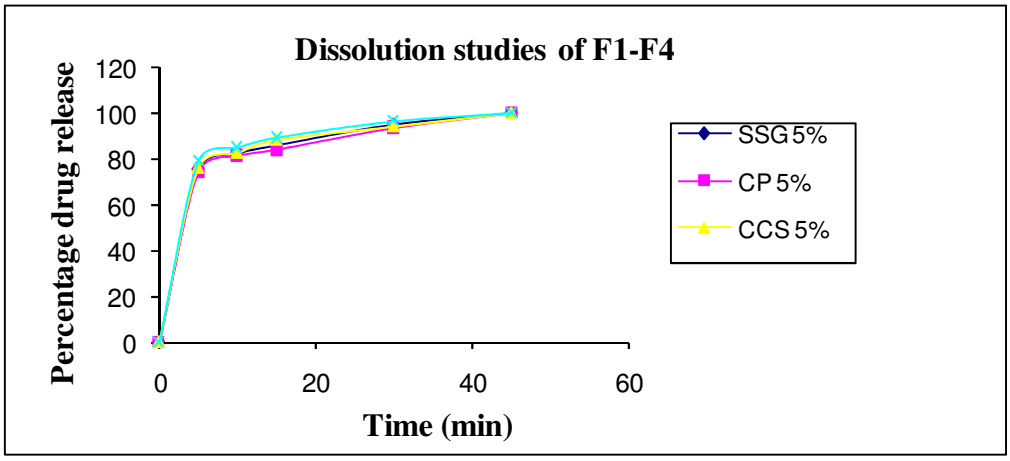

Figure 1.1: Comparative release profile of formulation F1 to F4

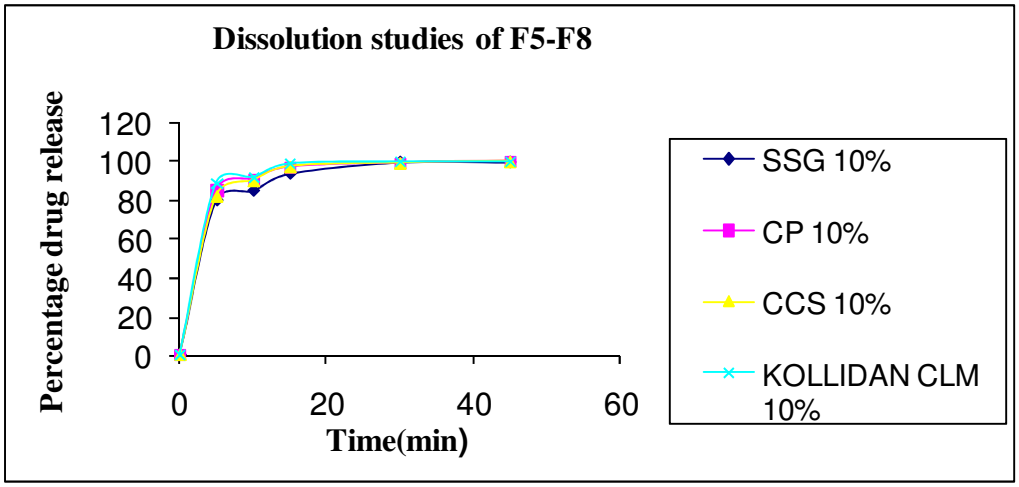

Figure 1.2: Comparative release profile of formulation F5 to F8

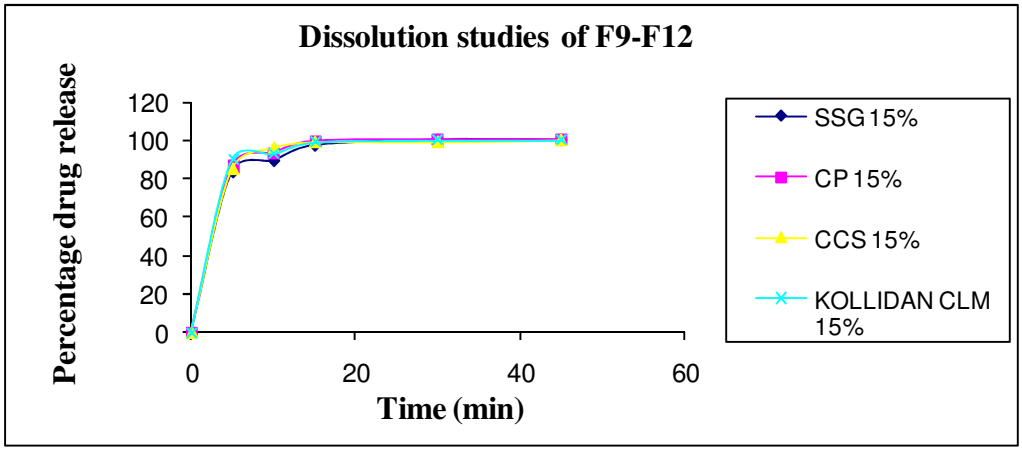

