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Research Article

Formulation and Evaluation of Oral Dispersible Tablets of Zidovudine with different Superdisintegrants.

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ABSTRACT

Oral dispersible tablets (ODTs) are patient friendly dosage form that rapidly disintegrate or dispersed in mouth without the need of water. In the present investigation eight ODT formulations of zidovudine, an antiretroviral drug, were prepared using different superdisintegrants *viz*. Crospovidone (PPXL), Crosscarmellose sodium (Ac-di-sol) and sodium starch glycollate by direct compression method. The effects of disintegrants in different concentration on the release profile of zidovudine ODTs were studied. Developed ODTs were studied for their physicochemical properties and *in vitro* drug release profile. The studied parameters were found to be satisfactory for all ODT formulations of zidovudine. Disintegration time for all the formulations was found to be less than 60 seconds. Disintegration time for all ODTs decreased with increase in disintegrant concentration. ODTs prepared using Ac-di-sol 6% possessed least disintegration time (13.9), offered better dissolution profile than that of all the ODTs formulations developed in the present investigation and that of marketed conventional tablet formulation of zidovudine. Ac-di-sol when tried in concentration above 6% resulted in an increase in disintegration time instead of further decreasing it. Accelerated studies proved that the optimized formulation was stable even after 3 months.

Key words: Dispersible tablets, Zidovudine, CCS, PPXL, SSG, Direct compression

INTRODUCTION

For most therapeutic agents used to produce systemic effects, the oral route still represents the preferred way of drug administration, owing to its several advantages and high patient

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compliance compared to many other routes.[1] Tablets and hard gelatin capsules constitute a major portion of drug delivery systems that are currently available. However, many patient groups such as the elderly, children, and patients who are mentally retarded, uncooperative, nauseated, or on reduced liquid-intake/diets have difficulties swallowing these dosage forms. Those who are traveling or have little or no access to water are similarly affected.[2-4]

Over the past one decade, there has been an enhanced demand for more patient-friendly and compliant dosage forms. As a result, the demand for developing new technologies has been increasing.[5] Since the development cost of a new drug molecule is very high, efforts are now being made to focus on the development of new drug dosage forms for existing drugs with improved safety and efficacy, bioavailability together with reduced dosing frequency, and the production of more costeffective dosage forms.

To fulfill these medical needs, pharmaceutical technologists have developed a novel oral dosage form known as oral dispersible tablet. Oral dispersible tablets (ODTs) are dosage forms that are placed in mouth, allowed to disperse/dissolve in the saliva without the need of water and provide a quick onset of action. Some drugs are absorbed from 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. ODTs are appreciated by a significant segment of population, particularly children and elderly, which have difficulty in swallowing conventional tablets or capsules.[6-8] The simplicity and cost effectiveness of the direct compression process have positioned this technique as an attractive alternate to traditional granulation technologies.[8] Usually superdisintegrants are added to a drug formulation to facilitate the break-up or disintegration of tablet into smaller particles that can dissolve more rapidly than in absence of disintegrants.[9] Superdisintegrants are disintegration agents, which can be used in a fractional amount of normal disintegrants to obtain the same effect. According to product information provided by the manufacturers of superdisintegrants, the superdisintegrants should be used in amount of 1-8% with amount of about 2% to about 4% being indicated as optimal.[10]The superdisintegrant may be a single superdisintegrant or a combination of superdisintegrants and will normally be used in combination with one or more common disintegrants, such as starch, finist, and corn-starch. An ideal disintegrant should have poor solubility, good hydration capacity. Also, disintegrant should not form any complex with the drug.[11]

Zidovudine is an antiretroviral drug of nucleoside reverse transcriptase inhibitor category. It is widely used in treatment of HIV infection. Zidovudine has good bioavailability (60-70%).[12]

MATERIALS AND METHODS

Materials

Zidovudine was obtained as gift sample from Ranbaxy research Laboratory, Gurgaon. Sodium starch glycolate, Crosscarmellose sodium, Crospovidone, Mannitol and all other chemicals/ Solvents were procured from market.

