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Research Article

Development and evaluation of Water dispersible tablets of Acyclovir

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Abstract

The present investigation concerns the development of water dispersible tablets of Acyclovir which were designed to enhance the onset of action of Acyclovir. The acyclovir water dispersible tablet was prepared by using Veegum F (Magnesium Aluminum Silicate) and Sodium Starch Glycolate as superdisintegrating agent, Avicel PH 102 as a diluent, Povidone K30 as a binder and carried out studies for weight variation, thickness, hardness, content uniformity, disintegrating time, dispersion time, wetting time and in vitro drug release. Tablets were prepared by using wet granulation method. Out of five, formulation F2 exhibited highest drug release 85.11% and formulation F4 showed drug release 85.42% in 10 min. They also exhibited the shortest wetting time 57.56 and 54.46 second with dispersion time 78 and 110 second respectively. It was concluded that water dispersible tablets with enhanced dissolution rate can be made using selective superdisintegrants.

Keywords: Acyclovir, Water Dispersible Tablet, Superdisintegrants, Dispersion Time

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 compliance compared to many other routes (Valleri et al., 2004). Most of the oral pharmaceutical dosage forms like conventional tablets and capsules are formulated to be swallowed or chewed. As results children, bedridden patients and elderly patients have difficulty in swallowing these dosage forms (Hanawa et al., 1995; Avani et al., 2008). To overcome this drawback novel drug delivery systems like orally disintegrating tablets have been developed (Bradoo et al., 2001) which disintegrate /dissolve/ disperse in saliva within few seconds without water. It becomes difficult to administer conventional tablet to patients. But administration of water dispersible tablets make the treatment becomes easier. Therefore, water dispersible tablets of this drug were considered. United States Food and Drug Administration (USFDA) defines water dispersible tablets as "A solid dosage form containing medicinal substances or active ingredient which disintegrates rapidly usually within a matter of seconds when placed in water" (Rangasamy, 2009). The major advantage of the water dispersible

tablets formulation is that it combines the advantages of conventional tablet formulations, thus allowing the ease of swallowing provided by the liquid formulation.

Acyclovir is a guanosine analogue ,one of the most commonly used antiviral drugs, it is primarily used for the treatment of *Herpes simplex* virus infections, as well as in the treatment of *Varicella zoster* (chickenpox) and *Herpes zoster* (shingles). It was originally extracted from a Caribbean sponge. It is selectively converted into Acyclovir-guanosine mono-phosphate (Acyclovir - GMP) by viral thymidine kinase, which is far more effective (3000 times) in phosphorylation than cellular thymidine kinase. Acyclovir is poorly water soluble and has poor oral bioavailability (15–30%), hence intravenous administration is necessary depending on the clinical condition of the patients, if high concentrations are required. When orally administered, peak plasma concentration occurs after 1–2 hours. Acyclovir has a high distribution rate; protein binding is reported to range from 9 to 33% (http://www.medicines. org.uk/EMC/ medicine /23721/SPC/Acyclovir). The elimination half-life of Acyclovir is approximately 3 hours. It is renally excreted, partly by glomerular filtration and partly by tubular secretion. The present study was designed to formulate water dispersible tablets of Acyclovir and pharmaceutically acceptable acid addition salts thereof in a view to solve some of the problems encountered in administration of drug to pediatric and elderly patients.

Materials and Methods

Materials

Acyclovir BP (China national native produce Ltd), Veegum F (Colorcon Asia Pvt. Ltd, USA), Sodium Starch Glycolate (Taiwan, Chunghwa chemical synthesis & Biotech co Ltd), Povidone K30 (Colorcon Asia Pvt. Ltd, USA), Avicel PH 102 - Microcrystalline cellulose (Mingtai Chemical Ltd. Taiwan), Magnesium Stearate (Remo Chemical Ltd. Bangladesh) and Talc (Remo chemicals, Bangladesh).

