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Formulation and Evaluation of Oro Dispersible Tablets of Stavudine by Direct Compression Technique

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ABSTRACT

The purpose of the present research was to optimize the formulation of Orodispersible tablets of Stavudine. Orodispersible tablets of Stavudine were prepared by direct compression method using different types of Superdisintegrant (Sodium Starch Glycolate, Crospovidone, Croscarmellose, and kollidan CLM) at different concentrations. The formulations were evaluated for effect of Superdisintegrant on Tablet weight variation, content uniformity, hardness, friability, wetting time, dispersion time, drug content and in vitro release also have been studied. All formulations showed satisfactory mechanical strength and tablet containing Kollidon CLM (20%) showed excellent in vitro dispersion time and drug release as compared to other formulation. The results revealed that the tablets containing 20% kollidan CLM (F20) showed short dispersion time (18 sec) with maximum drug release (100%) in 10 min. FTIR & DSC results showed no evidence of interaction between the drug and polymers. This study helps in revealing the effect of formulation processing variables on tablet properties. It can be concluded that the Orodispersible tablets of Stavudine tablets could be prepared by direct compression using kollidon CLM superdisintegrant.

INTRODUCTION

Recent advances in novel drug-delivery system aims to enhance the safety and efficacy of the drug molecule by formulating a dosage form being convenient for the administration. Difficulty in swallowing (i.e., dysphagia) is experienced by patients such as paediatrics, geriatric, bedridden, disabled, mentally ill, including motion sickness and sudden episodes of allergic attacks, hence resulting in higher incidence of noncompliance and ineffective therapy^[1]. In order to solve this problem and improve patient acceptance and compliance, the development of solid dosage forms that disintegrate rapidly or dissolve even when taken orally without water is being undertaken. Oral fast-disintegrating dosage forms (tablet or a capsule) are a relatively novel dosage technology that involves the rapid disintegration or dissolution of the dosage form^[2] into a solution or suspension in the mouth without the need for water^[3]. The dosage form begins to disintegrate immediately after coming into contact with saliva, with complete disintegration normally occurring within 30–50 s after administration^[4]. The solution containing the active ingredients is swallowed, and the active ingredients are then absorbed through the gastrointestinal epithelium to reach the target and produce the desired effect. Tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness, and ease in manufacturing^[5]. Orally disintegrating tablets are also called as Orodispersible tablets, quick-disintegrating tablets, mouth-dissolving tablets, fast-disintegrating tablets, fast dissolving tablets, rapid-dissolving tablets, porous tablets, and rapid melts. However, of all the above terms, the United States Pharmacopoeia (USP) approved these dosage forms as Orodispersible tablets (ODTs). Recently, the European Pharmacopoeia has used the term Orodispersible tablets for tablets that disperse readily and within 3 min in the mouth before swallowing. The United States Food and Drug Administration define ODT as “a

solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue.” The disintegration time for ODTs generally ranges from several seconds to about a minute^[6]. Other advantages of ODTs that have been investigated are their potential to increase the bioavailability of poorly water soluble drug through enhancing the dissolution profile of the drug^[7]. Moreover, pharmaceutical companies also have commercial reasons for formulating ODTs. As a drug reaches the end of its patent, the development and formulation of the drug into new dosage forms allow pharmaceutical companies to extend the patent life and “market exclusivity”^[8]. The ODTs could be prepared using various techniques such as tablet moulding, spray drying, sublimation, lyophilisation, solid dispersion, or addition of disintegrants^[9-13]. The basic approach to the development of ODTs is the use of superdisintegrants such as Croscarmellose sodium and sodium starch glycolate. Another approach used in developing ODTs is maximizing the pore structure of the tablet matrix. Freeze drying and vacuum drying techniques have been tried by researchers to maximize the pore structure of the tablet matrix^[14-16]. However, freeze drying is cumbersome and yields a fragile and hygroscopic product. Vacuum drying along with the sublimation of volatilizable ingredient has been employed to increase tablet porosity. While in designing dispersible tablets, it is possible to achieve effective taste masking as well as a pleasant feel in the mouth. The main criterion for ODTs is the ability to disintegrate or dissolve rapidly in saliva of the oral cavity in 15 to 60 s and have a pleasant mouth feel^[17]. To improve the quality of life and treatment compliance, great efforts have been made to develop fast-disintegrating tablets (FDTs) in the oral cavity, using jelly, water-absorbing, and swelling-gelated materials or water-soluble polymers^[18].