Table 1: Composition of zidovudine ODT formulations

Ingredients (mg/tablet)	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8
Zidovudine	100	100	100	100	100	100	100	100
Sodium starch glycollate	14	---	---	17.5	---	---	---	---
Crosscarmellose sodium(Ac-di-sol)	---	14	---	---	17.5	---	21	24.5
Crospovidone (PPXL)	---	---	14	---	---	17.5	---	---
Pearlitol SD 200	210.25	210.25	210.25	206.75	206.75	206.75	203.25	199.75
Aspartame	20	20	20	20	20	20	20	20
Lemon flavour	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Aerosil 200	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total weight	350	350	350	350	350	350	350	350

Methods

Preparation of ODTs

In present investigation oral dispersible tablets of zidovudine were prepared by direct compression technique. For this zidovudine and all other excipients according to the formula were weighed accurately. Zidovudine, mannitol (Pearlitol SD 200), crosscarmellose sodium and acesulfame potassium were passed through sieve # 22. Lemon flavour and aerosil 200

were passed through sieve # 60. All the above sieved ingredients were then mixed for 15 minutes. Magnesium stearate previously passed through sieve # 60 was then mixed with above blend for 5 minutes. The mixture(s) was then allowed to compress using 16 station rotary tablet compression machine with 9.0 mm flat round punches with tablet weight 350 mg. Composition of these tablet formulations is shown in table 1.

Evaluation of blend

The flow properties of blend (before compression) were characterized in terms of angle of repose, Carr's index and Hausner ratio. For determination of static angle of repose (□), the blend were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0 cm above hard surface.[13] The blends were poured till the time when upper tip of the pile surface touched the lower tip of the funnel. The $\tan^{-1}$ of the (height of the pile/radius of its base) gave the angle of repose. Angle of repose (θ) was calculated by using the eqn. 1

$\tan \theta = h/r$ **… (1)**

Both bulk density (BD) and tapped density (TD) were determined. A suitable amount of granules from each formulation, previously lightly shaken to break any agglomerates formed, was introduced into a 100 mL measuring cylinder. After observing its initial volume, the cylinder in the density tapper instrument and density is measured according to USP method II (up to1250 taps). The tapping was continued until no further change in volume was noted. Volume of packing after tapping was noted. BD and TD were calculated using eqn. 2 and 3respectively.

BD = weight of the powder / volume of the packing **… (2)**

TD = weight of the powder / tapped volume of the packing **… (3)**

Compressibility index[14] of the powder was determined by Carr's compressibility index as given by eqn. 4

Carr's index (%) = [(TD – BD) x 100] / TD **… (4)**

Hausner's ratio[15] is the ratio of tapped to bulk density and was calculated by using the eqn. 6

Hausner's ratio = TD/BD

Evaluation of ODT of zidovudine

The prepared tablets were evaluated for quality control tests like hardness, thickness, friability and drug content, weight variation, *in vitro* dispersion time and *in vitro* dissolution studies.

Tablet hardness

The crushing Kg/cm^2 of prepared tablets was determined for 10 tablets of each batch by using Monsanto hardness tester.

Friability

Friability test was done by Roche friabilator. Ten tablets were weighed and were subjected to combined effect of attrition and shock by utilizing a plastic chamber that resolve at 25 rpm dropping the tablets at distance of 6 inch with each revolution. Operated for 100 revolutions, the tablets were dusted and reweighed. The percentage friability was calculated as eqn. 5.

$$\% \text{ Friability} = W_0 - W / W_0 \times 100 \quad \textbf{…(5)}$$

Uniformity of weight

Twenty tablets from each batch were individually weighed and their average weight was calculated. From the average weight of the prepared tablets, the standard deviation was determined.

Thickness

Six tablets were examined for their thickness using Vernier calipers and the mean thickness value was calculated.

Disintegration time

Six tablets of each formulation were used to determine disintegration time. Phosphate buffer (pH 6.8) was used as a disintegration medium and temperature was maintained 37±0.5^{0}C. Average disintegration time of six tablets was determined.

In vitro dispersion time

In vitro dispersion time was measured by dropping a tablet in a beaker containing 100 mL of phosphate buffer (pH 6.8). Three tablets from each formulation were randomly selected and *in vitro* dispersion time was performed.

Estimation of drug content

Twenty tablets were powdered, and 100 mg equivalent weight of zidovudine tablet powder was accurately weighed and transferred into a 100 ml volumetric flask. Initially, 10 ml of phosphate buffer (pH 6.8) was added and shaken for 10 min. Then, the volume was made up to 100 ml with same phosphate buffer. The solution in the volumetric flask was filtered, diluted suitably and analyzed spectrophotometrically at 266 nm.

