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FORMULATION AND EVALUATION OF TASTE MASKED DISPERSIBLE TABLETS OF ZIDOVUDINE

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ABSTRACT

Zidovudine is an antiretroviral drug commonly used in the treatment HIV infection. But it is very bitter in taste and sparingly soluble in water. Thus the purpose of this investigation was to formulate and evaluate taste masked dispersible tablets of zidovudine. Dispersible tablets of zidovudine were prepared using crosscarmellose sodium (Ac-di-sol) as disintegrant. Surelease clear (E-7-19010) in concentration range of 0.044mL/tab to 0.052mL/tab completely masked the taste of zidovudine. The prepared tablets were evaluated for general appearance, drug content, weight variation, thickness, hardness, friability, taste evaluation, mouth feel, *in vitro* dispersion time and *in vitro* dissolution studies. Tablet formulations showed quick disintegration time, which is very characteristic of dispersible tablets. Results revealed that the tablets containing taste enhancers and surelease as binder had a good palatability. Oral dispersible tablets prepared using Surelease 0.044mL/tablet and Ac-di-sol 6% possessed least disintegration time (18.9), pleasant taste and offered better dissolution profile than that of all other dispersible tablet formulations developed in the present investigation and that of marketed conventional tablet formulation of zidovudine.

KEYWORDS

Taste making, Zidovudine, Dispersible tablets, Surelease, Wet granulation

INTRODUCTION

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[1]. 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 cost effective dosage forms.

To fulfill these medical needs, pharmaceutical technologists have developed a novel oral dosage form known as dispersible tablet, which disintegrate rapidly in small amount of water, usually in a matter of few seconds. Drug dissolution and absorption as well as onset of clinical effect and drug bioavailability may be significantly greater than those observed from conventional dosage forms[2].

Dispersible tablets offer advantage for patients who have difficulty in swallowing. It has been reported that disphagia[1] is common among all age groups of patients but is more specific to pediatrics, geriatrics along with institutionalized patients and patients with nausea, vomiting and motion sickness complications[3]. Dispersible tablets with good taste and flavour increase the acceptability of bitter drugs by various groups of population.

Although chewable tablets have been on the market for some time, they are not the same as the new dispersible tablets. Patients for whom chewing is difficult or painful can use these new tablets easily. Dispersible tablets can be used easily for pediatric patients who have lost their primary teeth but do not have full use of their permanent teeth[4].

Zidovudine an antiretroviral drug is widely used in the treatment of HIV infection. Zidovudine has good bioavailability (60-70%). As the half-life of zidovudine is very small (1 h) so, pediatric patients have to administer the tablets of zidovudine 3-4 times and women patients for the prevention of maternal to foetus transmission of HIV infection have to administer it for 4-5 times in a day[5]. Also, the drug is very bitter in taste. Hence, the multiple dosing with bitter tasting drug reduces the patient compliance especially in case of pediatrics.

Taste is one of the most important parameters governing patient compliance. More than 50 percent of pharmaceutical products are orally administered for several reasons and undesirable taste is one of the important formulation problem encountered with such oral products. Oral administration of bitter drugs with an acceptable degree of palatability is a key issue for health care providers, especially for pediatric patients. Several oral pharmaceuticals, numerous food and beverage products, and bulking agents have unpleasant, bitter-tasting components. So, any pharmaceutical formulation with a pleasing taste would definitely be preferred over a competitor's product and would translate into better compliance and therapeutic value for the patient and more business and profits for the company. The desire of improved palatability in these products has prompted the development of numerous formulations with improved performance and acceptability. Taste of a pharmaceutical product is an important parameter for governing compliance. Thus, taste masking of oral pharmaceuticals has become an important tool to improve patient compliance and the quality of treatment

especially in pediatrics[6]. In the present investigation an attempt has been made to formulate and evaluate taste masked dispersible tablets of zidovudine with improved patient compliance and enhanced bioavailability, as till date no dispersible tablet formulation of zidovudine is present in the Indian Pharma market.

