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Formulation and Evaluation of Acyclovir Orodispersible Tablets Using Sublimation Method

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Abstract

Difficulty in swallowing (dysphagia) is common among all age groups, especially for geriatric and paediatric patients. Oral dispersible tablets (ODT) constitute an innovative dosage form that overcome the problems of swallowing and provides a quick onset of action. The aim of the present research was to prepare oral dispersible tablets by sublimation method. The technique is to increase the porosity of the tablet whereby subliming material was sublimed from the tablets by exposing the tablets to vacuum and to investigate the effects of super disintergrants (Kollidon & Ac-Di-Sol). Acyclovir is an antiviral drug used for the treatment of herpes simplex virus (HSV), mainly HSV-1 and HSV-2 and varicella zoster virus. It is a BCS class III drug. Hence an orally disintegrating tablet formulation of acyclovir was prepared by direct compression,which was taken as the model drug for the study.The drug and finalized formulation were characterized using FTIR studies revelled that there is no interaction between drug and excipients. The powder blend was examined for angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio and prepared tablets were evaluated for general appearance, content uniformity, hardness, friability, wetting time, In-vitro disintegration and dissolution studies were found to be acceptable according to standard limits, In-vitro release studies were performed using USP apparatus-II (paddle method) in 500 ml of distilled water at 50rpm. The highest drug dissolved was obtained from SF4 (100.2%). Tablet with 5% of camphor 5% Crospovidone 4% Croscarmellose sodium shows quick dissolution, disintegration, and good dispersion pattern. It is concluded that Oral disintegrating acyclovir tablets could be prepared by direct compression using sublimation method.

Keywords: Acyclovir; Oral dispersible tablets; Direct compression; Kollidon; Ac-Di-sol; Sublimation method

Introduction

The US Food and Drug Administration, Center for Drug Evaluation and Research (CDER) defines, an orally disintegrating tablets as "a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue"[1]. Orally disintegrating tablets are also called as Orodispersible (ODT), quick disintegrating, fast dissolving, rapid dissolving, porous, and rapimelts tablets [2].

It has been reported that dysphasia is common among all age groups and more specific with paediatric, geriatric population along with institutionalized patients and patients with nausea, vomiting and motion sickness complications [3]. Oral drug delivery provides patients with conventional means of talking their medication. When placed in the mouth where it disappears rapidly before swallowing. Orodispersible tablets are also applicable when local action in them mouth is desirable such as local anaesthetic for toothaches, oral ulcers, cold sores [4].

Sublimation method has been used to produce ODTs with high porosity by compressing the volatile ingredients along with other excipients into tablets, which are finally subjected to a process of Sublimation upon removal of the volatile ingredients by heating under vacuum there by porosity is achieved due to the formation of many pores. These compressed tablets which have high porosity (approximately 30%) rapidly dissolved within 15 seconds in saliva [5,6].

Chemical name is 2-Amino-1,9-dihydro-9-[(2-hydroxyethoxy) methyl]-6*H*-purin-6-one; Acyclovir is poorly water soluble and has poor oral bioavailability (15-30%), the peak plasma concentration occurs after 1-2 hrs when taken orally. Protein binding is reported to range from 9 to 33% the elimination half-life ($t_{1/2}$) range from 2-4 hrs. Molecular formula $C_8H_{11}N_5O_3$ Molecular weight 225.20 g/mol water Solubility at 37°C is 2.5 mg/mL. pka's 2.27 and 9.25 [7].

Materials and Method

Materials

Acyclovir was obtained as a gift sample from MSN Labs (Hyderabad, India). Croscarmellose sodium, Crosspovidone, Microcrystalline cellulose, Camphor, was obtained from SD fine chemical Ltd, Mumbai, India. All other chemicals, solvents and reagents were used of are analytical grade.

Methods

Fourier transform infra-red spectroscopy (FTIR): FTIR spectra of pure acyclovir and formulation were recorded on Bruker ALPHA model, directly placing on probe analyzing for functional groups. Each spectrum was derived from single average scan collected in the region 400-4000 cm^{-1} at spectral resolution of 2 cm^{-2}. The obtained spectrum is

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allowed for peak picking [8-10].

Procedure for sublimation technique: Accurately weigh Acyclovir, fillers, super disintegrants, sweetener and flavour. Mix Acyclovir part quantity of filler and co-sift through ASTM #60. Sift remaining quantity of filler, super disintegrants, sweetener and flavours through ASTM#40. Camphor is added which is sieved through ASTM # 100 sieve size. Blend the sifted material together for 5 minutes. Weigh and sift magnesium stearate through ASTM # 40. Lubricate the blend with sifted magnesium stearate for 2 min as shown in Table 1. Compress the above blend in CEMACH Mini Rotary tableting Machine using 8mm concave punches, upper punch embossed with 'c'. The prepared tablets were subjected to vacuum drying in vacuum oven at 40°C for 2 hrs [11-13].