In-vitro dissolution studies

Dissolution studies were conducted to determine the release pattern of the drug from the product. Dissolution test for zidovudine was carried out as per USP method for dissolution test for tablets and capsules using apparatus II (paddle type). Dissolution medium used was

900 mL of 6.8 pH phosphate buffer, rotating at 50 rpm at 37±0.5^{0}C. An aliquot of 10 mL of samples were withdrawn at different time periods and replaced with fresh solvent. These samples were filtered and diluted. Absorbance of the resulting solution was measured at 266.0 nm (experimental λmax for zidovudine in pH 6.8 phosphate buffer). Percent drug release was calculated.

As, reference ODT product of zidovudine was not available so, selected ODT formulation of zidovudine was compared with marketed conventional tablet formulation of zidovudine in term of drug release performance.

Accelerated stability studies

Stability testing was done to check the physical, chemical and physiological properties of the product. Accelerated stability testing was carried out as per ICH guidelines (40ºC/75% RH) to ascertain the product stability for long period in a short period of time. Tablets of the optimized formulation were packed in HDPE bottles having silica pads were kept in a stability chambers. Tablets were then evaluated for change in drug release, assay and description.

RESULTS AND DISCUSSION

Water insoluble diluent such as microcrystalline cellulose expected to cause an unacceptable feeling of grittiness in the mouth. Among the soluble diluents; Pearlitol SD 200 has advantages in terms of easy availability, sweet taste and negative heat of solution. Aspartame and lemmon flavour were added in the formulations as sweetener and flavour respectively to make the formulations more palatable. In the present investigation ODTs of zidovudine were prepared by direct compression method. Flow properties of the powder, resistance to particle movement can be judged from the angle of repose. This measurement gives qualitative and quantitative assessment of internal cohesive and frictional force under low levels of external loading as might be applied in mixing and tableting [9]. Values for angle of repose were found in the range of 31.21^0 to 33.16^0. Carr's index of the prepared blends falls in the range of 11% to 15% and this is also supported by Hausner's ratio values which were in the range of 1.126 to 1.137. Hence the prepared blends possessed good flow properties and these blends can be used for tablet manufacture.

All the tablets were prepared under similar conditions. All the formulations exhibited white color, odorless with smooth surface. The characteristics of prepared ODTs of zidovudine are shown in Table 2. The average weight of the ODTs prepared by direct compression method

was 349.2 to 352.6 mg. Weight variation of ODTs was within 1.91 %. Hardness and friability of all formulations were within acceptable limits. Hardness of tablets prepared by direct compression was 4.1 to 5.1 kg/cm^2. The friability of all formulations was found to be less than 0.09% and hence the tablets with lower friability may not break during handling on machines and or shipping. Various studied parameters for oral dispersible tablet formulation of zidovudine are depicted in table 2.

Table 2: Characteristics of prepared ODTs of zidovudine

Parameters	**F-1**	**F-2**	**F-3**	**F-4**	**F-5**	**F-6**	**F-7**	**F-8**
Tablet wt. (mg) (±SD) n=20	349.2 ±1.81	350.6 ±1.61	351.1 ±1.66	350.9 ±1.91	352.2 ±1.01	351.8 ±1.71	352.1 ±1.22	351.8 ±1.41
Thickness (mm) (±SD) n=6	3.90± 0.018	3.91± 0.019	3.81± 0.014	3.90± 0.016	3.92± 0.016	3.89± 0.018	3.89± 0.015	3.87± 0.015
Friability (%)	0.07	0.06	0.06	0.1	0.07	0.06	0.08	0.07
Hardness (Kg/cm^2) (±SD) n=10	4.13± 0.29	5.11± 0.31	5.08± 0.28	4.09± 0.27	5.13± 0.23	5.11± 0.26	5.22± 0.39	5.14± 0.32
Disintegration time (sec) (±SD) n=6	59.1± 1.41	31.1± 2.10	44.3± 1.22	41.6± 1.57	19.8± 1.44	30.6± 1.51	11.9± 1.69	16.14 ±1.59
Dispersion time (±SD) n=3	73.1± 1.58	41.4± 2.11	56.7± 1.88	53.8± 1.98	31.3± 2.03	41.1± 1.79	23.8± 2.06	30.23 ±1.62

