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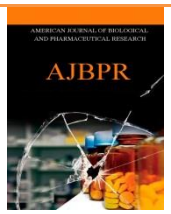

DESIGN AND DEVELOPMENT OF IMMEDIATE RELEASE ORAL SOLID DOSAGE FORM OF ADEFOVIR

Jolla Rajesh[1], K Sandhya[2]*, Divya E [1], Avinash Kumar G[3]

[1]Department of Pharmaceutics, Sun Institute of Pharmaceutical Education and Research, Kakupalli, Nellore-524346, Andhra Pradesh, India
[2]Department of Pharmaceutical Chemistry, Sun Institute of Pharmaceutical Education and Research, Kakupalli, Nellore-524346, Andhra Pradesh, India
[3]Department of Pharmacognosy & Phytochemistry, Sun Institute of Pharmaceutical Education and Research, Kakupalli, Nellore-524346, Andhra Pradesh, India

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ABSTRACT

Adefovir has a suboptimal bioavailability and requires formulation optimization to achieve immediate therapeutic effects. Adefovir tablets were developed and evaluated to improve its bioavailability and ensure rapid onset of action. In order to achieve optimal disintegration and dissolution profiles, the tablets were prepared by direct compression using varying concentrations of superdisintegrants. The physicochemical properties of adefovir and excipients were evaluated during the preformulation phase to ensure compatibility and stability. Physical properties of the tablets, such as hardness, friability, weight variation, and uniformity of drug content, were assessed. For the purpose of assessing the release profile of adefovir, in vitro disintegration and dissolution tests were conducted at 37°C. Tablets displayed satisfactory physical properties, including a range of hardness, friability, and uniform weight and drug content. Conclusions the immediate release tablets of adefovir developed in this study offer enhanced bioavailability and rapid drug release, potentially enhancing therapeutic efficacy in chronic hepatitis B treatment.

INTRODUCTION

The oral route of drug administration is the most important route of administering drugs for systemic effect. About 90% of drug used to produce systemic effects are administered by oral route. When a new drug is discovered one of the first questions a pharmacist asks is whether or not the drug can be effectively administered for its intended effect by the oral route.

Tablets

The drugs that are administered orally, solid oral dosage form represent the preferred class of products. The reasons for this preference are as follows.

Corresponding Author
K SANDHYA,

Email:sandhyakota1986@gmail.com

Tablet is unit dosage form in which one usual dose of the drug has been accurately placed by compression**.**

Liquid oral dosage forms, such as syrups, suspensions, emulsions, solutions and elixirs are usually designed to contain one dose of medication in 5 to 30 ml and the patient is then asked to measure his or her own medication using teaspoons, tablespoon or other measuring device. Such dosage measurements are typically in error by a factor ranging from 20 to 50% when the drug is self administered by the patient. [1].

ADVANTAGES:

- They are the lightest and most compact oral dosage forms.
- They are in general the easiest and cheapest to package.

- Product identification is potentially the simplest and cheapest,
- They lend themselves to certain special release profile products such as enteric or delayed release products.
- They are better suited to large-scale production.

DISADVANTAGES

- Resist compression into dense compacts.
- Drugs with poor wetability, dissolution properties, intermediate to large dosages, may be difficult to impossible to formulate .
- Bitter tasting drugs, drugs that are sensitive to oxygen or atmosphere moisture can not be formulated [2].

TABLET PROPERTIES

Tablets can be made in virtually any shape, although requirements of patients and tabulating machines mean the most are round, oval or capsule shaped. More unusual shapes have been manufactured but patients find these harder to swallow, and they are more vulnerable to chipping or manufacturing problems [3].

The machine determines tablet diameter and shape tooling used to produce them a die plus an upper and a lower punch are required. This is called a station of tooling. The thickness is determined by the amount of the tablet material and the position of the punches in relation to each other during compression. the shorter the distance between the punches, thickness, the greater the pressure applied during the compression and sometimes the harder the tablet. Tablets need to be hard enough that they don't break up in the bottle, yet friable enough that they disintegrate in the gastric tract.

