Academic Sciences Asian Journal of Pharmaceutical and Clinical Research
Vol 5, Suppl 4, 2012 ISSN - 0974-2441

Research Article

FORMULATION AND EVALUATION OF ORO DISPERSIBLE TABLETS OF STAVUDINE BY DIRECT COMPRESSION TECHNIQUE

SREE GIRI PRASAD. B*[1], V.R.M GUPTA[2], DEVANNA.N[3], RAMA DEVI. M[1], HARISH N[2], VAMSI KRISHNA[1], RAMAN KOUNDINYA[1]

[1*]**Teegala Krishna Reddy College of Pharmacy, Hyderabad, A.P, India;** [2] **Pulla Reddy Institute of Pharmacy, Hyderabad, A.P, India;** [3]**Jawaharlal Nehru Technological University, Anantapur, A.P, India; Email:** Prasad.bsreegiri@yahoo.co.in

Received: 25 September 2012, Revised and Accepted: 3 October 2012

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.

Keywords:

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

Stavudine was chosen as an active ingredient and was kindly gifted by Novartis, Turkey. Lactose (Tablettose 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- 22]:

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.

FRABILITY [19- 22]:

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

Percentage Friability = $(W_1 – W_2) \times 100/W_1$

Where, W1 = Initial weight of the 20 tablets.

W_2 = Final weight of the 20 tablets after testing.

Friability values below 1% are generally acceptable.

HARDNESS [19- 22]:

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 [23- 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 0f 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- 22]:

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 declaration[28]. 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/cm^2 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.

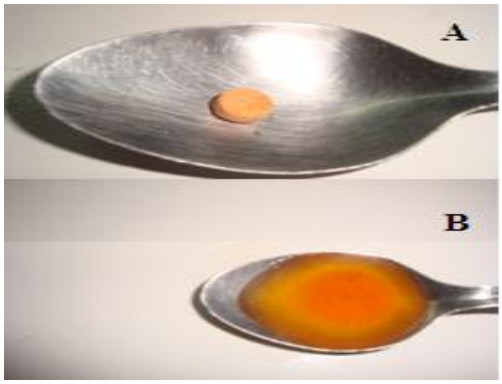
Fig 1: Wetting time of Kollidon CLM (20%) at 5 (a), 25 (b) & 33 (c) Seconds.

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.



(c)

Figure 2: A, B represents Invitro Dispersion time in spoonful of water and C represents invitro 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 /cm^2 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

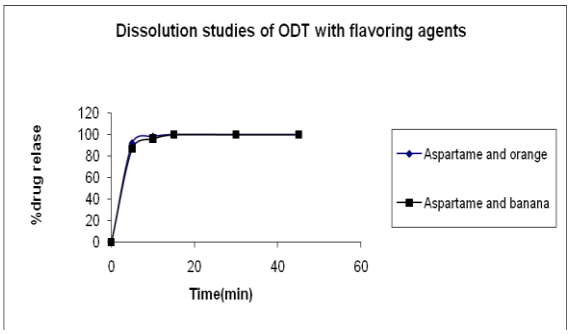


Figure 4: Cumulative %drug release vs time profiles of Stavudine ODT prepared

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 – 5shows 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.

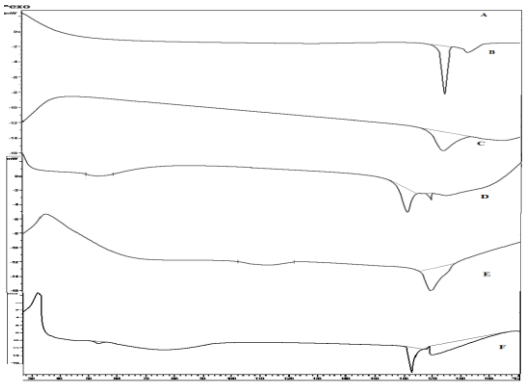


Fig 5: DSC Thermograms of Pure Drug with different concentrations of Superdisintegrants.

SUMMARY

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 concentratrion of Superdisintegrant formulations).

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 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}
	mg/tablets															
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 ± S.D (n=3).

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/cm²)	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.