In vitro dispersion time of all the formulations were in the range of 26 to 73 seconds. ODTs of formulation F-7 showed the least (26 sec.) dispersion time. Disintegration time is very important for ODTs, which is desired to be less than 60 seconds for orally disintegrating tablets. This rapid disintegration assists swallowing and also plays a role in drug absorption in buccal cavity, thus promoting bioavailability. Disintegration time of prepared ODTs was in the range of 14 to 59 seconds and the order was Ac-Di-Sol < Crospovidone < SSG. Among all the formulations formulation F-7 prepared with Ac-di-sol in conc. 6% as disintegrant exhibit least disintegration time (12 sec.). As the concentration of superdisintegrants in the formulations increased the disintegration time was found to decrease. It is worthwhile to note that Ac-di-sol above this concentration increased the disintegration time of zidovudine ODTs. The drug content of all the formulations (F-1 to F-15) was found to be between 99.6 – 101.2%, which was within the acceptable limits as per USP XXVII. *In vitro* dissolution data of all the zidovudine ODT formulations are shown in table 3 and corresponding dissolution

Table 3: Comparative % drug release of zidovudine ODT formulations and conventional marketed tablet formulation (F-Marketed)				
Formulation	**Cumulative % release ±SD (n=3)**			
	0 min	**5 min**	**10 min**	**15 min**
F-1	0±0	75.5±0.13	85.3± 0.28	100.7± 0.24
F-2	0±0	79.3±0.16	96.1± 0.32	100.95± 0.14
F-3	0±0	77.40±0.21	91.23± 0.09	100.34±0.15
F-4	0±0	76.97±0.31	89.31± 0.13	100.99± 0.16
F-5	0±0	84.00±0.17	96.93± 0.25	100.20±0.16
F-6	0±0	81.68± 0.18	95.12± 0.15	100.67±0.16
F-7	0±0	90.26±0 .21	100.93± 0.10	100.1± 0.36
F-8	0±0	83.40±0.09	98.23±0.28	100.34±0.27
F-marketed	0±0	38.71±0.12	49.78±0.14	72.15±0.09

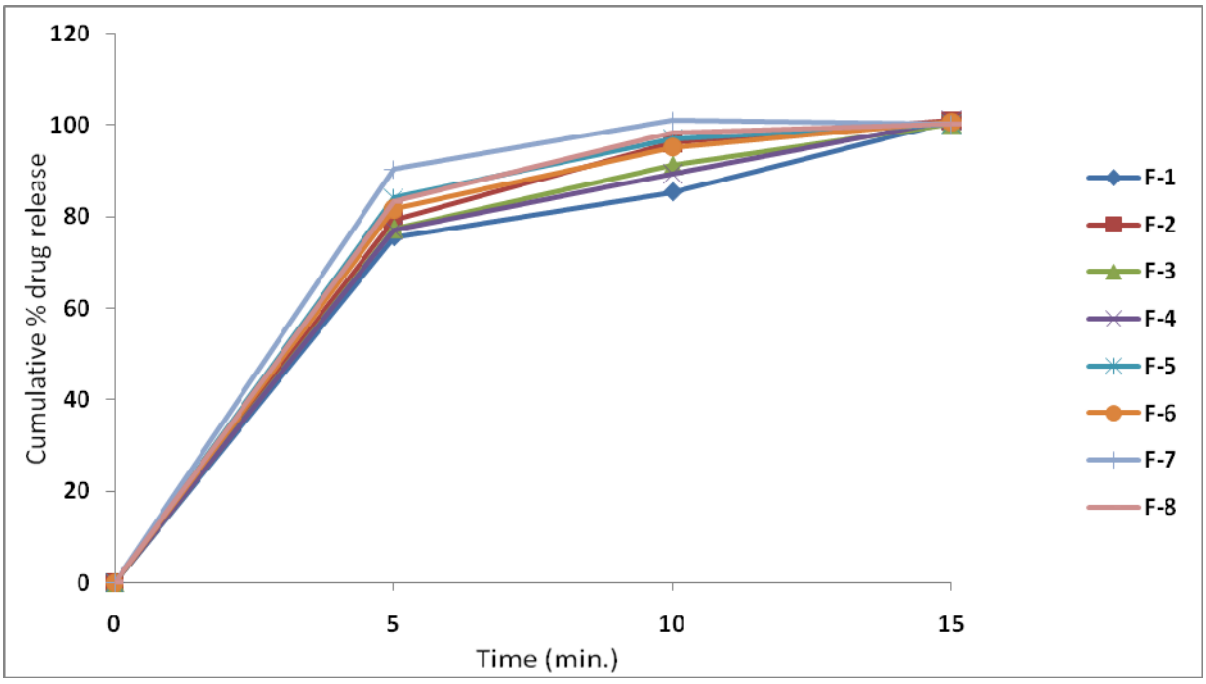

Fig 1: Cumulative % drug release versus time profile of F-1 to F-7 and marketed formulation (F-Marketed)