MATERIALS AND METHODS

(i) Materials:

Zidovudine, Surelease clear (E-7-19010), Lemmon flavour, PVPk-30, magnesium stearate and mannitol (Pearlitol SD 200) were a obtained as gift samples from M/S Ranbaxy Research Laboratory Ltd., Gurgaon. Colloidal silicon dioxide (Aerosol 200), Crospovidone (Polyplasdone XL), Crosscarmellose sodium (Ac-di-sol), Sodium starch glycollate (Primojel), Peppermint flavour, Acesulfame potassium, Aspartame and all other chemicals/ Solvents were procured from market.

(ii) Formulation of dispersible tablets of zidovudine:

Dispersible tablets of zidovudine were prepared by direct compression (F-1 to F-8) and wet granulation (F-9 to F-14) methods. The composition of formulation F-1 to F-8 and F-9 to F-14 are shown in table 1 and table 2 respectively.

For the formulation of zidovudine dispersible tablet by direct compression, zidovudine and all other excipients according to the formula were weighed accurately. Zidovudine, Pearlitol SD 200, acesulfame potassium, crosscarmellose sodium (Ac-di-sol) and aspartame were passed through sieve # 22. Lemon flavour, peppermint 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 machines with 16.0×8.0mm flat oval punches with tablet weight 550mg.

Table 1

Composition of dispersible tablet formulations of zidovudine prepared by direct compression method

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
Crosscarmellose sodium(Ac-di-sol)	24	24	24	24	24	24	24	24
Pearlitol SD 200	387	357	382	382	367	382	383	382
Aspartame	15	30	10	25	25	25	25	25
Acesulfame potassium	15	30	25	10	25	10	10	10
Lemon flavour	1.5	1.5	1.5	1.5	1.5	1.0	1.0	2.0
Peppermint flavour	1.5	1.5	1.5	1.5	1.5	2.0	1.0	1.0
Aerosil 200	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Magnesium stearate	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
Total weight	550	550	550	550	550	550	550	550

Six formulations of dispersible tablets of zidovudine (F-9 to F-14) were prepared with wet granulation with surelease E-7-19010 clear. Surelease is an aqueous dispersion of ethylcellulose and plasticizers. Surelease contains 25% solid contents of its volume. So, tablet weight was finalized by considering this. For the formulation of dispersible tablets, drug and all other excipients were weighed accurately. Zidovudine was passed through sieve # 22. Zidovudine was granulated with accurately measured amount of Surelease. The wet granulated mass was dried in tray dryer for 70-80 minutes at 60^0C. Dried granules were passed through sieve # 22. Pearlitol SD 200, acesulfame potassium, crosscarmellose sodium (Ac-di-sol) and aspartame were passed through sieve # 22. Lemon flavour, peppermint flavour and aerosil 200 were also passed through sieve # 60. All the sieved excipients were mixed with # 22 passed granules for 15 minutes. The blend so formed was allowed to mix with the sieve # 60 passed magnesium stearate for 5 minutes. Tablets were compressed using 16 station rotary tablet compression machine with 16.0×8.0mm flat oval punches with tablet weight 550mg. Surelease contains 25% solid contents of its volume so, tablet weight was calculated by keeping it in mind.

Table 2
Composition of dispersible tablet formulations of zidovudine prepared by wet granulation method

Ingredients (mg/tablet)	F-9	F-10	F-11	F-12	F-13	F-14
Zidovudine	100	100	100	100	100	100
Crosscarmellose sodium(Ac-di-sol)	24	24	24	28	33	38
Pearlitol SD 200	373	371	369	367	362	357
Surelease E-7-19010	0.036 mL (9 mg)	0.044 mL (11 mg)	0.052 mL (13 mg)	0.044 mL (11 mg)	0.044 mL (11 mg)	0.044 mL (11 mg)
Aspartame	25	25	25	25	25	25
Acesulfame potassium	10	10	10	10	10	10
Lemon flavour	2.0	2.0	2.0	2.0	2.0	2.0
Peppermint flavour	1.0	1.0	1.0	1.0	1.0	1.0
Aerosil 200	2.0	2.0	2.0	2.0	2.0	2.0
Magnesium stearate	4.0	4.0	4.0	4.0	4.0	4.0
Total weight	550	550	550	550	550	550

(iii) 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. 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

$$\text{Tan } \theta = h/r \quad \text{... (1)}$$

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 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 is the ratio of tapped to bulk density and was calculated by using the eqn. 6

Hausner's ratio = TD/BD

(iv) Evaluation of dispersible tablets 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.