MATERIALS AND METHODS

Stavudine was chosen as an active ingredient and was kindly gifted by Novartis, Turkey. Lactose (Tabletose 70, Meggle, Germany), sucrose (Di-Pac, Domino, USA), directly compressible (DC) mannitol (Roquette, France), cross-linked sodium carboxymethylcellulose (Ac-di-sol, Asahi Kasei, Japan), magnesium stearate (Turkey) were used. All other reagents were of analytical grade.

METHOD OF FORMULATION

Stavudine Oro-dispersible tablets were formulated by using direct compression method. The drug and all other excipients were sifted through #40 sieves and mixed thoroughly. The above blend was pre lubricated with aerosil and lubricated with magnesium stearate. The above lubricated blend was compressed using 6mm round punch at a tablet weight of 100mg.

CHARACTERIZATION OF ORODISPERSIBLE TABLETS:

The prepared tablets were evaluated for different Post Compressional properties like weight variation, friability, hardness, thickness, disintegration time, wetting time, assay and In vitro dissolution studies.

WEIGHT VARIATION^[19-25]:

20 tablets were selected at a random and then the average weight was determined. All the 20 tablets were weighed individually and compared with the average weight the tablets meet USP specifications if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

FRIABILITY^[19-25]:

The friability test was performed for all the formulated Oro-dispersible stavudine tablets. Twenty tablets were taken and their weight was determined. Then they were placed in the Roche friabilator and allowed to make 100 revolutions. The tablets were then de-dusted and reweighed. The percentage weight loss was calculated. Percentage Friability was calculated as follows

$$\text{Percentage Friability} = (W_1 - W_2) \times 100/W_1$$

Where, W₁ = Initial weight of the 20 tablets.

W₂ = Final weight of the 20 tablets after testing.

Friability values below 1% are generally acceptable.

HARDNESS^[19-25]:

Monsanto hardness tester was used for measuring the hardness of the formulated Oro-dispersible Stavudine tablets. From each batch five tablets were taken and subjected to test. The mean of the five tablets were calculated. The breaking strength (in kg) of each tablet was tested using a Stokes-Monsanto hardness tester (DT Stokes, Bristol, PA). The formulated as well as the commercial tablets were circular and flat. After the dial on the tester was set to

zero, a tablet was placed between the two jaws. The breaking point was determined by gradually increasing the force on the tester. Breaking strength is the force applied (in kg) to break the tablet radially into two halves.

WETTING TIME [19- 25]:

The wetting time of the tablets was measured using a simple procedure. 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.

THICKNESS OF TABLETS [19- 25]:

Thickness is measured by using instrument called digital “vernier calipers”. Randomly 10 tablets were taken and thickness was measured for each tablet by placing between two anvils and rotating sliding knob until the tablet was tightly fitted and the reading was noted on the digital scale.

IN- VITRO DISPERSION TIME [26]:

In vitro dispersion time was measured by dropping a tablet in spoonful of water or in 20ml of water in a beaker. The time for the tablet to completely disintegrate into fine particles was noted. Three tablets from each batch were randomly selected and *in vitro* dispersion time was performed.

DRUG CONTENT:

10 tablets were taken, powdered well and a quantity of powder equivalent to 100mg of stavudine was accurately weighed and dissolved in 100ml of 0.01N HCl and filtered. The absorbance of the solution was measured at 266nm against blank (0.01N HCl). The concentration of the sample was calculated using standard graph.

COLOR, TASTE AND MOUTH FEEL EVALUATION [27]:

A panel of 6 volunteers was employed to assess the color, taste and mouth feeling of prepared Stavudine Orodispersible tablets. The human test was performed according to the guidelines of WMA Helsinki declaration²⁸. The comments of the panel members were recorded.

FTIR:

The FT-IR spectrums of pure drug and formulation were determined. A FT-IR (Thermo Nicolet 670 spectrometer) was used for the analysis in the frequency range between 4000 and 400 cm^{-1} , and 4 cm^{-1} resolution. The results were the means of 6 determinations. A quantity equivalent to 2 mg of pure drug was used for the study.

DSC:

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 50°C min⁻¹ from 500°C to 2000°C temperature range under nitrogen flow of 25 ml min⁻¹.

