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Formulation and evaluation of immediate release tablets of ganciclovir.

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ABSTRACT: Ganciclovir 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 Ganciclovir using different Super disintegrants (Sodium Starch Glycolate, Croscarmellose, Crosspointe), Povidone K-30 and Magnesium stearate by wet granulation method. The drug-excipients interaction was investigated by UV-spectrophotometer. The granules and tablets of Ganciclovir tablet hardness, friability and in vitro disintegration and dissolution studies, weight variation, Thickness and hardness 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. It can be concluded from the study that formulation of dispersible tablet using sodium starch glycolate as a super disintegrants showed improved solubility and hence better disintegration.

KEYWORDS: Ganciclovir, ODT, Super disintegrants. TABLE OF CONTENTS.

I. INTRODUCTION

More than 50% of pharmaceutical products are orally administered for several reasons. This route of administration is considered as the most widely used route as it offers advantages like ease of administration, versatility, patient compliance and accurate dosing. Undesirable taste is one of the important formulation problems that are encountered with such oral product.

Virus:

• A virus is a sub microscopic infectious agent that replicates only inside the living cells of an organism. [1]

• Viruses infect all life forms, from animals and plants to microorganisms, including bacteria and archaea. [2][3] Viruses are found in almost every ecosystem on Earth and are the most numerous type of biological entity.[4][5]•

• When infected, a host cell is often forced to rapidly produce thousands of copies of the original virus. • When not inside an infected cell or in the process of infecting a cell, viruses exist in the form of independent viral particles, or virions, consisting of (I) genetic material, i.e., long molecules of DNA or RNA that encode the structure of the proteins by which the virus acts; (ii) a protein coat, the capsid, which surrounds and protects the genetic material; and in some cases (iii) an outside envelope of lipids.

• The shapes of these virus particles range from simple helical and icosahedralforms to more complex structures. Most virus species have virions too small to be seen with an optical microscope and are one-hundredth the size of most bacteria.

Herpes simplex virus:

• Herpes simplex virus (HSV), known as herpes, is a common infection that can cause painful blisters or ulcers. It primarily spreads by skin-to-skin contact. It is treatable but not curable.

• There are two types of herpes simplex virus;

• Type 1 (HSV-1) mostly spreads by oral contact and causes infections in or around the mouth (oral herpes or cold sores). It can also cause genital herpes. Most adults are infected with HSV-1.

• Type 2 (HSV-2) spreads by sexual contact and causes genital herpes.

• Most people have no symptoms or only mild symptoms. The infection can cause painful blisters

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or ulcers that can recur over time. Medicines can reduce symptoms but can't cure the infection

• Recurrent symptoms of both oral and genital herpes may be distressing. Genital herpes may also be stigmatizing and have an impact on sexual relationships. However, in time, most people with either kind of herpes adjust to living with the infection.

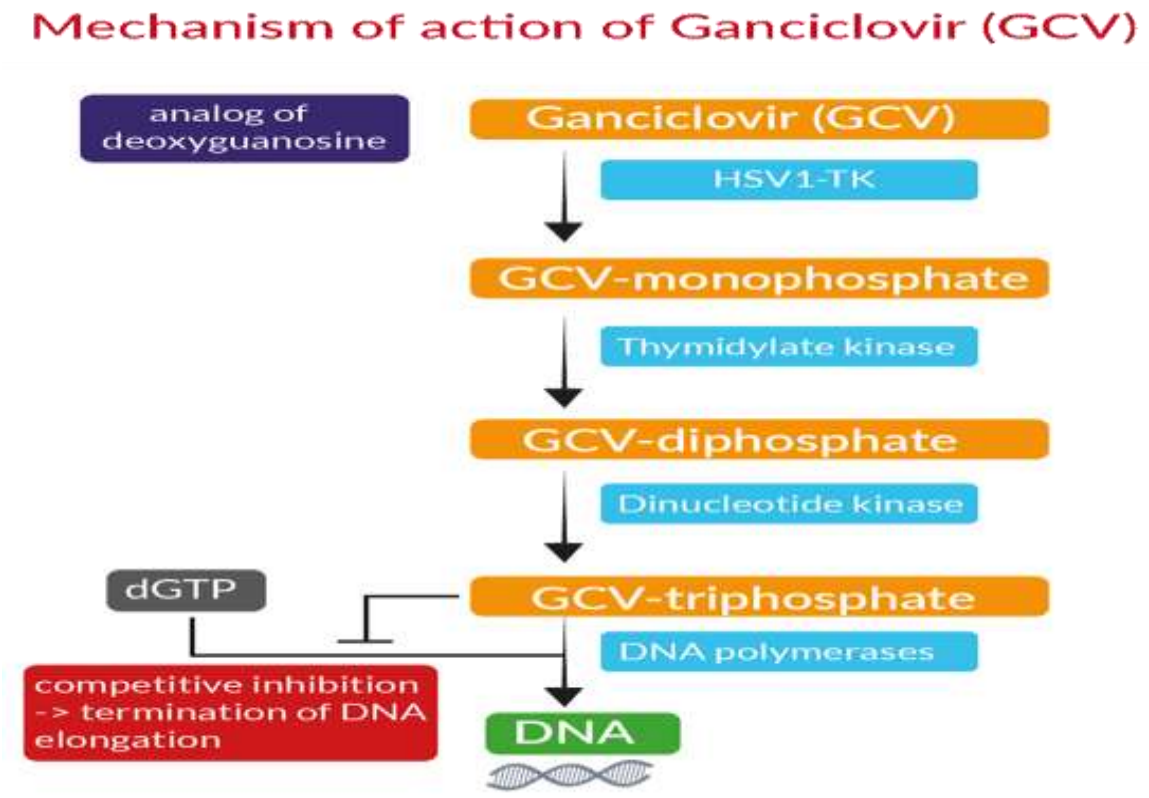
Antiviral drugs:

• Antiviral drugs are a class of antimicrobials, a larger group which also includes antibiotic (also termed antibacterial), antifungal and antiparasitic drugs,[3] or antiviral drugs based on monoclonal antibodies. [4] Most antivirals are considered relatively harmless to the host, and therefore can be used to treat infections.

Ganciclovir mechanism of action:

• Ganciclovir's antiviral activity inhibits virus replication. This inhibitory action is highly selective as the drug must be converted to the active form by a virus-encoded cellular enzyme, thymidine kinase (TK). • TK catalyses phosphorylation of ganciclovir to the monophosphate, which is then subsequently converted into the diphosphate by cellular guanylate kinase and into the triphosphate by a number of cellular enzymes.

• In vitro, ganciclovir triphosphate stops replication of herpes viral DNA. When used as a substrate for viral DNA polymerase, ganciclovir triphosphate competitively inhibits dATP leading to the formation of 'faulty' DNA. This is where ganciclovir triphosphate is incorporated into the DNA strand replacing many of the adenosine bases. This results in the prevention of DNA synthesis, as phosphodiester bridges can longer to be built, destabilizing the strand.



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II. MATERIALS AND METHODS:

2.1 Materials:

Ganciclovir was kindly gifted by Hetero drugs LTD, Hyderabad, India, Sodium starch glycolate and povidone K30 was obtained Akin laboratories, Hyderabad. Microcrystalline cellulose and Crospovidone purchased from signet chemicals, Mumbai India. Magnesiumsterate was purchased fromSD fine chemicals limited, Mumbai, India, FD&C Blue No2 was purchased from Colorcon Mumbai, India.

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2.2 Preparation of immediate release Ganciclovir tablets:

Immediate release tablets of ganciclovir were prepared by wet granulation method according to the formula given Table 1.

Ganciclovir, Microcrystallinecellulose, FD&C Colour blue and super disintegrants (sodium starch glycolate, crospovidone) were sift through sieve No,40 thoroughly mixed in arapid mixer granulator for 10 Min. a binder solution. PovidoneK-30 Dissolved in sufficient quantity of water, and used as. Granulation was done in rapid mixer granulator using povidone as binder solution. Wet granules were dried in fluid bed dryer at 60-65^{0}c till a LOD(loss on 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 super disintegrants for 5mins which was already passed through sieve No 40. Above mixer was lubricated for 5mins with magnesium stearate which was already passed through sieve No60.

The lubricated granules were then compressed into tablets on a 16 station rotatory machine to get a tablet of 400mg weight.

SL NO	INGRIDENTS	F1	F2	F3	F4	F5	F6
01.	GANCICLOVIR	250	250	250	250	250	250
02.	FDLC	1	1	1	1	1	1
03.	SODIUM STARCH GLYCOLATE	-	-	-	10	20	30
04.	CROSS POVIONE.	10	20	20	-	-	-
05.	POVIDONE K30	30	30	10	30	20	20
06.	PURIFIED WATER	QS	QS	QS	QS	QS	QS
07.	MAGNESIUM STERATE	9	9	9	9	9	9
08.	TOTAL	400	400	400	400	400	400

2.3 EVALUATION OF IMMEDIATE RELEASE OF GANCICLOVIR TABLETS:

1. Uniformity of weight:

Twenty tablets were selected at random from the lot, weighed individually and the average weight was determined. The percent deviation of each tablets weight against the average weight was calculated.