Evaluation of Powder Blend

Precompression parameters

Prior to compression into tablets, the blend was evaluated for properties such as:

Angle of repose: Angle of repose (θ) was determined using fixed funnel method. The height of the funnel was adjusted that the tip of the funnel touches tip of the heap of the granules. The granules were allowed to flow freely through the funnel onto the surface. The diameter of the granular cone was measured and angle of repose was calculated using formula given below [14].

θ=tan-1 (h/r) Where, h and r are the height and radius of the cone.

Carr's compressibility index: The simplex way of measurement of the free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility index of the granules was determined by Carr's compressibility index (I) which is calculated by using the given formula [14].

CI (%)=(TD-PD) × 100/TD Where, TD=Tapped Density, P=Poured Density, CI=Carr's compressibility index.

Hausner ratio: Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula [14].

Hausner Ratio=TD/PD Where, TD=Tapped Density, PD=Poured density.

Tapped density: Tapped density is the ratio between mass of granules and volume of the granules after tapping is done. It is expressed by gm/cc [15,16].

Evaluation of post compression parameters

Ingredients	SF1	SF2	SF3	SF4	SF5	SF6
Acyclovir	200	200	200	200	200	200
Mannitol	50	49	53	40	42	40
Avicel pH102	35	33	35	29	35	21
Camphor	16	16	16	16	8	24
Croscarmellose sodium	13	--	--	13	13	13
Crospovidone	--	16	--	16	16	16
Aspartame	3	3	3	3	3	3
Orange flavor	2	2	2	2	2	2
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5
Average weight	320	320	320	320	320	320

Table 1: Formulation development of acyclovir tablets Sf1-Sf6.

The formulations were evaluated for hardness, weight variation, thickness, friability, disintegration time, *in vitro* dispersion time, wetting time and water absorption ratio, assay, content uniformity and *in vitro* dissolution [17].

Hardness test: Tablets require a certain amount of hardness and resistance to friability to withstand mechanical shock in manufacture, packing and shipping. To perform this test tablets were placed between two anvils, force to the anvils and the crushing strength that just causes the tablets to break was recorded. Monsanto hardness tester was used to measure the hardness of tablets. Six tablets from each batch were used for hardness studies and results were expressed in kg/cm^2.

Weight variation test: Randomly, twenty tablets are selected during compression and the mean weight was determined none of the tablets should deviated from the average weight by more than ± 10%.

Thickness: Tablet thickness can be measured using a simple procedure. Tablets were randomly selected from each formulation and their thickness was measured using Varnier calipers. The thickness was measured by placing a tablet between two arms of the Varnier calipers, which is expressed in mm.

Friability: Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm/min for 4min dropping the tablets at distance of 6 inches with each revolution. Pre weighed sample of 20 tablets were placed in the friabilator. Tablets were de- dusted and reweighed [18-20].

The percent friability was measured using the formula:

Friability=Initial weight-Final weight/Initial weight × 100

Disintegration time: The *in-vitro* disintegration time was determined using disintegration test apparatus. Six tablets were placed in each of the six tubes of the apparatus. The basket with the bottom surface made of a stainless steel screen (mesh no.10) was immersed in water bath at 37 ± 2°C the time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds [21].

***In vitro* dispersion time:** *In-vitro* dispersion time was measured by dropping a tablet in measuring cylinder containing 6 ml of water six tablets from each formulation were randomly selected and *In-vitro* dispersion time was performed [22].

Wetting time &water absorption test: Wetting time is closely related to the inner structure of tablets and to the hydrophilicity of the excipients. It is obvious that pore size becomes smaller and wetting time increases with an increase in compression force or a decrease in porosity. A linear relationship exists between wetting time and disintegration time. Thus wetting time is an important step for disintegration process to take place. A piece of tissue paper folded twice was placed in a small petridish (internal diameter=6.5 cm) containing 6 ml of water. A tablet was placed on the paper, and the time for complete wetting of the tablet was measured in seconds. The method was slightly modified by maintaining water at 37°C [23].

The same procedure was repeated for determining water absorption ratio. The wetted tablet was then weighed. Water absorption ratio, R, was determined according to following equation [24].

$R=\{(W_a-W_b)/W_a\} \times 100$

W_a=Weight of tablet before study.

W_b=Weight of tablet after study.

R=water absorption ratio.