(a) Tablet hardness:

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

(b) 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.

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 distilled water phosphate buffer). Percent drug release was calculated.

All dispersible tablet formulations of zidovudine were also compared with marketed conventional tablet formulation of zidovudine in term of drug release performance.

(i) Taste evaluation:

The objective of this study is to conduct and evaluate the Palatability of different formulations of zidovudine dispersible tablets. Zidovudine dispersible tablet was a new development; reference product is not available in market for this product for comparison of the taste evaluation. Total nine formulations were selected for taste evaluation study; eight test formulations and one positive control (Placebo for zidovudine). All formulations (formulation code) were randomized. Each randomization order was assigned with sequence code. For this study ten healthy human male volunteers were selected, and were assigned volunteer code. All the ten volunteers were evaluated all nine formulations as per the randomization order. Each of the nine formulations were transferred to HDPE bottles and labeled only with formulation code. Palatability evaluation feedback format prepared and submitted to each individual volunteer and were provided with instructions before starting study. One tablet of each formulation was given to volunteer for palatability study evaluation. The time interval between evaluations of each test formulation in the same volunteer was 30min, at after evaluated each formulation, one half of a bread slice was given to each volunteer followed by half glass of water and coca powder for neutralizing the taste buds. After completion of the study, data was compiled and evaluated the formulations and allotted the rank for all formulation, based on the average value of the each formulation given by volunteers.

(v) 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 have advantages in terms of easy availability, sweet taste and negative heat of solution. Aspartame and acesulfame potassium as sweeteners, lemon and peppermint flavour as flavouring agents were added in the formulations in order to make the formulations more palatable. In the present investigation dispersible tablets of zidovudine were prepared by direct compression and wet granulation 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[7]. 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 can be used for tablet manufacture.

All the tablets were prepared under similar conditions. All the formulations exhibited white colour, odourless with smooth surface. The characteristics of prepared dispersible tablets of zidovudine are shown in Table 3. The average weight of the dispersible tablets prepared by direct compression method was 550.5 to 553.2 mg. Weight variation of dispersible tablets was within 2.91%. Hardness and friability of all formulations were within acceptable limits. Hardness of tablets prepared by direct compression was 4.8 to 5.3 kg/cm^2. The friability of all formulations prepared by direct compression method was found to be less than 0.09%. Formulations prepared by wet granulation with Surelease offers no friability. Hence the tablets with lower or no friability may not get break during handling with machines or during shipping. Various studied parameters for oral dispersible tablet formulation of zidovudine are depicted in table 3.

Table 3
Characteristics of prepared dispersible tablets of zidovudine

Formulations	Tablet wt. (mg) (±SD) n=20	Thickness (mm) (±SD) n=6	Friability (%)	Hardness (Kg/cm^2) (±SD) n=10	Disintegration time(sec) (±SD) n=6	Dispersion time(±SD) n=3
F-1	550.5±2.81	3.80±0.018	0.07	4.9	30.2±1.41	41.9±1.89
F-2	553.2±2.61	3.81±0.019	0.06	5.1	31.1±2.10	44.1±1.87
F-3	551.7±2.66	3.81±0.014	0.06	5.5	29.3±1.22	40.9±2.17
F-4	550.8±2.91	3.78±0.016	0.1	4.8	29.6±1.57	41.4±2.19
F-5	553.2±2.01	3.82±0.016	0.07	5.3	30.8±1.44	42.5±2.29
f-6	551.8±2.71	3.79±0.018	0.06	5.1	32.6±1.51	45.3±1.17
F-7	552.1±2.22	3.82±0.015	0.08	5.1	31.2±1.69	45.1±2.31
F-8	551.7±1.93	3.79±0.013	0.05	5.3	31.1±1.23	42.8±1.79
F-9	552.2±2.12	3.81±0.016	NIL	5.2	33.9±1.16	45.6±2.16
F-10	551.9±2.13	3.82±0.012	NIL	5.1	34.7±1.26	45.8±1.78
F-11	550.8±1.98	3.79±0.019	NIL	5.2	35.2±1.54	46.8±1.56
F-12	551.9±2.16	3.80±0.017	NIL	5.1	22.8±1.45	43.9±1.68
F-13	550.8±2.16	3.79±0.016	NIL	4.9	18.9±1.37	27.8±1.78
F-14	552.6±1.89	3.82±0.018	NIL	5.0	23.8±1.61	36.6±1.96