IN-VITRO DRUG RELEASE:

In vitro dissolution studies for all the formulated tablets was carried out using USP paddle method at 50 rpm in 500ml of 0.01N HCl as dissolution media, maintained at 37±0.5°C. 5 ml aliquot was withdrawn at the specified time intervals, filtered through wattmann filter paper and assayed spectrophotometrically at 266nm. An equal volume of fresh medium, which was pre-warmed at 37°C, was replaced into the dissolution media after each sampling to maintain the constant volume throughout the test. Dissolution study of conventional marketed tablet of stavudine is also carried out using same method.

RESULTS AND DISCUSSION

Hardness:

Table - 2 shows the hardness of all formulations, and the hardness was constantly maintained between 3-4 kg/cm² for all formulations during compression.

Friability:

Table 2 shows the friability values all the formulations. The results indicated that the % friability was between 0.45 to 0.68%. The low values of friability indicate that tablets were mechanically hard enough.

Thickness:

As shown in Table - 2, thickness of tablets ranged from 2mm to 3 mm.

Disintegration Time:

Table -1 show the disintegration time of the formulations. As the percentage of superdisintegrant increased (5% to 20%) the disintegration time decreased significantly ($p < 0.05$). It is because kollidon CLM (20%) containing tablets rapidly exhibits high capillary activity and pronounced hydration with a little tendency to gel formation and disintegration the tablets rapidly.

Wetting Time:

Table - 2 & Figure - 1 shows the wetting time studies of all formulations. Wetting time is lesser in case of kollidon CLM (20%) because of higher capillary action.

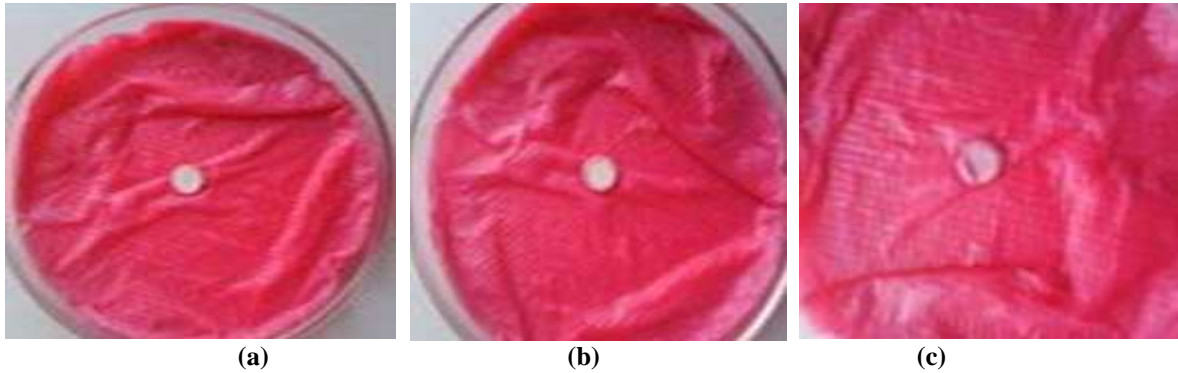


Fig - 1: Wetting time of Kollidon CLM (20%) at 5 (a), 25 (b) & 33 (c) Seconds.

Drug Content of Tablets:

Table -2 show the drug content of tablets ranged between 98 to 101%.

In Vitro Dispersion Time:

In vitro dispersion time was measured by dropping a tablet in spoonful of water or in 20ml of water in a beaker. The time for the tablet to completely disintegrate into fine particles was noted. Three tablets from each batch were randomly selected and *in vitro* dispersion time was performed.