Figure 1.3: Comparative release profile of formulation F9 to F12

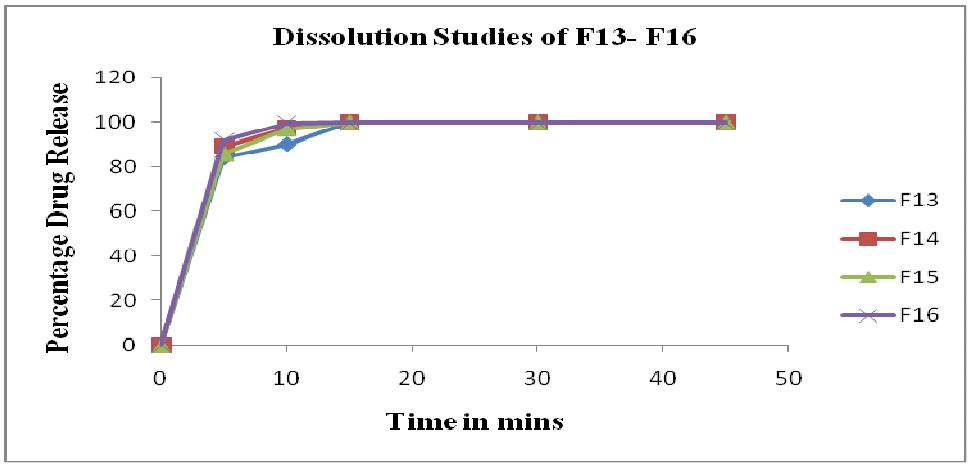

Figure 1.4: Comparative release profile of formulation F13 to F16

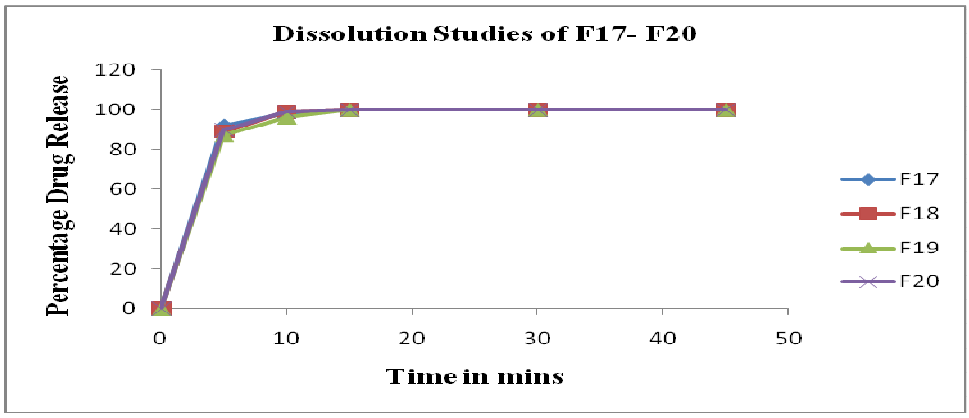

Figure 1.5: Comparative release profile of ODT formulation with different flavoring agents