In vitro dispersion time of all the formulations were in the range of 27.8 to 46.8 seconds. Dispersible tablets of formulation F-13 showed the least (27.8 sec.) dispersion time. Disintegration time is very important for dispersible tablet, which is desired to be less than 60 seconds for dispersible tablets. This rapid disintegration assists swallowing and also plays a role in drug absorption in buccal cavity, thus promoting bioavailability. Among all the bathes formulation; F-13 prepared with Ac-di-sol in concentration of 6% as disintegrant exhibit least disintegration time (18.9 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 dispersible tablets. 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 dispersible tablet formulations are shown in table 4 and corresponding dissolution profile is shown in fig 1. It is evident from table 4, that all the dispersible tablet formulations exhibit rapid and complete dissolution profile except formulation F-11,

which shows incomplete drug release in stated period of time. This delay seems due to excessive concentration of surelease. As evident from table 4 and fig 1, dispersible tablet of formulation F-13 shows the better dissolution profile than that of all the zidovudine dispersible tablet formulations developed in present investigation. Also, dissolution profile of formulation F-13 was observed to be far better than that of marketed conventional tablet formulation of zidovudine as is evident from fig 2.

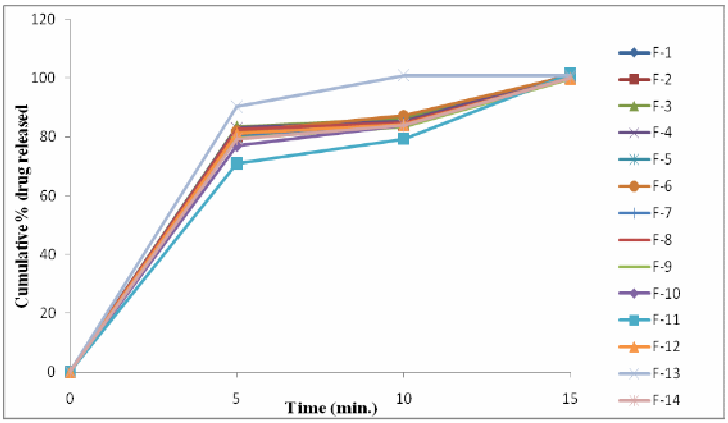
Table 4

Comparative % drug release of zidovudine dispersible tablet formulations and conventional marketed tablet formulation

Formulations	Cumulative % release ±SD (n=3)			
	0 min	**5 min**	**10 min**	**15 min**
F-1	0±0	81.1±0.13	86.3± 0.28	100.7± 0.24
F-2	0±0	80.3±0.16	84.1± 0.32	100.95± 0.14
F-3	0±0	83.40±0.21	86.23± 0.09	100.34±0.15
F-4	0±0	82.97±0.31	85.31± 0.13	100.99± 0.16
F-5	0±0	79.98±0.17	83.93± 0.25	100.20±0.16
F-6	0±0	81.68±0.18	87.12± 0.15	100.67±0.16
F-7	0±0	79.78±016	84.47±0.18	100.14±0.20
F-8	0±0	81.40±0.09	86.23±0.28	100.34±0.27
F-9	0±0	82.45±0.17	84.67±0.14	99.98±0.13
F-10	0±0	79.56±0.08	83.23±0.09	99.60±0.17
F-10	0±0	76.98±0.16	83.89±0.21	100.13±0.18
F-11	0±0	70.98±0.21	79.34±0.24	101.41±0.16
F-12	0±0	81.18±0.09	84.12±0.15	99.89±0.20
F-13	0±0	90.26± 0.21	100.93± 0.10	100.1± 0.16
F-14	0±0	79.21±0.17	83.98±0.16	100.09±0.18
F-Marketed	0±0	38.78±0.13	50.78±0.18	78.15±0.16