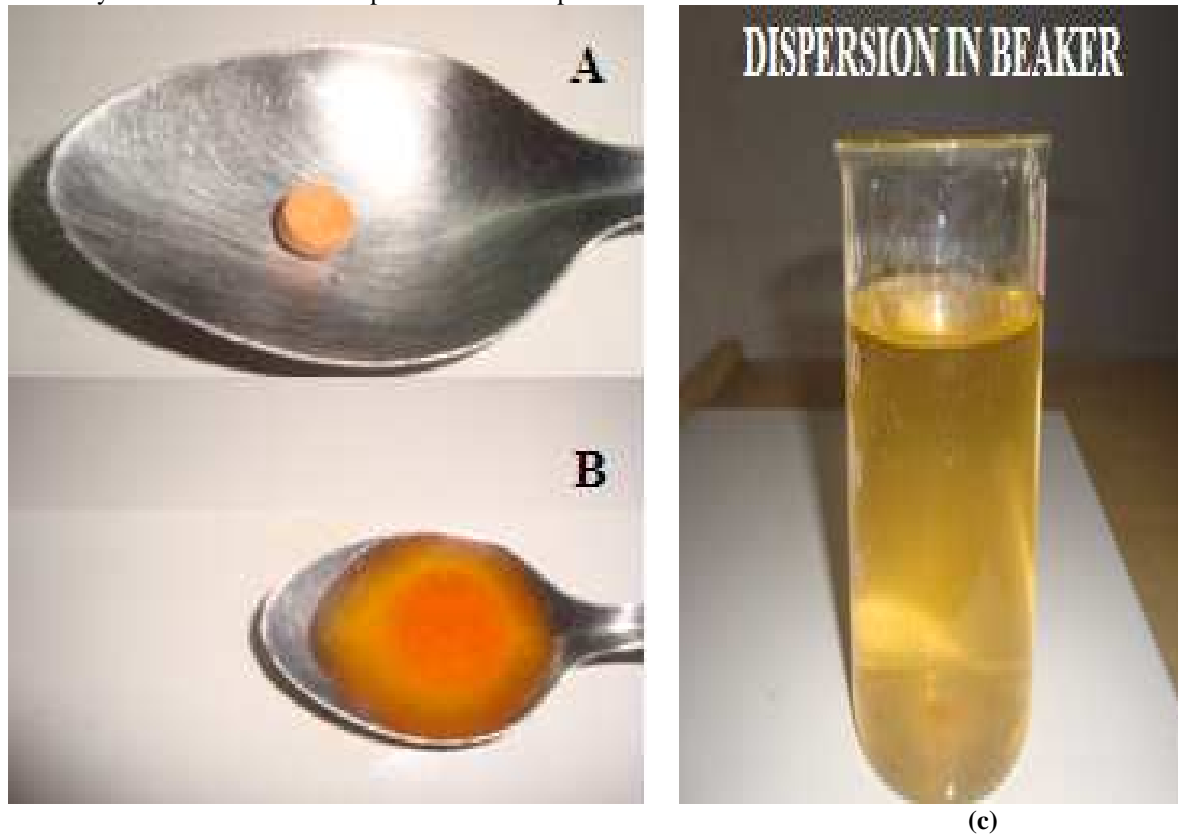


Figure - 2: A, B represents *In vitro* Dispersion time in spoonful of water and C represents *in vitro* dispersion in 20ml of water in a beaker in 15 Seconds.

Color, Taste and Mouth Feel Evaluation:

Table – 3(a), Figure - 3 shows formulations using two flavoring agents such as banana, orange with Aspartame. The tablets were compressed using 7mm round punch, each tablet weight is adjusted to 150mg. The prepared tablets were evaluated for different physico-chemical properties like weight variation, friability, hardness, thickness, disintegration time, wetting time, assay, taste/mouth feel and in vitro dissolution studies.

The weight variation of all formulations was in the range. Drug content of Stavudine from all the formulations was found to be in the range of 98% to 101%. The hardness was constantly maintained between 4-5 g /cm² during compression. Friability for all the formulation shown less than 0.69% which is in the acceptable limits which indicates formulations have good mechanical strength. Thickness of the tablets found to be 3.55 mm to 4.58mm. Disintegration time of formulations found to be between 18-25 seconds. The results were summarized in table – 3(b).

Figure -4 shows the formulations were evaluated for in-vitro dissolution studies, the formulations released 100% drug within 15 minutes. The results were summarized in table -3(b).



Figure - 3. Photograph 1 & 2 shows the colored tablets of Stavudine ODT

Dissolution studies of ODT with flavoring agents

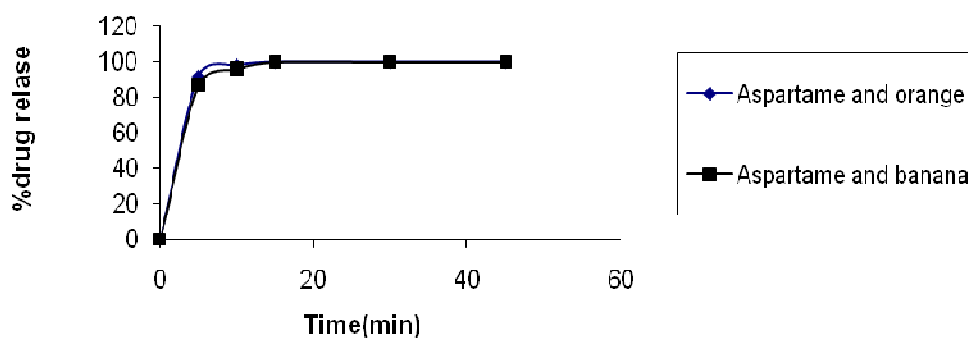


Figure - 4: Cumulative %drug release vs time profiles of Stavudine ODT prepared with (-♦-) Aspartame & orange, (-■-) Aspartame & banana.