CHOICE OF EXCIPIENTS

The desired characteristics of tablet may be achieved by adding colors, pigments, flavors, sweeteners and a sugar or film coating. The types of excipients selected for a formulation depend on the basic process used to manufacture the tablets [4, 5]

Drug-Excipient Interactions and their Effect on Absorption

The use of co processing is totally unexplored avenues in disintegrants.the widely used super disintegrants are Crospovidone and Croscaramellose sodium. Like diluents each super disintegrants have strength and weakness [6].

Excipients Used In Tablets

Excipients are inert substances used as diluents or vehicles for a drug. In the pharmaceutical industry it is a catch all terms, which includes various sub groups. Comprising diluents or fillers, binders or adhesives, disintegrants, lubricants, glidants or flavors fragrances and sweeteners [7]

Fillers (Diluents)

Tablet fillers of comprise a heterogeneous group of sub- -stances. Since they often comprise the bulk of the tablet selection of candidate from this group as carrier for a drug of prime importance

Binders

Binders are the glue that holds powders together to form granules. They are the adhesives that are added to tablet formulation to provide the cohesiveness required for that bonding together of the granules under compaction to form a tablet. Must remain intact when swallowed and then release its medicament. Binders are either sugar or polymeric materials. Commonly used binders are gelatin, glucose, methyl cellulose acacia, starch paste, povidone, alcohol, PVP in water, PVP in alcohol, and sorbital in water.

Lubricants

Lubricants are used in tablet formulation to ease the ejection of the tablet from the die, to prevent sticking of tablets to the punches, and to prevent excessive wear on punches and dies. They function by interposing a film of low shear strength at the interface between the tablet and the die wall and the punch face. Lubricants should be carefully selected for efficiency and for the properties of the tablet formulation [8, 9].

Disintegrants

Disintegrants are used in tablet preparation to break the tablet faster. But some of the disintegrants are also having property of enhancing solubility of insoluble drug.

Glidants

Glidant's are materials that improve the flow characteristics of granules by reducing the inter particulate friction. In proper amounts they also serve to assure smooth and uniform flow at all times. Many of the excipients commonly used in tablet formulations are especially applicable for use in chewable tablets due to their ability to provide the necessary properties of sweetness and chew ability in general; these fall into the sugar category, although a combination of excipients with artificial sweeteners may provide a satisfactory alternative.

Super Disintegrants in Immediate Release Tablets

A disintegrants is an excipient, which is added to a tablet, or capsule blend to aid in the breakup of the compacted mass when it is put into a fluid environment this is especially important for immediate release

products where rapid release of drug substance is required. A disintegrant can be added to a powder blend for direct compression or encapsulation it can also be used with that are wet granulated while there are some tablets fillers which aid in disintegration, there are more effective agents referred to as superdisintegrants [10,11].

Method of Preparation Of Tablets

Compressed tablets may be made by three basic methods.

- Wet granulation
- Direct compression
- Slugging [12-14].

Immediate Release Drug Delivery System

Immediate release drug delivery system is also conventional type of drug delivery system and it is defined as – immediate release tablets are designed to disintegrate and release their medicaments with no special rate controlling features such as special coatings and other techniques [15, 16].

HEPATITIS B

Hepatitis is a general term that means inflammation of the liver .the liver can become inflamed as a result of infection, a disorder of the immune system, or exposure to alcohol, certain medications, toxins, poisons, etc. Hepatitis B is caused by infection with the hepatitis B virus .the infection has 2 phases: acute and chronic. Acute (new, short-term) hepatitis B occurs shortly after exposure to the virus. A small number of people develop a very severe, life threating form of acute hepatitis called fulminate hepatitis. Chronic (ongoing, long term) hepatitis B is a infection with hepatitis B virus that lasts longer than 6 months. Once the infection is chronic, it may never go away completely. About 90-95% of people who are infected are able to fight off the virus so their infection never becomes chronic infection [17, 18].

