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Formulation and Evaluation of Immediate Release Tablets of Acyclovir

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Abstract

Acyclovir is a synthetic purine nucleoside analogue with *in vitro* and *in vivo* inhibitory activity against herpes simplex virus types 1 (HSV-1) and (HSV-2) and varicella zoster virus (VZV). The aim is to formulate various formulations of immediate release tablet of Acyclovir using different Superdisintegrants (Sodium Starch Glycolate, Croscarmellose, Crospovidone), Povidone K-30 and Magnesium stearate by wet granulation method. The drug-excipients interaction was investigated by UV-spectrophotometer. The granules and tablets of Acyclovir were evaluated for various pre and post compression parameters like angle of repose, compressibility index, hausners ratio, tablet hardness, friability and *in vitro* disintegration and dissolution studies and their results were found to be satisfactory. These results suggest that maximum *in vitro* dissolution profile of formulation F6 were found to have equivalent percentage of drug release and concluded that F6 is better and similar to innovator product.

Key Words: Acyclovir, immediate release tablet, superdisintegrants, sodium Starch Glycolate.

INTRODUCTION

An immediate release dosage form allows a manufacturer to extend market exclusivity, while offering patients a convenient dosage form or dosage regimen. Immediate release tablets are those tablets which are designed to disintegrate and release their medication with no special rate controlling features, such as special coatings and other techniques [1, 2]. Immediate release and fast dispersing drug delivery system may offer a solution to these problems. Recently immediate release tablets have started gaining popularity and acceptance as a drug delivery system, mainly because they are easy to administer, has quick onset of action is economical and lead to better patient compliance. They are also a tool for expanding markets, extending product life cycles and generating opportunities[3,4].

Acyclovir structurally an Antiviral It is designated 2-Amino-1,9-dihydro-9-((2-hydroxyethoxy)methyl)-6*H*-Purin-6-one chemically . It is a synthetic purine nucleoside analogue with *in vitro* and *in-vivo* inhibitory activity against herpes simplex virus types 1 (HSV-1) and (HSV-2) and varicella –zoster virus (VZV). The mode of action of acyclovir on virus it converts acyclovir into acyclovir monophospate further into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes. In vitro acyclovir triphosphate stops replication of herpes viral DNA[5].

When it is given orally only 20% of the dose is absorbed and peak plasma concentrations and reached 1-2 hours. The drug is widely distributed, reaching concentrations in the CSF that are 50% of those in the plasma and excreted by the kidneys partly by glomerluar filtration and partly by tubular secretion and average oral bioavailability 10%to 20%.

The plan of present research is to develop patient compliance and cost effective Acyclovir immediate release tablets by wet granulation method. Thus eight different formulations were designed to obtain best optimized product by comparing with innovator.

MATERIALS AND METHODS

Materials:

Acyclovir was kindly gifted by Hetero drugs LTD, Hyderabad, India. Sodium starch Glycolate and Povidone K30 was obtained Akin laboratories, Hyderabad. Microcrystalline cellulose and crosspovidone purchased from signet chemicals, Mumbai India. Magnesium stearate was purchased from SD fine chemicals limited, Mumbai, India. FD&C Blue No2 was purchased from Colorcon Mumbai, India.

Preparation of Immediate Release Acyclovir Tablets:

Immediate release tablets of acyclovir were prepared by wet granulation method according to the formula given in Table 1. Acyclovir, Microcrystalline cellulose,FD&C colour blue and Superdisintegrants(Croscarmellosesodium , Sodium starch Glycolate, Crospovidone) were sift through sieve No.40 thoroughly mixed in a Rapid Mixer Granulator(RMG) for 10 min. PovidoneK-30 dissolved in sufficient quantity of water, and used as a binder solution. Granulation was done in Rapid Mixer Granulator using Povidone as binder solution. Wet granules were dried in fluid bed dryer (FBD) at 60-65^{0}C till a LOD (Loss of drying) of dried granules obtained not more than 2.5% w/w. Dried granules were passed through sieve No.24. The dried granules were blended in a blender with microcrystalline cellulose and Superdisintegrants (Croscarmellosesodium, Sodium starch Glycolate, Crospovidone) for 5 min which was already passed through sieve No. 40. Above mixer was lubricated for 5 min with Magnesium Stearate which was already passed through sieve No. 60. The lubricated granules were then compressed in to tablets on a 16 station rotary machine to get a tablet of 600 mg weight.