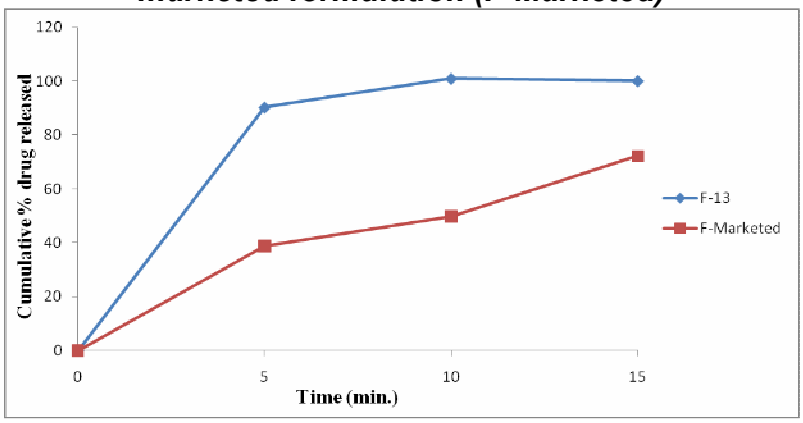
Graph 1

Cumulative % drug release versus time profile of all dispersible tablet formulations (F-1 to F-7) of zidovudine



Graph 2

Cumulative % drug release versus time profile optimized dispersible formulation (F-13) and marketed formulation (F-Marketed)



Results of taste evaluation study are shown in table 5 and their corresponding graphical representation is shown in fig 3. Although table 5 depicts that F-11 and F-13 have very good taste and acceptability but formulation F-13 was preferred over F-11 keeping in view the comparatively better dissolution profile of formulation F-13. Dispersible tablets of zidovudine of optimized batch (F-13) were of sufficient stability during 3 months of stability studies.

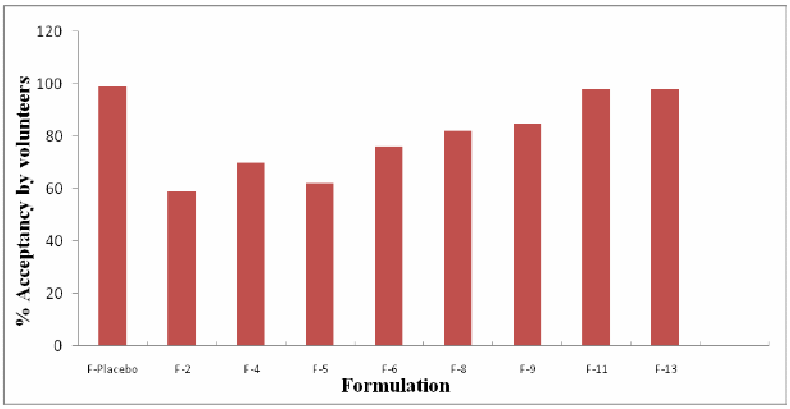
Table 5

Overall summary report of taste evolution study

S. no.	Formulations	Average points by volunteers	Acceptability	Rank
1	Placebo of Zidovudine	99	Very good	1
2	F-2	59	Very poor	7

S. no.	Formulations	Average points by volunteers	Acceptability	Rank
3	F-4	70	Poor	5
4	F-5	62	poor	6
5	F-6	76	Poor	4
6	F-8	82	Acceptable	3
7	F-9	8	Acceptable	2
8	F-11	98	Very good	1
9	F-13	98	Very good	1

Graph 3
Graphical representation of taste evaluation study report



CONCLUSION

From the present investigation it can be concluded that dispersible tablets of zidovudine can be successfully prepared by direct compression as well wet granulation method. Taste of dispersible tablet formulation prepared by direct compression could not mask even by adding sweeteners and flavours. Bitterness of zidovudine can be completely masked by wet granulation with surelease E-7-1090. Undoubtedly the availability of various technologies and the manifold advantages of taste masked dispersible tablets 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. So, dispersible tablets developed by wet granulation with Surelease (E-7-19010) clear with sweeteners and flavours are of very acceptable taste with the advantage of quick onset of action and improved bioavailability. Further *in vivo* studies in human volunteers are required to correlate *in vitro* release data.

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