Figure 2: Photograph showing the colored tablets of Stavudine ODT1. Sunset yellow lake 2. FDC Red No. 40

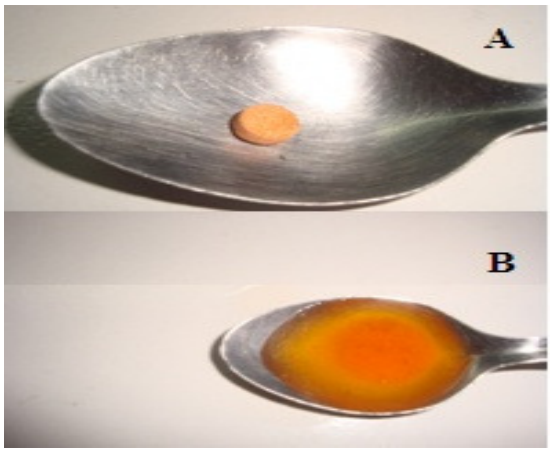

Figure. 3: A- Represents tablet before dispersion; B- Represents tablet after dispersion in 15 seconds

In the color identification most of the people in the age group of 50-60 years likes FDC Red No.40. People in the age group of 25-30 years like Sunset yellow lake as shown in figure 2 & 3 (Table 5). The optimized formulations F18 contain 20 % Kollidon CL M with orange flavor exhibited least disintegration time (18sec) and faster drug dissolution (100% in 10min) will lead to enhance the patience compliance.