Finally the prepared tablets were evaluated for taste and mouths feel in 6 volunteers. The formulations with aspartame and banana flavor scored good and average result where as the formulations prepared with aspartame and orange flavor was scored excellent. So this formulation (F18) was the optimized formulation.

Differential scanning calorimetric study (DSC)

Figure – 5 shows DSC results with sharp endothermic peak for the pure Stavudine at 172.21. Similar sharp endothermic peaks were observed in the formulations at almost similar temperatures. This clearly indicates that there is no drug excipient interaction.

Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR spectrum shows all the functional groups of pure drug Stavudine at 419.14, 483.27, 578.49, 652.59, 691.02, 750.70, 775.36, 810.66, 857.03, 906.92, 988.84, 1080.79, 1109.18, 1171.26, 1263.46, 1339.38, 1460.26, 1691.58, 2818.97, 2881.26, 3041.56, 3167.60, and 3425.31. Similar spectrum peak points were observed in all the formulations. This clearly indicates that there is no drug excipient interaction.

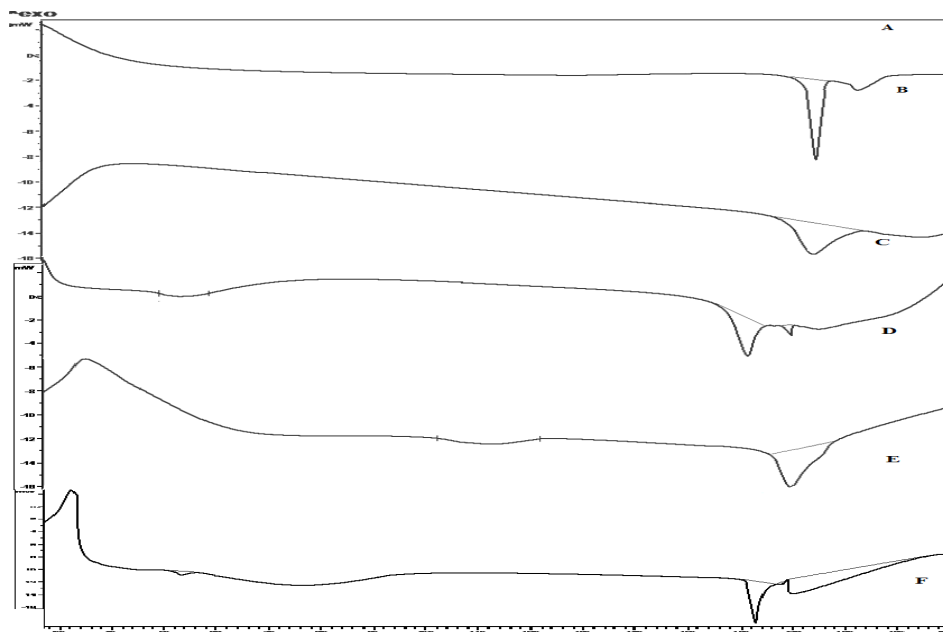


Fig – 5: DSC Thermograms of Pure Drug with different concentrations of Superdisintegrants.

DISCUSSION

Stavudine Orally dispersible tablets were developed with an aim to improve the patient's compliance. The formulations were developed with an objective to use by the pediatric and geriatric patients.

The Stavudine ODT formulation were developed with different superdisintegrants such as Crospovidone, Kollidan CLM, Sodium starch glycolate, Croscarmellose sodium.5, 10, 15, 20% used in each formulation. The formulation prepared with lower concentration of Crospovidone, Kollidan CL M, Sodium starch glycolate, Croscarmellose sodium yields rapid disintegration and dissolutions. However DT was a little more in the lower concentration of Superdisintegrant formulations).

Table – 1: Formulae used in the preparation of tablets containing different concentrations of Superdisintegrants.