MATERIALS AND METHODS

MATERIALS USED

Adefovir, Lactose, Microcrystalline cellulose, Crospovidone, Magnesium stearate.

EQUIPMENT USED

Balance, Tablet Compression machine, Friability apparatus, Hardness tester, Disintegrator, UV-Visible Spectro Pthotometer, Dissolution Apparatus, Dryer.

METHODS

Standard Curve Of Adefovir

A spectrophotometric method based on the measurement of absorbance at 254 nm in buffer 0.01 N HCl was used in the present study for the estimation of Adefovir.

Standard Solutions

100 mg Adefovir of was dissolved in 0.01N HCL in 100 ml volumetric flask and the solution was made up to volume with 0.01N HCL.

Procedure:

The standard solution of Adefovir was subsequently diluted with 0.01N HCl buffer to obtain a series of dilutions containing 10,20,30,40 and 50 µg of Adefovir in 1ml solution. The absorbance of these solutions was measured in UV-VIS Spectrophotometer at 254 nm using 0.01N HCl buffer as blank. The concentration of Adefovir and corresponding absorbance are given in. The absorbance was plotted against concentration of Adefovir.

Drug Excipient Compatibility Studies

The compatibility studies provide the framework for the drugs combination with the excipents in the fabrication of the dosage form. The study was carried out to establish that the pharmaceutically active drug has not undergone any changes, after it has been subjected to processing steps during formulation of tablets. Compatibility studies are carried out by mixing definite properties of the drug and excipient and kept in glass vials, which is stored at 55'c for one month.

Fourier Transform Infrared spectroscopy (FTIR)

The Fourier transform infrared analysis was conducted to verify the possibility of interaction of chemical bonds between drug and polymer. The FTIR spectrum was 93 performed by using a PerkinElmer 1600 spectrophotometer with a resolution of 2 cm-1. The samples were scanned in the spectral region between 4000 and 400 cm-1 by taking an average of 8 scans per sample. Solid powder samples were oven dried at around 300C, finely crushed, mixed with potassium bromide (1:10 ratio by weight) and pressed at 15000 psig (using a Carver Laboratory Press, Model C, Fred S. carver Inc., WIS 53051) to make disc. The detector was purged carefully by clean dry nitrogen gas to increase the signal level and reduce moisture. For the analysis of the data, the spectrum GX series model software was used.

Differential scanning calorimetric (DSC) studies

Interaction studies were carried out to investigate any interaction between drug and polymer as well as other excipients interactions is accelerated

stability studies, but it is time consuming and tedious. DSC is fast and reliable method to screen Drug-Excipients compatibility and provide maximum information about the possible interactions. Differential scanning calorimetry.

In DSC, the sample and the reference are thermally isolated from each other and each is fitted with its own temperature sensitizer and a heater. A signal proportional to the differences in power supplied to the sample and reference material is plotted against the sample temperature, whenever, there is any change in the sample due to heating, more power is supplied to keep the temperature of the reference and the sample same. This difference in power supplied between the reference and the sample is recorded as a peak. The area under the curve (AUC) obtained from a DSC scan is proportional to the enthalpy change, which is recorded as a positive peak exothermic or a negative peak (endothermic). To check potential, the drug and excipients are mixed and scanned at a heating rate of 10˚C per minute under an inert atmosphere of nitrogen. The temperature range selected must encompass all thermal features of the drug and excipients like melting point, desolation, polymorphism and decomposition. An interaction is concluded by elimination of endothermic or exothermic peaks, appearance of new peak(s), changes in peak shape and its onset, melting point and relative peak height. The resultant peaks for compatibility studies.

DSC Interpretation

The DSC thermograms of drug exhibited an endothermic in the regions of 233˚C respectively corresponding with their melting points. However, an endothermic peak corresponding with the melting of adefovir absent in the DSC of pure drug with excipients. By comparing the thermo grams of pure drug, pure drug with placebo we can say that the drug is compatible with the given excipients. The thermo grams of drugs, drug with placebo.