TABLE 1: FORMULA FOR PREPARATION OF IMMEDIATE RELEASE ACYCLOVIR TABLETS

S.NO	INGREDIENS	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
1	Acyclovir	400	400	400	400	400	400	400	400	400
2	Avicel $_{P}$H101	60	50	40	60	50	40	60	50	40
3	FD&C colour	1	1	1	1	1	1	1	1	1
4	Croscarmellose sodium	10	20	30						
5	Sodium starch Glycolate				10	20	30			
6	Crospovidone							10	20	30
7	Povidone K-30	30	30	30	30	30	30	30	30	30
8	Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
9	Avicel $_{P}$H102	84	74	64	84	74	64	84	74	64
10	Magnesium stearate	5	5	5	5	5	5	5	5	5
11	Total weight	600	600	600	600	600	600	600	600	600

Evaluation of Immediate Release Acyclovir Tablets

1. **Uniformity of Weight:**
   Individually 20 tablets were weighted at random using electronic balance and average weight was determined[6].
2. **Tablet Hardness:**
   Automatic Tablet Hardness Tester (Pfizer hardness tester) was used to determine the crushing strength. 6 tablets were randomly selected from each formulation and the pressure at which each tablet crushed was recorded.
3. **Tablet Friability:**
   20 tablets of each formulation were weighed and subjected to abrasion by employing at 25 rev/min for 4 min. The tablets were then weighed and compared with their initial weights and percentage friability was obtained.
4. ***In-vitro* Disintegration Test:**
   6 tablets from each formulation were employed for the test in distilled water at 37°C using Tablet Disintegration Tester. The time required for disintegrating the tablet and to broken down from large particle to small particle completely was recorded.
5. ***In-vitro* Dissolution Study:**
   The release rate of Acyclovir from immediate release tablets was determined using United State Pharmacopoeia (USP) XXIV dissolution testing apparatus II (Paddle method). The dissolution test was performed using 900 ml of 0.01N of Hydrochloric Acid in water, at 37±2^{o}C and 50 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus 5, 10, 15, 20, 25, and 30 minutes. The samples were replaced with fresh dissolution medium of same quantity. The samples were filtered through a 0.20µm PTFE membrane filter (hydrophilic) and measure the absorbance at 255 using UV-spectrophotometer.

TABLE 2: EVALUATION OF PRE-COMPRESSION PARAMETERS

Batch Code	Angle of repose (θ) Mean ±S.D	Bulk Density (gm/cc) Mean ±S.D	Tapped density (gm/cc) Mean ±S.D	Compressibility index Mean ±S.D	Hausner's ratio Mean ±S.D
F1	33º01' ±1.18	0.22 ± 0.02	0.25 ± 0.25	13.10 ± 1.14	1.15± 0.15
F2	30º01'± 1.37	0.25 ± 0.02	0.29 ± 0.04	13.32 ± 5.22	1.15 ± 0.07
F3	31º09'±2.12	0.26 ± 0..03	0.29 ± 0.02	10.44 ± 3.94	1.11 ± 0.05
F4	34º06' ±0.53	0.27± 0.06	0.31 ± 0.07	11.83 ± 2.85	1.13 ± 0.03
F5	34 º17'±1.07	0.23 ± 0.01	0.28 ± 0.01	17.04 ± 2.82	1.20 ± 0.04
F6	32º29' ±0.91	0.29 ± 0.01	0.33 ± 0.01	7.09 ± 2.82	1.13 ± 0.03
F7	33º21' ±0.83	0.24 ± 0.03	0.27 ± 0.03	11.22 ± 4.21	1.12 ± 0.05
F8	33º28'±0.83	0.28 ± 0.01	0.31 ± 0.05	11.55 ± 3.52	1.13 ± 0.04
F9	32º47' ± 0.62	0.25 ± 0.01	0.27 ± 0.01	10.41 ± 0.27	1.08 ± 0.03