INGREDIENTS (mg)	F ₁	F ₂	F ₃	F ₄	F ₅	F ₆	F ₇	F ₈	F ₉	F ₁₀	F ₁₁	F ₁₂	F ₁₃	F ₁₄	F ₁₅	F ₁₆
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

*Each value represents mean \pm S.D (n=3).

To improve the disintegration time, the formulations were prepared with increased concentrations of superdisintegrants such as crospovidone, Kollidan CLM, Sodium starch glycolate, croscarmellose sodium. Increased concentrations of superdisintegrants improved the disintegration time with any changes in the physico-chemical properties. 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.

Table – 2: Post – Compressional Parameters, Disintegration times, Wetting time, Drug Content & Dissolution time of different Tablet formulations.

Parameters	F ₁	F ₂	F ₃	F ₄	F ₅	F ₆	F ₇	F ₈	F ₉	F ₁₀	F ₁₁	F ₁₂	F ₁₃	F ₁₄	F ₁₅	F ₁₆
Weight Variation*(mg)	102±1.5	101±1.8	102.3±1.6	102±1.8	101.1±1.1	101.2±1.6	102.2±1.5	102.2±1.5	102.1±1.8	101.6±1.9	101.6±1.8	101.1±1.5	100.3±1.8	102.3±1.6	100.3±1.5	101.3±1.5
Friability (%)	0.54	0.54	0.68	0.64	0.45	0.53	0.63	0.55	0.54	0.65	0.55	0.64	0.65	0.55	0.65	0.68
Hardness* (Kg/cm ²)	3.5±0.5	3±0.5	4±0.5	3.5±0.5	3.5±0.5	4±0.5	3.5±0.5	3±0.5	3.5±0.5	4±0.5	3.5±0.5	4±0.5	3.5±0.5	3.5±0.5	3.9±0.5	3.5±0.5
Thickness(mm)	2.69±0.03	2.44±0.03	2.5±0.09	2.48±0.5	2.65±0.02	2.55±0.09	2.45±0.09	2.45±0.5	2.6±0.03	2.48±0.06	2.5±0.09	2.52±0.4	2.61±0.02	2.54±0.03	2.44±0.09	2.67±0.2
Disintegration time*(Sec)	65±1.1	47±2.1	41±1.5	42±1.1	40±0.8	30±0.8	25±0.8	25±0.8	28±0.9	25±0.9	24±0.9	20±0.9	25±1.1	20±1.5	22±1.5	18±1.1
Wetting time*(sec)	37±1.6	35±2.8	33±2.2	31±1.9	30±2.5	33±3.2	35±1.7	31±1.8	27±1.5	29±2.4	33±1.9	28±1.7	33±1.8	32±2.8	28±1.6	33±1.9
Drug Content (%)	98	100	99	101	98	99	100	98	98	98	100	101	98	101	100	100
Dissolution Time* (min)																
5	75.35±1.1	74.22±1.5	76±1.5	79.1±1.6	80.22±1.5	85.02±1.5	82.11±1.5	89±1.5	83.31±2.1	86.12±1.7	85±1.9	90±1.9	84.22±1.9	89.21±2.1	86±1.5	92±1.8
10	82.44±0.9	81.42±2.1	82.61±1.8	85±1.5	85.21±1.3	91.01±1.6	90.12±0.8	92±0.7	89.16±1.5	93.22±1.9	96±1.5	93±1.5	90.15±1.7	97.11±1.9	97±1.8	99.35±1.8
15	86±0.5	84.12±0.9	88.23±1.1	89.31±0.9	94.12±0.8	97.12±1.9	97.33±0.5	99±0.5	97.14±0.9	96.23±0.3	97±0.5	99±0.8	97±0.9	98±1.5	97±1.1	100±0.9
30	95±0.1	93.47±0.6	94.15±0.9	96.43±0.5	100±0.7	99.22±1.6	99.22±0.2	100±0.7	100±0.7	100±0.1	99±0.6	100±0.7	98±0.6	99±0.5	98±0.9	100±0.7
45	100±0.1	100±0.2	100±0.2	100±0.1	100±0.5	100±0.9	100±0.0	100±0.6	100±0.4	100±0.5	100±0.2	100±0.9	100±0.9	100±0.3	100±0.2	100±0.6

*Each value represents mean ± S.D (n=3).