Preformulation Studies [19]

a. Determination of bulk density

The bulk density is ratio of the powder to volume it occupies. It is expressed as g/cc3.bulk density is imparted in determining the size of the container needed for handling and processing. The bulk density, and tapped density calculated.

b. Angle of repose

This is the maximum angle possible between the height of file of powder and horizontal plane. The frictional forces in the lose powder can be measured by angle of repose. The tangent of angle of repose is equal to the co efficient friction between the particles. Hence the rougher and more irregular the surface of particles the greater will be angle of repose.

Preparation of Adefovir Tablets Usign Direct Compression

Tablets containing 1 mg of Adefovir were prepared by direct compression method and various formulations used. The drug, superdisintegrant and diluents were passed through sieve no#40.all the above ingredients were co ground and properly mixed together. Magnesium stearate was passed through sieve no #40, mixed, and blended with the initial mixture in a poly-bag. The powder blend was compressed into tablets using diamond shaped punches to get tablets of 100 mg weight on a station rotary tablet machine (Rimek mini press-1). The formulated tablets were stored in a tightly closed glass containers and evaluated for various characteristics [20].

Evaluation Of Tablets

To design tablets and later monitor tablet production quality, quantitative evaluation and assessment of tablet chemical, physical and bioavailability properties must be made. The important parameters in the evaluation of tablets can be divided into physical and chemical properties.

a. Physical appearance

The general appearance of tablets, its visual identity and overall elegance is essential for consumer acceptance. The control of general appearance of tablets involves measurement of number of attributes such as tablet size, shape, color, presence or absence of odor , taste , surface texture and consistency of any identification marks.

b. Tablet weight and thickness

Control of physical dimensions of the tablets such as size and thickness is essential for consumer acceptance and tablet-tablet uniformity. The diameter size and punch size of tablets depends on the die and punches selected for making the tablets. The thickness of tablets is measured by vernier calipers scale. The thickness of tablet related to the tablet hardness and can be used an initial control parameter. Tablet thickness should be controlled within a 5%. In addition thickness must be controlled to facilitate packaging.

c. Average weight of tablets

It is desirable that all the tablets of a particular batch should be uniform in weight.

d. Hardness test

This is the force required to break a tablet in a diametric compression. Hardness of the tablet is determined by stock's Monsanto hardness tester, which consists of a barrel with a compressible spring. The pointer moves along the gauze in the barrel fracture.

The tablet hardness of 5kg is considered as suitable for handling the tablet

e. Friability

This test is performed to evaluate the ability to withstand abrasion in packing, handling and transporting. Initial

weights of 20 tablets is taken and are placed in the Roche Friabilator, rotating at 25 rpm for 4 min. the difference in the weight is noted and expressed as percentage. It should be preferably between 0.5 to 1.0.

f. Disintegration test

For most tablets the first important step toward solution is break down of tablet into smaller particles or granules, a process known as disintegration. This is one of the important quality control tests for disintegrating type tablets. Six tablets are tested for disintegration time using USP XXII apparatus. Disintegration type sustained release tablets are tested for disintegrating time.

g. Assay: Accurately weighed 10 tablets and transferred into a mortar crush the tablets to this take about 1.0 mg of Adefovir into a 100 ml volumetric flask, to this add 50ml of 0.01N HCL was added and sonicated for 10 min with occasional shaking. The solution was cooled to room temperature and diluted to volume with 0.01N HCL and filtered through 0.45 membrane filter.

h. Dissolution [21]