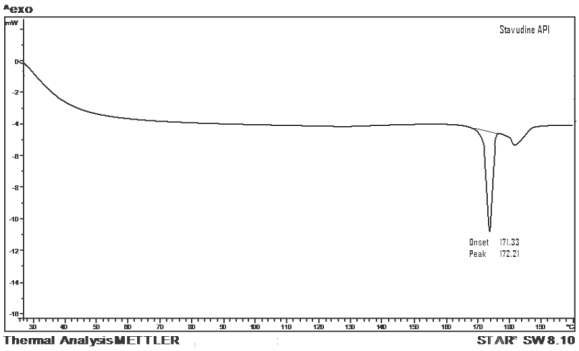

Figure 4.1. DSC thermogram of Stavudine pure drug

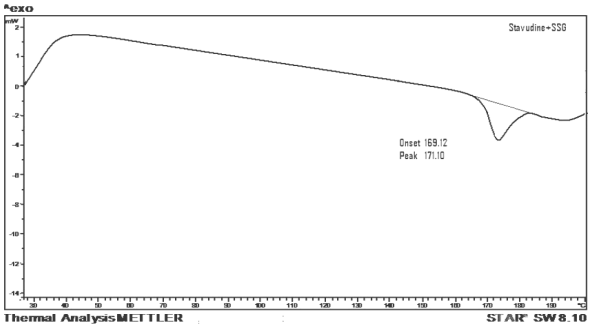

Figure 4.2: DSC thermogram of formulation with SSG

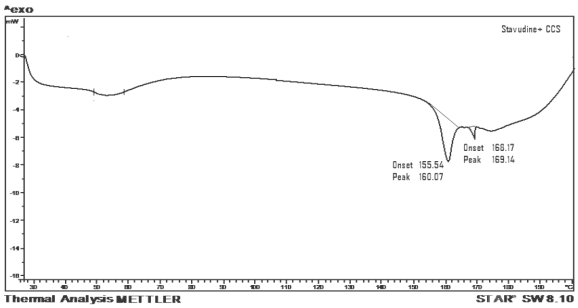

Figure 4.3: DSC thermogram of formulation with CCS

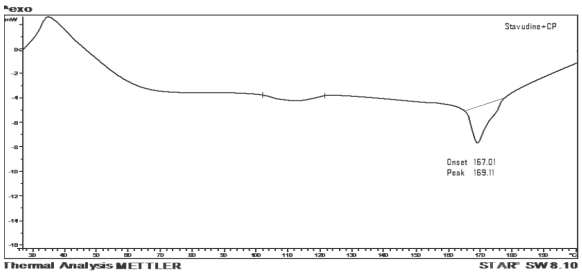

Figure 4.4: DSC thermogram of formulation with CP

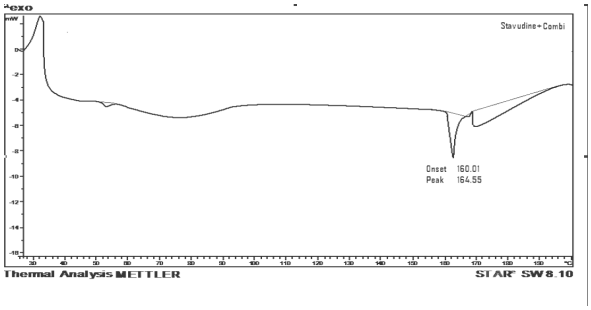

Figure 4.5: DSC thermogram of formulation F18

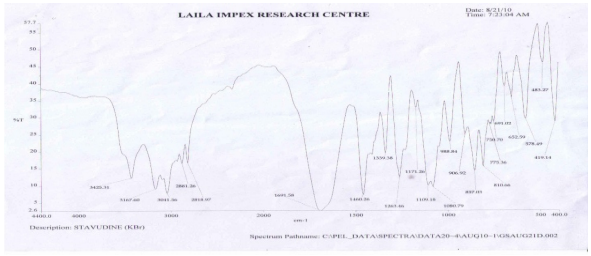

Figure 5.1: FTIR spectra of pure drug Stavudine

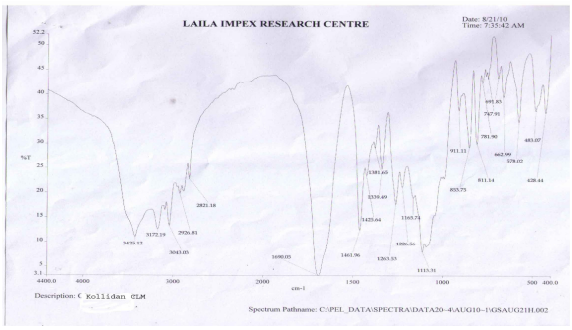

Figure 5.2 : FTIR spectra of formulation F18

FT-IR results revealed that there was no significant difference in the peaks of Stavudine and Superdisintegrants in ODTs tablets compared to pure Stavudine as shown in figure 5.1& 5.2. It was found that there was no interference to the drug with excipients and Superdisintegrants used in the formulations. Pure powdered Stavudine showed a melting endotherm at 172.21 ^{0}C, and Superdisintegrants in different formulation also showed their identical peaks at defined temperature range as shown in figure 4.1-4.5. Presence of all peaks indicates that all ingredients are compatible with drug and there is no incompatibility between the selected Superdisinte grants and Stavudine.

4. CONCLUSION

Oro dispersible tablets of Stavudine were successfully prepared with different Superdisinte grants by direct compression method were found to have adequate hardness and friability. The present studies were helped in understanding the effect of formulation process variables especially the concentration of different super disintegrants on the dispersion time and drug release profile. An overall result indicates that formulation F18 that contain 20 % Kollidon CL M with orange flavor exhibited least disintegration time and faster drug dissolution will lead to enhance the patience compliance. FTIR & DSC studies proved that no chemical interaction between stavudine and Super disintegrants of the developed ODTs tablets .Taste masked oro dispersible tablets of Stavudine formulated in this investigation may possibly help in administration of Stavudine in a more palatable form without water, thus, the "patient-friendly dosage form" of bitter drug Stavudine, especially for pediatric, geriatric, bedridden, and non cooperative patients. By the availability of various technologies and manifold advantages ODT will su rely enhance the patience compliance, rapid onset of action, increase bioavailability, low side effects, and good stability. These formulations may be commercialzed after establishing chemical and biological parameters.

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