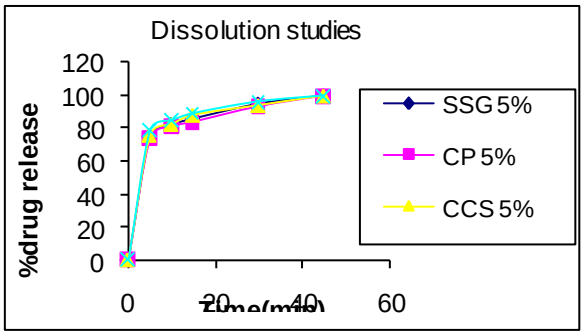


Figure 6: Cumulative %drug release vs time profiles of Stavudine ODT prepared with(-♦-), SSG (-■-) CP, (-▲-) CCS, and (-×-) Kollidan CLM

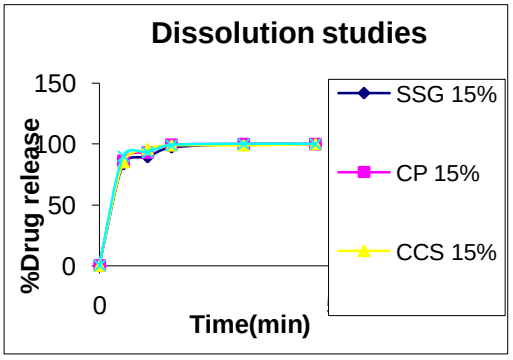


Figure 8: Cumulative %drug release vs time profiles of Stavudine ODT prepared with (-♦-) SSG,(-■-) CP, (-▲-) CCS, and (-×-) Kollidan CLM

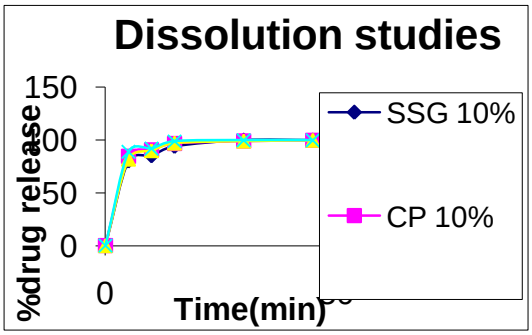


Figure 7: Cumulative %drug release vs time profiles of Stavudine ODT prepared with (-♦-) SSG, (-■-) CP, (-▲-) CCS, and (-×-) Kollidan CLM

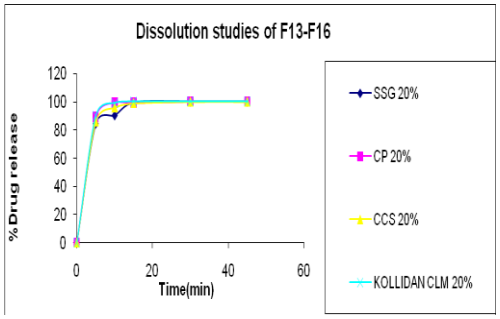


Figure 9: Cumulative %drug release vs time profiles of Stavudine ODT prepared with (-♦-) SSG, (-■-) CP, and (-▲-) CCS, (-♦-) Kollidan CL M

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 patiencecompliance, low dosing, rapid onset of action, increasedbioa vailability, low side effects, good stability. These formulations may b e commercialized after establishing chemical and biological parameters.

Acknowledgement

The authors are thankful to Novartis, Turkey and also all people for providing necessary facilities to carry out research work.