Equipments

Rapid Mix Granulator, # 25 Mesh Screen, Rotary Tablet Punch (8 station), Tablet Hardness Tester (YD-1 hardness tester), Friability Tester (Electrolab EF-1), Electrolab Tablet Dissolution Test Machine (08L), Electronic Balance, Double Beam UV Spectrophotometer, Karl Fischer Instrument, Tap Density Tester.

Preparation of matrix tablet (Krishnaiah et al., 2002)

Tablets were prepared by wet granulation method. The drug (Acyclovir) and excipients such as Veegum F, Sodium Starch Glycolate, Avicel PH 102 were mixed properly in poly bags and were granulated with Povidone K30 was dissolved in 50% aqueous alcohol (Ethyl Alcohol) as granulating agent. The resultant granules were dried in a tray drier at a temperature of 70^0C for approximately 25 minutes. The granules were then shifted through a 1000 µm diameter mesh sieve dry granules were lubricated with magnesium stearate and talc. The matrix tablets were prepared by compression using 8 station rotary machine (Kambert Machinery). Each tablet contained 800 mg drug (Table 1).

Evaluation of physical properties of formulation granules (Fiese et al., 1987; Ansel et al., 1995)

Bulk density

Apparent bulk density (ρb) was determined by placing presieved drug excipients blend into a graduated cylinder and measuring the volume (V_b) and weight (M) “as it is”.

$$\rho b = M/V_b$$

Tapped density

The measuring cylinder containing a known mass of blend was tapped for a fixed number of taps. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (ρt) was calculated using following formula.

$$\rho t = M/ Vt$$

Compressibility index

The compressibility index of the granules was determined by Carr's compressibility index:

Carr's index (%) = [(TBD – LBD) X 100]/TBD

Total porosity

Total porosity was determined by measuring the volume occupied by a selected weight of powder (V_{bulk}) and the true volume of granules (the space occupied by the powder exclusive of spaces greater than the intermolecular space (V).

Porosity (%) = $(V_{bulk} – V) / V_{bulk} \times 100$

Angle of repose

The angle of repose of granules was determined by the funnel method. Accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation:

Angle of repose, $\theta = \tan^{-1} (h/r)$

Where, h = Height in cm of the powder cone, r = Radius in cm of the powder cone.

Moisture content

Moisture content of granules was determined using Mettler Karl Fischer Titrator. About 120mg granules was weighed and added into the reagent solutions of the instrument, which was stirred and the tare weight was fed into the instrument. Then after certain duration of time the moisture content as % w/w was read on the monitor.

Hausner Ratio

Flow property, a very important parameter to be measured since it affects the mass of uniformity of the dose. It is usually predicted from Hausner ratio and angle of repose measurement. Hausner ratio is determined from the following equation-

Hausner Ratio = Tapped Density/Bulk Density

Evaluation of physical properties of Acyclovir matrix tablets

Weight variation test

To study weight variation, 20 tablets from each formulation were weighed using an electronic balance and the test was performed according to the British Pharmacopoeia.

Hardness

For each formulation, the hardness of 6 tablets was determined using Monsanto hardness tester.

Friability

Friability of 6 tablets of each proposed formulations were determined using the Friability tester.

Surface area

As the shape of the tablet was round flat, so it can be compared with a cylinder. Surface area of a cylinder is calculated by using the following equation:

Cylinder surface area = $\pi r^2 h$

Where, r = Radius in mm of tablet and h= thickness in mm of the tablet.

Drug content (Indian Pharmacopoeia, 1996)

Two tablets were powdered and the blend equivalent to 800 mg of Acyclovir was weighed and dissolved in suitable quantity of 0.1 N hydrochloric acid of pH (1.3). The solution was filtered, suitably diluted and the drug content was analyzed spectroscopically at 255 nm. Each sample was analyzed in triplicate.

Water absorption ratio

A piece of tissue paper was folded twice and placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper and the time required for complete wetting was recorded. The wetted tablet was then weighed. Water absorption ratio R, was determined using the following equation:

$$R = 100 (W_a - W_b)/W_b$$

Where,

W_b is the weight of tablet before water absorption and Wa is the weight of tablet after water absorption.