Assay: 20 tablets were weighed and triturated. The tablet triturate equivalent to 200 mg of the drug was weighed accurately dissolved in water and diluted to 100ml with water and assayed individually at respective λ max against the reagent blank. The drug content should be within 90% to 110% of the labeled claim [25,26].

***In-vitro* dissolution studies:** The release rate of Acyclovir from orodispersible tablets was determined using USP dissolution testing apparatus II (paddle type). The dissolution test was performed using 500 ml of water 37 ± 5°C at 50 rpm. A sample of 2 ml of the solution was withdrawn from the dissolution apparatus every 5 min. for 15 min and the sample were replaced with fresh dissolution medium. The samples were filtered through watmann filter paper no.41. Absorbance of their solution was measured at 252 nm using UV spectrophotometer [27-29].

Evaluation of Tablet

In the present investigation oral dispersible tablets of Acyclovir were prepared by using camphor as subliming agent and Kollidon & Ac-Di-Sol (Crosspovidone and Croscarmellose sodium) as superdisintegrants. These directly compressed six formulations were prepared by sublimation method. The data obtained from pre-compressional parameters such as angle of repose, Carr's index and Hausner ratio were found to be within acceptable pharmacopoeia range as shown in (Table 2). The weights of tablets were within ± 5% which falls within the acceptable weight variation range of ± 7.5%. Hardness of all formulations was in the range of 2-3 kg/cm^2. Friability values of the batches by addition of super disintegrants and subliming agents was found in the range of 0.48%-0.72%. This is due to increase in porosity of the tablets due to camphor. The results of friability indicate that the tablets were mechanically stable and could handle the rigors of transportation and handling. Thickness of all formulations was between 2.31-2.42 mm indicating fairly acceptable tabulating. Disintegration time is very important parameter of ODT. The disintegration time of Formulation SF1-SF6 was satisfactory, because it disintegrates within 30 sec. among all the batches SF4 gives best disintegrating time i.e. 4-6 Sec hence SF4 is considered as finalized formulation. Percentage drug content (Assay) of Formulation SF1-SF6 was found to be between 99.1%-100.1% w/w. *In vitro* dispersion time was measured by the time taken to undergo uniform dispersion. The dispersion time of Formulations SF1–SF6 was in the range of 6-11sec. Among the batches by sublimation method (SF1-SF6) except batch SF3 all the batches shown dispersion time between 6-11 sec. The rapid and uniform dispersion was observed in the Formulation SF4 due to presence of both disintergrants and subliming agent (Crospovidone, Croscarmellose sodium and Camphor). Wetting time of the tablets decreasing (18-22 sec) with increase in concentration of camphor which is due to the increase in the porosity of the tablet.

Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Bulk density (g/ml)	0.4	0.4	0.39	0.49	0.51	0.5	0.4	0.49	0.5
Tapped density (g/ml)	0.5	0.48	0.49	0.58	0.6	0.57	0.48	0.58	0.59
Compressibility Index (%)	13	15.7	15.5	14.4	15	13.8	19.1	14.2	14
Hausner's ratio	1.2	1.18	1.18	1.17	1.17	1.16	1.17	1.17	1.18
Angle of repose (°)	27	29.4	28.7	27.1	28.3	27.9	30	26.2	28.1

Table 2: Evaluation of precompression properties.

Evaluation	SF1	SF2	SF3	SF4	SF5	SF6
Weight variation (mg)	320.1 ± 0.3	322.1 ± 0.2	323.5 ± 0.3	323.4 ± 0.2	322.6 ± 0.1	323.3 ± 0.2
Thickness (mm)	2.31-2.34	2.32-2.33	2.34-2.35	2.31-2.34	2.34-2.35	2.41-2.42
Friability (%)	0.62	0.64	0.48	0.5	0.48	0.72
Hardness(Kg/cm^2)	1.5-2	1.5-2	1.5-2.5	1.5-2.5	1.5-2.5	1.5-2.5
Disintegration time (sec)	04-Jun	03-Apr	30-35	04-Jun	05-Jul	04-Jun
Dispersion time(sec)	10-Nov	08-Oct	38-40	06-Aug	08-Oct	06-Aug
Water absorption ratio	61-63	63-65	53-55	65-68	64-68	61-65
Assay(% w/w)	100.1	99.8	100.4	99.9	100.1	99.1
Wetting time(sec)	19-20	20-22	25-26	18-19	20-22	18-19

Table3: Evaluation of formulation no.SF1-SF6.