Table – 3(a): Formulation data for Stavudine ODT with Flavoring 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

Table – 3(b): Physico-chemical parameters and dissolution data of Stavudine ODT with Flavoring Agents

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
Dissolution time(min)				
5	92.11±1.6	89.2±1.3	87.1±1.5	90±1.4
10	98.2±1.5	99.1±1.5	96.2±1.5	99.1±1.5
15	100±0.9	100±0.9	100±0.9	100±0.9
30	100±0.5	100±0.5	100±0.5	100±0.5
45	100±0.1	100±0.1	100±0.1	100±0.1

Invitro – Dissolution Studies:

Table – 2 & Figures -6, 7, 8 shows dissolution studies of Stavudine in 0.01 HCl.

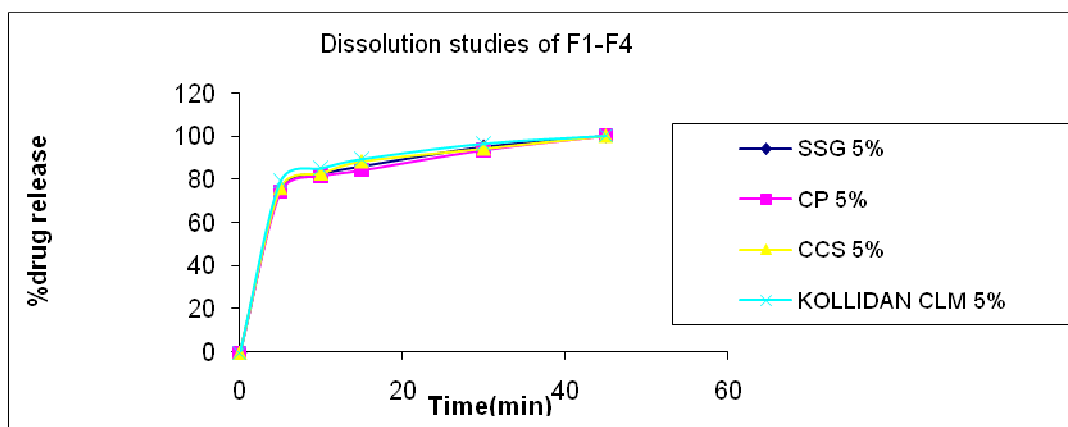


Figure - 6: Cumulative %drug release vs time profiles of Stavudine ODT prepared with(◆), SSG (■) CP, (▲) CCS, and (×) Kollidan CLM

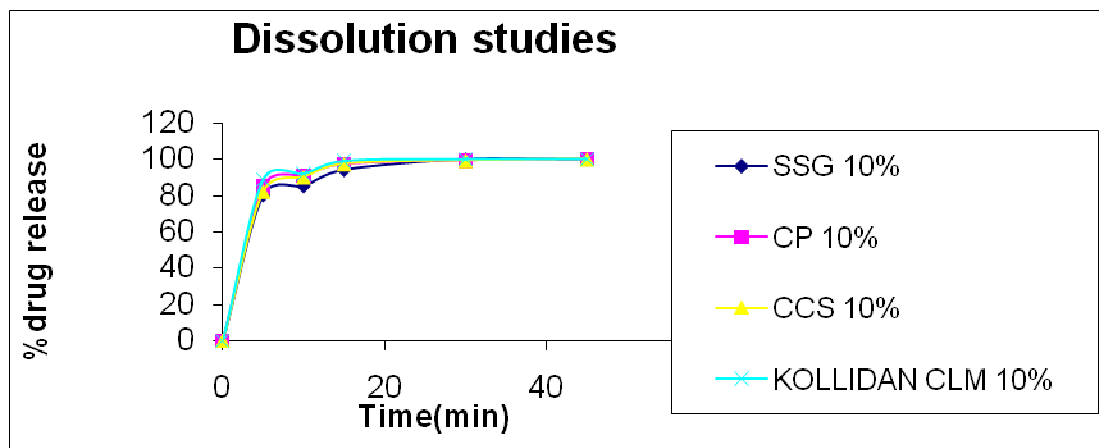


Figure -7: Cumulative %drug release vs time profiles of Stavudine ODT prepared with (-♦-) SSG, (-■-) CP, (-▲-) CCS, and (-x-) Kollidan CLM