Wetting time (Sunada et al., 2002)

A piece of tissue paper (10.75×12 mm) folded twice was placed in a culture dish (d=6.5 cm) containing 6 ml of water. A tablet was put on the paper and the time for complete wetting was recorded.

***In vitro* dispersion time** (Mohapatra et al., 2009)

Tablet was added to 10 ml of phosphate buffer solution (pH 7.4) at 37±0.5°C. Time required for complete dispersion of a tablet was recorded.

***In vitro* release studies of Acyclovir tablets**

Dissolution studies were conducted to determine the release pattern of the drug from the product. Dissolution test for Acyclovir 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 0.1 N hydrochloric acid (simulated gastric fluid, pH 1.3) rotating at 50 rpm at 37 ± 0.5^0C. An aliquot of 10 ml of samples were withdrawn at different time periods and replaced with fresh medium. These samples were filtered and diluted. Absorbance of the resulting solution was measured at 255.0 nm (experimental λ_{max} for Acyclovir in pH 0.1 N hydrochloric acid). Percent drug release was calculated.

Results and Discussion

Acyclovir dispersible tablets were prepared by wet granulation method. The excipients such as Veegum F, Sodium Starch Glycolate, Avicel PH 102, Povidone K30, magnesium stearate, talc and citric acid were mixed properly in different stages of the formulations containing acyclovir 800 mg (table 1). The physical properties of the granules were studied in terms of loose bulk density (0.327 – 0.394), tapped bulk density (0.315 – 0.412), angle of repose (25.61 – 27.95) and moisture content (0.926 – 1.014). The particle size of the blend granules was on an average of 700 µm and flow property was determined by Hausner ratio (1.18-1.22) and Carr's index (15.48-17.72) (table-2).

The dispersible tablets were prepared by compression using 8 station rotary machine (Kambert Machinery). The tablets of different formulations were subjected to various evaluation tests, such as weight variation, friability, hardness, thickness and content uniformity according to procedure specified in British Pharmacopoeia 2010. The weight variation of the tablets from all batches varied between 0.38-0.58%, thickness between 8.89-8.97 mm and hardness 4.12- 5.2 N as shown in table 3. Friability of tablets from different batches showed below 1.87%. Drug content was found to be high (≥98.86%) in all the tablet formulations. Thus wetting times and dispersion time of tablets was found to be of all tablets from different batches shown to be satisfactory. All tablets found satisfactory release profile (Table-4). The influence of superdisintegrants on the dissolution of Acyclovir from the tablets is shown in figure -2. The drug release in 10 min and 25 min increased with increasing level of Veegum F and Povidone K30. However values decreased with increase in the level of sodium starch Glycolate. Out of five formulations F2 and F4 formulation are the best, show drug release 85.11% and 85.42% in 10 min and cumulatively 88.38% and 89.01% in 25 min (table -4). In the study, the relatively larger fragments generated by tablets were not small enough to pass through the screen of the dispersion vessels. The percentage drug release of all the batches was found to be between 79.42 to 89.01 % within 10 to 25 minutes. Comparative dissolution

Table 1. Formulation of Acyclovir Tablets (F-1 to F-5)

		Formulations				
Ingredients	**Justification**	**F1**	**F2**	**F3**	**F4**	**F5**
Acyclovir BP	Active Ingredient	800	800	800	800	800
Avicel Ph 102	Tablet diluents	76	74	76	76	66
Veegum F (Magnesium Aluminum Silicate)	Dispersing Clay	53	60	55	50	55
Sodium Starch Glycolate	Disintegrant	40	35	35	40	45
Povidone K30	Superdisintegrant	15	15	20	20	18
Magnesium Stearate	Tablet lubricant	10	10	8	8	10
Talc	Tablet lubricant	4	4	4	4	4
Citric acid	Flavor enhancer & helps breakdown of tablet in water	2	2	2	2	2
Total weight (in mg)		**1000**	**1000**	**1000**	**1000**	**1000**

Table 2. Physical properties of Acyclovir granules (F-1 to F-5)