TABLE 3: EVALUATION OF POST-COMPRESSION PARAMETERS

S.No	Batch code	Weight Variation Mean ±S.D	Hardness n=6 Mean±S.D	Thickness n=6 Mean ±S.D	Friability n=3 Mean ±S.D	Disintegration Time (mins)n=3 Mean ±S.D	Assay n=10 Mean ±S.D
1	F1	600.2±0.2	4.73 ± 0.64	4.16 ±0.13	0.56 ± 0.31	1.43 ± 0.61	98.01 ± 0.42
2	F2	600.5±0.2	4.76 ± 0.68	4.11± 0.27	0.55 ± 0.18	1.01 ± 0.22	97.74 ± 0.75
3	F3	600.7±0.6	4.66 ± 0.57	4.08 ± 0.24	0.52 ± 0.43	0.50 ± 0.06	102.29 ± 1.70
4	F4	600.3±0.8	4.86 ± 0.80	4.04 ± 0.12	0.56 ± 0.12	0.56 ± 0.08	97.70 ± 0.68
5	F5	600.3±0.6	4.73 ± 0.46	4.07 ± 0.08	0.62 ±0.06	0.52 ± 0.07	98.49 ± 0.44
6	F6	600.9±0.4	5.33 ± 0.57	4.06 ± 0.14	0.66 ± 0.07	0.47 ± 0.07	98.97 ± 0.95
7	F7	600.6±0.5	5.06 ± 1.06	4.11 ± 0.13	0.55 ± 0.05	1.12 ± 0.04	95.49 ± 0.85
8	F8	600.2±0.3	5.26 ± 0.64	4.18 ± 0.24	0.54 ± 0.04	0.50 ± 0.02	98.04 ± 1.35
9	F9	600.4±0.3	5.33 ± 1.15	4.29 ± 0.20	0.58 ± 0.07	0.66 ± 0.05	97.85 ± 0.61

TABLE 4: DISSOLUTION PROFILE OF FORMULATIONS COMPARED WITH INNOVATOR

S.NO	TIME (Mins)	F1	F2	F3	F4	F5	F6	F7	F8	F9	INNOVATOR
1.	0	0	0	0	0	0	0	0	0	0	0
2.	5	25.31	32.28	45.92	38.51	33.43	46.72	40.70	38.94	44.64	45.82
3.	10	46.40	47.24	55.34	42.94	59.64	54.82	53.82	55.62	57.87	61.73
4.	15	67.34	65.83	69.56	58.72	69.54	69.64	65.84	78.24	79.91	79.35
5.	20	78.54	79.26	82.64	78.89	85.48	78.42	89.46	90.40	92.61	90.74
6.	25	86.63	83.38	91.31	89.94	90.56	92.63	94.24	92.26	96.69	95.49
7.	30	89.82	92.68	93.23	94.44	94.82	97.45	96.50	97.65	99.50	95.32