Hardness test:

The prepared tablets were subjected to hardness test28,38. It was carried out by using hardness tester and expressed in kg/cm2.

Friability test:

The friability was determined using friabilator and expressed in percentage (%). 20 tablets from each batch were weighed separately (Winitial) and placed in the friabilator, whichwas then operated for 100 revolutions at 25 rpm. The tablets were reweighed (Wfinal) and the percentage friability (F) was calculated.

In-vitro disintegration test:

6 tablets each formulation were employed for the test in distilled water at 37^{0}c using tablet disintegrating tablet tester

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The time required for disintegrating to tablet and to broken down from large particles to small particles was recorded.

In-vivo dissolution study:

The release rate of ganciclovir immediate release tablet was determined using united state pharmacopeia(USP) XXIV dissolution test apparatus II (PADLE METHOD).

TABLE 2: EVALUATION OF POST COMPRESSION PARAMETERS:

SNO:	BATCHCODE	WEIGHT VARIATION TEST	HARDNESS	THICKNESS	FRIABILI-Y	DIS INTEGRATION	ASSAY
1	F1	400.2+0.1	42.3+-0.64	4.16+-0.12	0.43+-0.64	0.45+-0.32	98.01+-0.32
2	F2	400.6+0.2	4.36+-0.67	4.10+-0.24	0.56+-0.31	0.56+-0.32	96.54+-0.52
3	F3	400.7+0.3	4.55+-0.75	4.09+-0.32	4.08+-0.13	0.55+-0.82	97.02+-0.64
4	F4	400.3+0.8	4.86+-0.89	4.05+-0.12	4.07+-0.08	0.52+-0.32	95.09+-0.76
5	F5	400.4+0.6	4.72+-0.45	4.07+-0.08	4.07+-0.01	0.56+-0.32	98.97+-0.78
6	F6	400.8+0.56	4.22+-0.54	4.19+-0.34	4.18+-0.32	0.68+-0.32	95.49+-0.85

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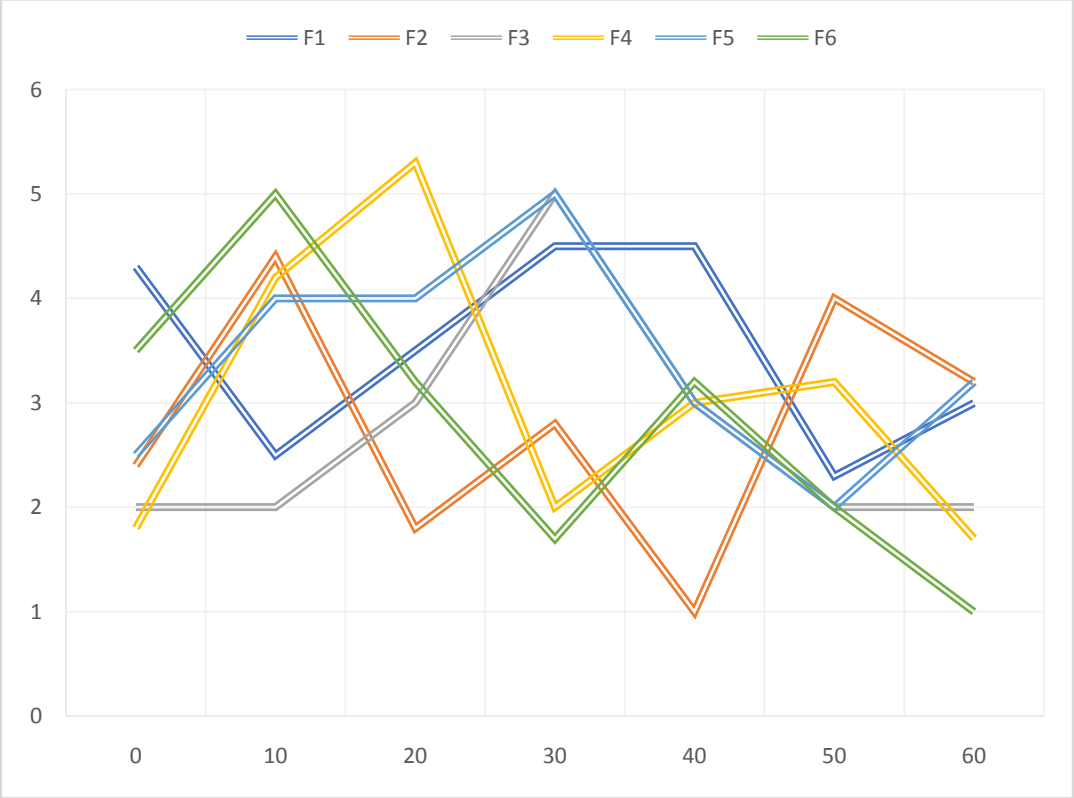
TABLE 3: DISSOLUTION ROFILE OF FORMULATION COMPARED WITH INNOVATOR:

SNO	TIME	F1	F2	F3	F4	F5	F6	INNOVATOR
1	0	0	0	0	0	0	0	0
2	10	25.13	49.52	45.92	32.45	33.65	33.45	45.98
3	20	48.24	32.64	39.51	45.56	45.67	45.76	54.86
4	30	68.43	24.52	56.78	67.56	56.75	56.76	66.76
5	40	52.54	79.26	69.56	52.32	67.67	65.66	76.99
6	50	86.63	85.48	65.89	65.32	76.85	76.83	75.87
7	60	89.82	65.98	78.93	45.56	82.45	88.98	98.89



III. RESULT AND DICUSSION:

Present study was done on enteric coating tablets with different formulation F1 to F6. acyclovir were prepared by direct compression method using different concentration of, microcrystalline cellulose, mannitol, dicalcium phosphate, croscarmellose sodium, magnesium stearate. Pre-formulation studie

FTIR spectral study FT-IR spectroscopy study was carried out separately to find out the compatibility between the drug acyclovir and Microcrystalline cellulose, mannitol, croscarmellose sodium. The FT-IR was performed for drug, the physical mixture of drug-polymer. The spectral obtained from FT-IR spectroscopy studies shows in and The peaks obtained in the spectra of drug mixtures . This indicates that the drug was compatible with the formulation components. IR studies indicated no interaction between drug and polymers>

The International Pharmaceutical Excipients Council (IPEC) defines excipients as "Substances, other than the Active Pharmaceutical Ingredient (API) in finished dosage form, which have been appropriately evaluated for safety and are included in a drug delivery system to either aid the processing or to aid manufacture, protect, support, enhance stability, bioavailability or patient acceptability, assist in product identification, or enhance any other attributes of the overall safety

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and effectiveness of the drug delivery system during storage or use". Solvents used for the production of a dosage form but not contained in the final product are considered to be excipients, i.e. the granulation fluids, which might be dried off later, should comply with relevant requirements of Pharmacopoeia unless adequately justified. Excipients no longer maintain the initial concept of "inactive support" because of the influence they have both over biopharmaceutical aspects and technological factors.

Direct compression is economic compare to wet granulation since it requires fewer unit operations. This means less equipment, lower power consumption, less space, less time and less labour leading to reduced production cost of tablets

• More suitable for moisture and heat sensitive APIs, since it eliminates wetting and drying steps and increases the stability of active ingredients by reducing detrimental effects

• Changes in dissolution profiles are less likely to occur in tablets made by direct compression on storage than in those made from granulations. This is extremely important because the official compendium now requires dissolution specifications in most solid dosage form.

• Disintegration or dissolution is the rate-limiting step in absorption in the case of tablets of poorly soluble API prepared by wet granulation. The tablets prepared by direct compression disintegrate into API particles instead of granules that directly come into contact with dissolution.

All the ganciclovir drugs are white odour less some are pink depending upon colour and circular shape with smooth shinning.

Thickness and hardness of all formulations are 4.04kg\cm^2 approximately.

Rapid disintegration test is done assist swaalloing and also plays a key role in fast absorption of drug.

Tablets have disintegration time less than 2 mins.

Dissolution profile of the batches f5 and f6 passed disintegration test.

Super disintegrating agents is greater in proportion to the other batches which lead to improved dissolution tablets.

Two types of super disintegrating agents are used.it can be conclude from the study that formulation of dispersed tablet using sodium starch glycolate as super disintegrating agent and hence it shows better disintegration.

IV. CONCLUSION:

We study about two method wet granulation and direct compression were evaluated.

We learnt that direct compression works better for orally& acts as immediate release tablet.

Two types of disintegrating agents are used i.e sodium starch glycolate & croscaramellosesodium.

By using superdisintegrating gent we learnt that solubility improved and shows better disintegration.

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CONFLICT OF INTREST:

The author declares no conflict of interest.

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