Formulation	Loose Bulk Density (LBD) (gm/ml)	Tapped Bulk Density (TBD) (gm/ml)	Carr's Index (%)	Hausner ratio	Angle of repose (^{0})	Moisture content (%)
F-1	0.327	0.359	16.51	1.20	27.95	1.014
F-2	0.298	0.315	15.68	1.19	25.61	0.963
F-3	0.336	0.394	15.48	1.18	29.19	1.003
F-4	0.339	0.402	16.07	1.19	25.67	0.930
F-5	0.394	0.412	17.72	1.22	27.47	0.926

Table 3. Physical properties of Acyclovir tablets (F-1 to F-5)

Formulations	**Average weight (mg)**	**Diameter (mm)**	**Thickness (mm)**	**Hardness (N)**	**Friability (%)**	**Dispersion time(S)**	**wetting Time(S)**	**Drug Content (%)**	**Water absorption ratio**
F-1	1022±0.17	10	8.97±0.01	4.12±0.04	1.87	158	57.43	99.31	1.3
F-2	1018.1±0.11	10	8.93±0.02	4.3 ± 0.07	0.76	78	57.56	99.43	1.7
F-3	1017.8±0.15	10	8.90±0.02	4.5 ± 0.05	1.36	144	56.23	99.12	1.2
F-4	1019.5±0.08	10	8.92±0.01	4.32±0.02	1.1	110	54.46	99.56	1.5
F-5	1020.05± 0.09	10	8.89±0.01	5.2 ± 0.04	1.42	110	55.56	98.86	0.98

Table 4. Percentage (%) of release of five formulations **(F-1 to F-5)** of Acyclovir tablets

	Cumulative percentage (%) of drug release				
Time (in Min)	F1	F2	F3	F4	F5
0	0	0	0	0	0
10	81.63	85.11	79.42	85.42	81.32
15	85.24	87.14	80.82	87.46	82.71
20	85.70	87.92	81.27	88.55	83.80
25	86.47	88.38	82.35	89.01	84.25

Figure 1. Comparative *In Vitro* Dispersion time of Acyclovir water dispersible tablets