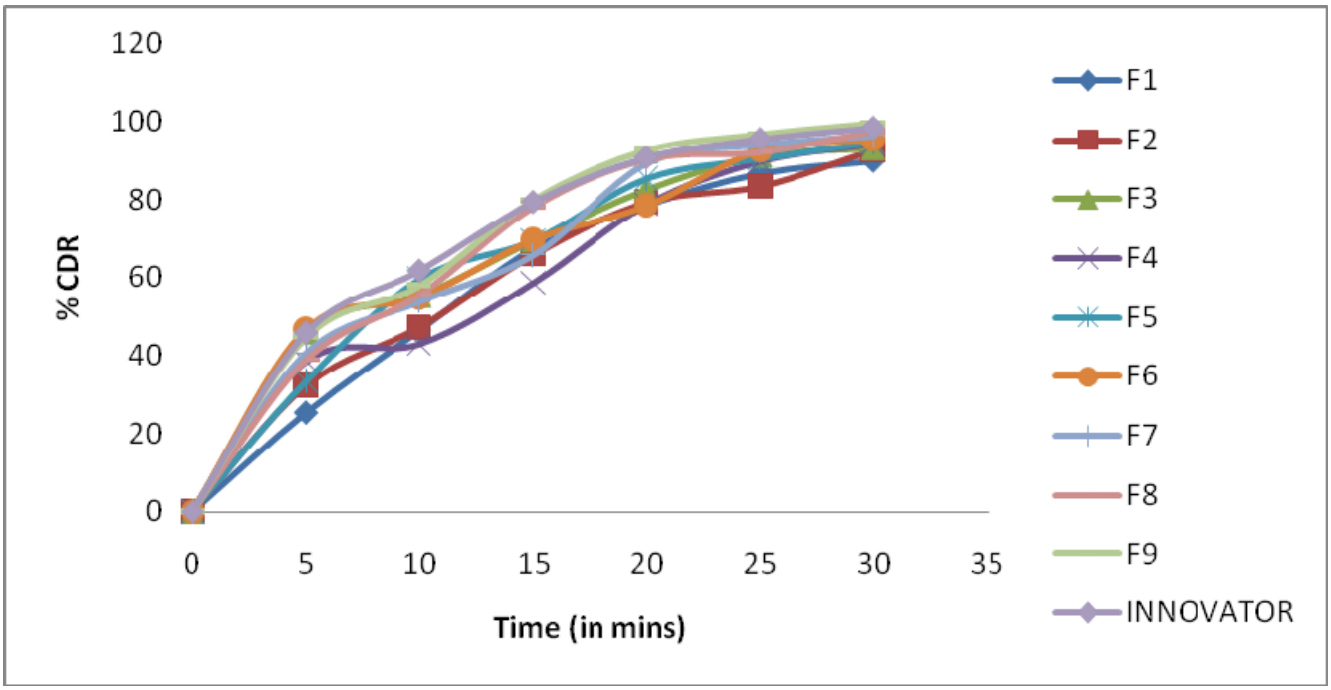

FIGURE 1: DISSOLUTION PROFILE OF FORMULATIONS WITH INNOVATOR

RESULTS AND DISCUSSION

In the present study, various formulations of immediate release Acyclovir tablets were prepared by wet granulation method. The use of super disintegrants for the preparation of immediate release tablets are highly effective and commercially feasible. These super disintegrants accelerate disintegration of tablets by virtue of their ability to absorb a large amount of water when exposed to an aqueous environment. The absorption of water results in breaking of tablets and therefore faster disintegration. This disintegration is reported to have an effect on dissolution characteristics as well (**Table 3, figure 1**).

Flow properties of the powder, resistance to particle movement can be judged from the angle of repose. Based on angle of repose it was observed that F6 showed excellent flow properties than the rest of formulations. Hausner's factor values were in the range of 1.61. Based on the results obtained we can conclude that F6 showed excellent flow.

Disintegration time is very important for immediate release tablets as it assists swallowing and also plays a role in increasing drug absorption, thus promoting bioavailability.

Disintegration time of prepared tablets was within the range (**Table 3**). *In-vitro* drug release study on the prepared tablets were done using 0.01N of Hydrochloric Acid in water as medium, at 37±2^{o}C from the results it was observed that F6 showed maximum drug release of 97.5% which was higher than other formulations .

Flow properties of the powder mixture are the determinant of the uniformity of the weight and thus content of the tablets. Results of evaluation of flow properties of powder blend prepared for direct compression and granules prepared by wet granulation The results of angle of repose, percent compressibility and Hausner's ratio ranged between 30.02 to 34.15; 7.09 to 17.04 and 1.082 to 1.20, respectively. Percent compressibility of all the granules and powder blends was found to be less than 15 which indicate excellent flow properties. The results of evaluation of Acyclovir tablets prepared by wet granulation are as shown in Table 4. All the Acyclovir dispersible tablets, formulated by wet granulation, were white, odorless, circular in shape with smooth shining surface. Thickness and hardness of all the formulations ranged in between 4.04mm to 4.29mm and 4.66 kg/cm2 to 5.33kg/cm2 , respectively. Friability of all the tablets was found to be less than 1% which was in accordance to the IP specifications for friability and which confirms the mechanical stability of tablets. Percent drug content of all the formulations was found to be in the range of 95.49% to 102.29% which was acceptable. Also weight variation of all the formulation batches was found to be in the permissible limits of ± 5% which may be due to good flow properties of the powder blend and granules. Rapid disintegration of tablet assists swallowing and also plays a role in fast absorption of drug. Tablets had disintegration time of less than 3 minutes. Disintegration time for tablets F5 and F6 was 47 sec and 52 sec, respectively. According to pharmacopoeial specifications, disintegration time of the fast disintegrating tablet should be less than 3 minutes, thus only formulation F5 and F6 passed the disintegration test and all other formulation were rejected for further evaluation. Dissolution profile of the batches F5 and F6 were studied. The batch F6 consists of sodium starch glycolate as superdisintegrant in greater proportion as compared to the other batches which lead to improved dissolution of the tablets. Sodium starch glycolate swells 7-12 folds in less than 30 sec in three dimensions as compared to croscaramellose sodium which swells 4-6 folds in less than 10 sec in two dimentions. The mechanism of disintegration is mostly swelling in case of Sodium starch glycolate while swelling and wicking in case of croscaramellose sodium (Gupta et al., 2010) Two types of superdisintegrants were used namely sodium starch glycolate and crosscaramellose sodium. It can be concluded from the study that formulation of dispersible tablet using sodium starch glycolate as a superdisintegrants showed improved solubility and hence better disintegration.

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