REFRENCES

1. Mishra DN, Bindal M, Singh SK, Kumar SGV. Spray dried excipient base: A novel technique for the formulation of orally disintegrating tablets, Chem Pharm Bull, 2006, 54(1), 99– 102.
2. Seager H. Drug delivery products and the Zydis fast dissolving dosage forms. J Pharmrmacol, 1998, 50,375–82.
3. Ciper M, Bodmeier R. Modified conventional hard gelatin capsules as fast disintegrating dosage form in the oral cavity, Eur J Pharm Biopharm., 2006,62(2),178–84.
4. Suresh B, Rajendar KM, Ramesh G, Yamsani MR. Orodispersible tablets: an overview. Asian J Pharm, 2008,2,2–11.
5. Dobetti L. Fast-melting tablets: developments and technologies, Pharma Tech. 2001, (Suppl.),44–50.
6. Koizumi K, Watanabe Y, Monita K, Utosuchi N. New method of preparing high porosity rapidly saliva soluble compressed tablets using mannitol with camphor, a subliming material. Int J Pharm., 1997,152,127–31.
7. FuY,Yang S, Jeong Sh,Kimura S, ParkK.Orally fast disintegrating tablets: developments, technologies, taste-masking and clinical studies. Crit Rev Ther Drug Carrier Sys., 2004,21,433–76.
8. Ahmed IS, Aboul-Einien MH. In vitro and in vivo evaluation of a fast-disintegrating lyophilized dry emulsion tablet containing griseofulvin. Eur J Pharm Sci., 2007,32(1),58–68.
9. Biradar SS, Bhagavati ST, Kuppasad IJ. Fast dissolving drug delivery systems: a brief Overview, Internet J Pharmacol, 2006, 4(2). 21- 27.
10. maima AS, Mohammed AH, Nagia AM, Ahmed SZ. Formulation and optimization of mouth dissolve tablets containing rofecoxib solid dispersion. AAPS PharmSciTech. 2006,7,55 - 58.
11. Suresh S, Pandit V, Joshi HP. Preparation and evaluation of mouth dissolving tablets of salbutamol sulphate. Indian J Pharm Sci., 2007,69,467–9.
12. Bolhuis GK, Zurman K, Wierik GHP. Improvement of dissolution of poorly soluble drug by solid deposition on a super disintegrant. Eur J Pharm Sci., 1997,5,63–9.
13. Patel M, Patel N, Patel M. Fast-dissolving rofecoxib tablets: formulation development & optimization using factorial design. Drug Del Technol., 2007,7,33–8.
14. Ahmed IS, Fatahalla FA. Pilot study of relative bioavailability of two oral formulations of ketoprofen in healthy subjects, a fast dissolving lyophilized tablet as compared to immediate release tablet. Drug Develop Ind Pharm., 2007, 33,505–11.
15. Gohel M, Patel M, Amin A, Agrawal R, Dave R, Bariya N. Formulation design and optimization of mouth dissolve tablets of nimesulide using vacuum drying technique. APS PharmSci-Tech., 2004,5,36.
16. Ahmed IS, Nafadi MM, Fatahalla FA. Formulation of fast dissolving ketoprofen tablet using freeze-drying in blister technique. Drug Develop Ind Pharm., 2006, 32,437–42.
17. Indurwade NH, Rajyaguru TH, Nahat PD. Novel approach in fast dissolving tablets. Indian Drugs., 2002,39(8),405–9.
18. [18] Shu T, Suzuki H, Hironaka K, Ito K.. Studies of rapidly disintegrating tablets in the oral cavity using co-ground mixtures of mannitol with crospovidone. Chem Pharm Bull,, 2002, 50(2),193–8.
19. YX Bi, M Sunanda, Y Yonezana, K Daujo. *Drug. Dev. Ind. Pharm*., 1999, 25(8), 571- 81.
20. NG Avasi, M Bhalakar., Indian Drugs, 2004, 4(1), 19-23.
21. United States Pharmacopeia XXIV-NR XIX, Asian Edition, VSP Convention Inc., 2001, 1941 – 1943.
22. N Vaja Diveyesh Kumar, M Patel Maulik, T Joshi Ujjwal, M Patel Jaykishan., J. Chem. Pharm. Res., 2010, 2(5), 307 -352.
23. Meyers GL, Battist GE, Fuisz RC. Process and apparatus for making rapidly dissolving dosage units and product there from. PCT Patent W/C 95/34293-A1. 1995.
24. Cherukuri SR, Myers GL, Battist GE, Fuisz RC. Process for forming quickly dispersing comestible unit and product there from. US Patent 5587172, 1996.
25. Fuisz R. Ulcer prevention method using a melt-spun hydrogel. US Patent 5622717; 1997.
26. S. Kimura, T. Imai and M. Otagiri, Pharmaceutical evaluation of Ibuprofen syrup containing low molecular weight gelatin. J. Pharm. Sci., 1992, 81, 141-144.
27. Ashiqul Islam, Syed Shabbir Haider and Md. Selim Reza. Formulation and Evaluation of Orodispersible tablet of Domperidone. Dhaka Univ.J. Pharm. Sci., 2011, 10 (2), 117-122.
28. World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. Adopted in the 18th WMA General Assembly and subsequent amendments, 1964.