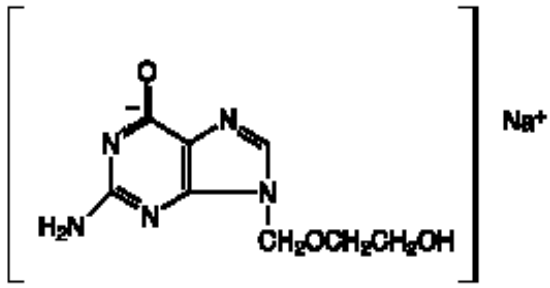

Figure 1: Chemical structure of Acyclovir.

Water absorption ratio is closely related to inner structure of tablets. The water absorption ratio value of Formulation SF1-SF6 was to found in the range of 53-68% were given in the Table 3.

***In vitro* dissolution study**

The dissolution study on formulation SF1-SF6 was carried out using 500 ml of double distilled water at 50 rpm using USP dissolution apparatus II (paddle). The formulations SF1, SF2, SF3, SF4, SF5, SF6 shows 100.8%, 99.6%, 99.8%, 100.1%, 99.8%, 99.9%, in 15 min respectively. The rapid *In-vitro* dissolution was found in the formulation containing Crospovidone and Croscarmellose sodium and camphor. Higher dissolution rate was resulted due to faster breakdown and rapid dispersion of tablet; it may be due to rapid diffusion or the porous nature of the tablet. The dissolution graphs are shown in Figures 1-4. The percent drug release of formulation SF4 correlates with drug content. By this study, an important conclusion can be drawn that addition of super disintegrating agent and subliming agent has improved the dissolution profile of the water soluble drug besides decreasing the disintegration time.

Conclusion

From the results of the study, we conclude that formula SF4 (Mannitol, Avicel pH102, Crospovidone, Croscarmellose sodium, Aspartame, Magnesium stearate, Orange Flavor, Camphor,) pocesses good disintegration and dissolution profile with additions of super disintegrating agent and subliming agent (Crospovidone, Croscarmellose sodium and camphor). On comparing with all batches, the prepared tablets by sublimation method passing all the quality control tests viz., friability, disintegration time dispersion time, wetting time. An FTIR study reveals that there is no interaction between

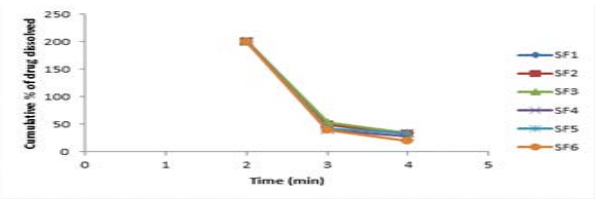

Figure 2: In vitro dissolution of SF1-SF6.

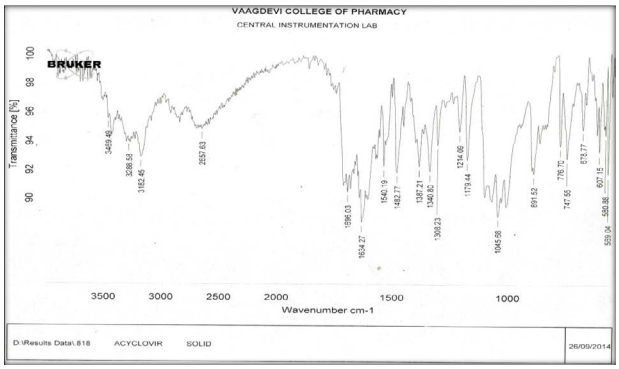

Figure 3: FTIR spectrum of Acyclovir.

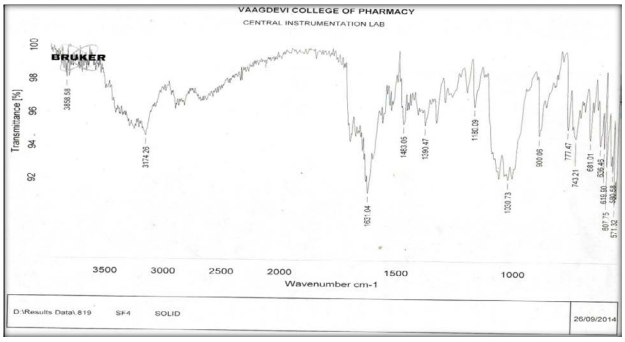

Figure 4: FTIR spectrum of Formulation SF4.

drug and excipients. The addition of super disintegrating agent and subliming agent can be used to prepare ODTs of several categories of drug such as antiallergic, anti-emetics, cardiovascular agent's, analgesic, neuroleptics which need rapid onset of action. Easy disintegration of orally disintegrating tablets of above mentioned pharmacological categories improves the availability of drug for absorption in a faster rate which enhances the bioavailability. Hence faster disintegration and dissolution of Acyclovir ODT may give better therapy for the treatment of viral infection.

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