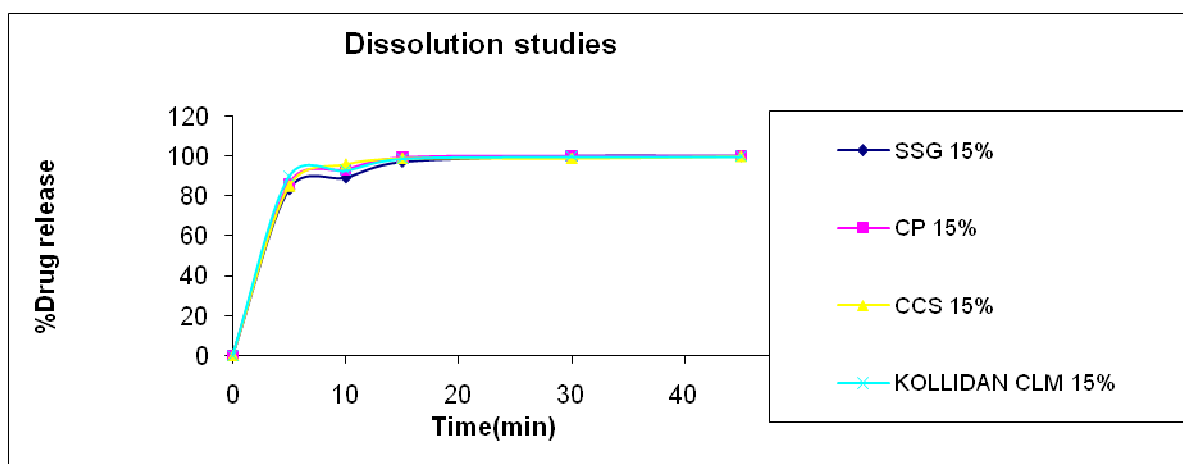


Figure -8: Cumulative %drug release vs time profiles of Stavudine ODT prepared with (-♦-) SSG, (-■-) CP, (-▲-) CCS, and (-x-) Kollidan CLM

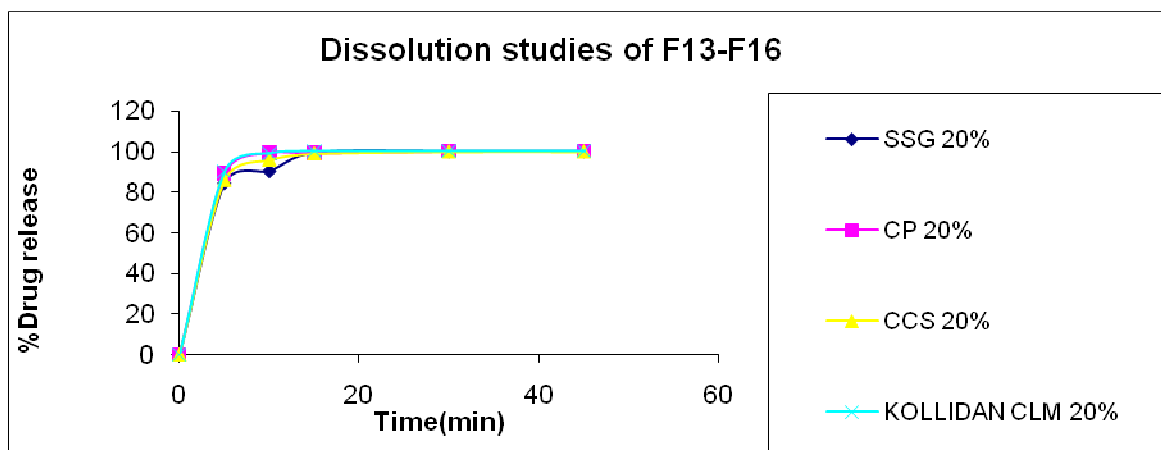


Figure -8: Cumulative %drug release vs time profiles of Stavudine ODT prepared with (-♦-) SSG, (-■-) CP, and (-▲-) CCS, (-♦-) Kollidan CLM

CONCLUSION

Oral disintegrating tablets of Stavudine were successfully prepared using different Concentrations of superdisintegrants by direct compression method. The present investigations 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. The present study concluded that 20% Kollidon CLM is comparatively for the preparation

of Stavudine Orodispersible tablets. Taste masking and rapid disintegration of tablets 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 paediatric, geriatric, bedridden, and non-cooperative patients. By the availability of various technologies and manifold advantages ODT will surely enhance the patient compliance, low dosing, rapid onset of action, increased bio availability, low side effects, good stability. These formulations may be commercialized after establishing chemical and biological parameters.

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