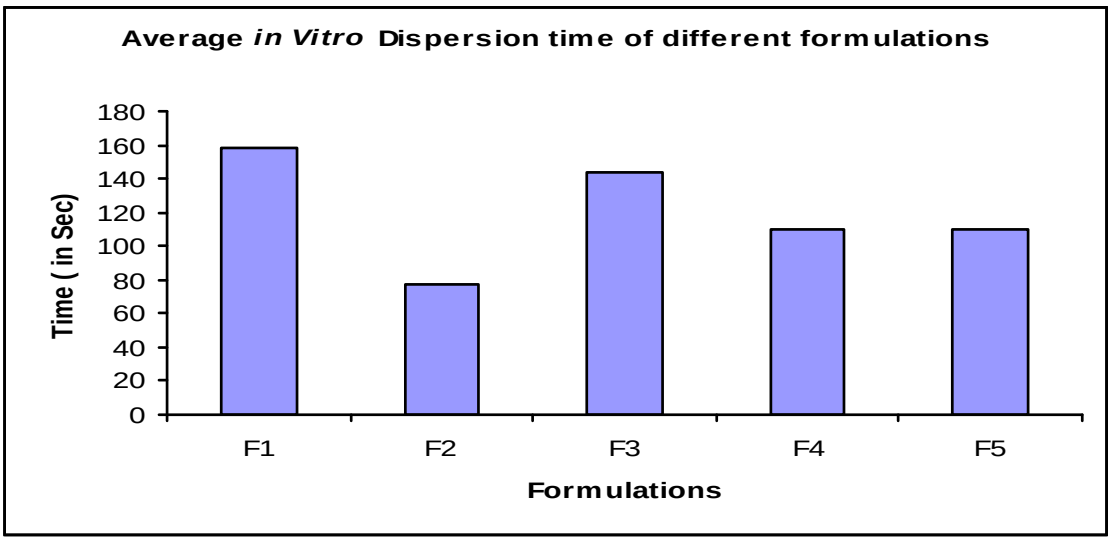
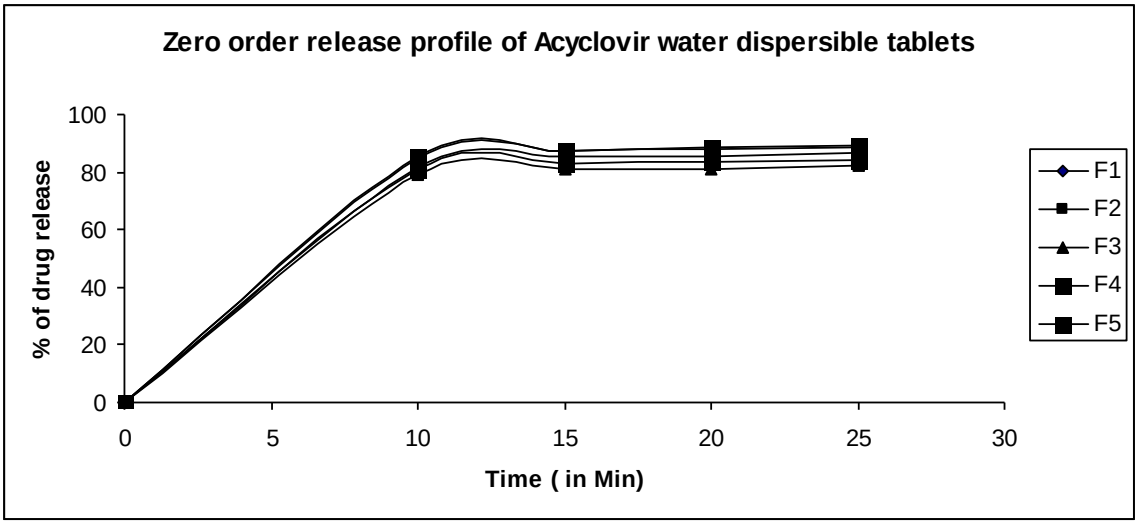


Figure 2. Zero order release kinetics of Acyclovir water dispersible tablets



profile of all batches (F1to F5) is given in figure -2. It was observed that as the concentration of superdisintegrants increased the drug release also increased.

The various technologies used to prepare water dispersible tablet's include direct compression, wet granulation, sublimation, tablet moulding, spray drying, and freeze drying and mass extrusion. The fast disintegration and dissolution effect of water dispersible tablets mainly depends on the type of superdisintegrants used in the tablet formulation (Caraballo et al., 1997). According to product information provided by the manufacturers of superdisintegrants, the excipients should be used in amount of 1-8% or with amount of about 2% to 4% being indicated as optimal (Liberman et al., 1989). Most commonly used superdisintegrants include sodium starch Glycolate, croscarmellose sodium (cross linked carboxymethylcellulose), cross povidone (cross linked Povidone) (Mallikarjuna et al., 2008). Use of Veegum F and sodium starch glycolate in combination mainly reduces the disintegration and dissolution time of acyclovir water dispersible tablets. From the comparative dissolution profile of all batches (F1to F5) of the dispersible tablets it was observed that as the concentration of superdisintegrant is increased the drug release form the tablet is also increased. Out of them F2 and F4 were the best considering the highest percentage of drug was released within 10 min and exhibited the shortest wetting time 57.56 and 54.46 second with dispersion time 78 and 110 second respectively.

Conclusions

The results obtained suggest that water dispersible tablets of Acyclovir containing Veegum F and Sodium Starch Glycolate can successfully be formulated with low concentration. Among the formulations, batch F2 and F4 showed superior micromeritic properties along with excellent *in vitro* dispersion time and drug release as compare to other formulations. It was concluded that addition technique of superdisintegrants is a useful technique for preparing dispersible tablets by wet granulation method. Rapid absorption, improved bioavailability, effective therapy and better patient compliance may be predicted from such acyclovir water dispersible tablet formulation.

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