profile is shown in fig 1. It is evident from table 3, that all the formulations exhibit rapid and complete dissolution profile. Formulation F-7 exhibits the better dissolution profile than that of all zidovudine ODT formulations. On comparing the dissolution profile (fig 2) of selected ODT formulation (F-7) with that of marketed conventional tablet formulation, it can be concluded that zidovudine ODT formulation (F-7) have much faster drug release rate than that of marketed conventional tablet formulation of zidovudine within 15 minute time point. Also, ODTs of formulation F-7 shows the best dissolution profile amongst all the zidovudine ODT formulations as well as marketed conventional tablet formulations. Dispersible tablets of zidovudine of optimized batch (F-7) were of sufficient stability during 3 months of accelerated stability studies.

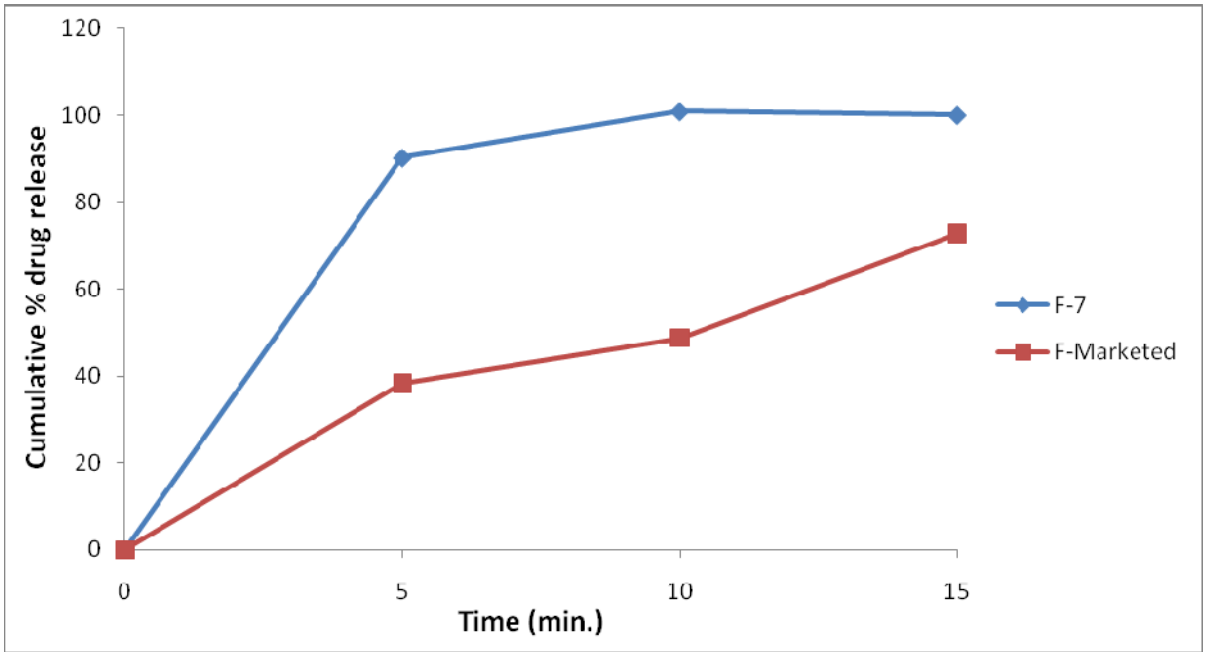

Fig 2: Cumulative % drug release versus time profile optimized ODT formulation (F-7) and marketed formulation (F-Marketed)

CONCLUSION

Oral disintegrating tablets (ODT) of zidovudine are successfully prepared by using direct compression method. Undoubtedly the availability of various technologies and the manifold advantages of ODT will surely enhance the patient compliance, low dosing, rapid onset of action, fast disintegration, low side effect, good stability and its popularity in the near future. From the present study it can be concluded that oral dispersible tablets of zidovudine can be successfully prepared employing three different disintegrants viz. sodium starch glycollate, crosscarmellose sodium or crospovidone by direct compression method. The prepared tablets

disintegrate within few seconds without need of water; thereby enhance the patient compliance and the absorption leading to its increased bioavailability. Direct compression technique would be an effective and simple alternative approach compared with the use of more expensive process and adjuvant in the formulation of oral disintegrating tablets. From the characterization of oral dispersible tablets of zidovudine it can be concluded that formulation containing Crosscarmellose sodium 6% is most acceptable. Further *in vivo* studies in human volunteers are required to correlate *in vitro* release data.

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