Table 1: Evaluation of drug powder properties

BULK DENSITY (gm/ cc^3)	TAPPEDDENSITY (gm/ cc^3)	HAUSNER'S RATIO	ANGLE OFREPOSE
0.442	0.565	1.25	32.1

Table 2: Evaluation of tablet powder properties

S.NO	FORMULATIONCODE	BULK DENSITY (gm/cc^3)		HAUSNER RATIO	ANGLE OF REPOSE
		UNTAPPED	TAPPED		
1	F1	0.462	0.539	1.16	27.0
2	F2	0.469	0.561	1.19	36.6
3	F3	0.462	0.591	1.27	36.6
4	F4	0.451	0.565	1.25	38.1
5	F5	0.480	0.560	1.16	31.1
6	F6	0.475	0.565	1.19	31.6

Table 3: Results of inprocess quality control parameters

F. CODE	AVGWT (%)	THICKNESS (mm)	HARDNESS kg/cm^2	FRIABILITY (%)	% OF DRUG CONTENT	DT.TIME (Min)
F1	102.9	2.83	4.29	0.403	97.9	1.51
F2	103.5	2.57	5.19	0.287	98.8	1.38
F3	103.9	2.83	4.77	0.455	98.7	1.53
F4	103.5	2.85	5.49	0.395	99.6	1.53
F5	106.5	2.84	5.34	0.527	97.8	2.56
F6	102.7	2.85	4.46	0.523	99.7	1.07

Figure 1: STANDARD CURVE OF ADEFOVIR.

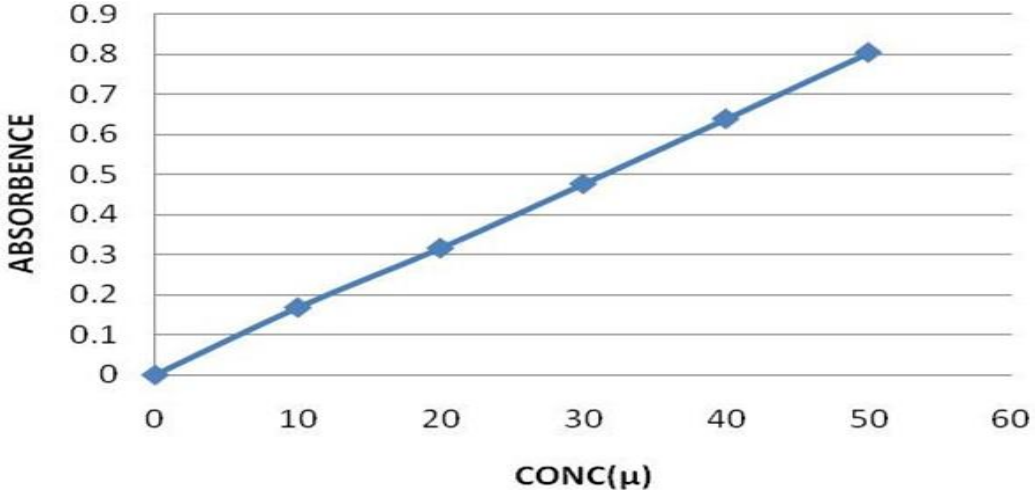


Figure 2: FTIR studies of the drugs and excipients

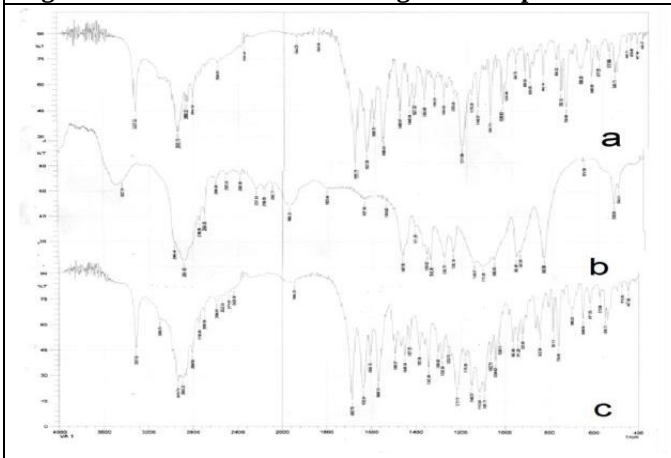


Figure 3: DSC Studies of the drugs and physical mixutre

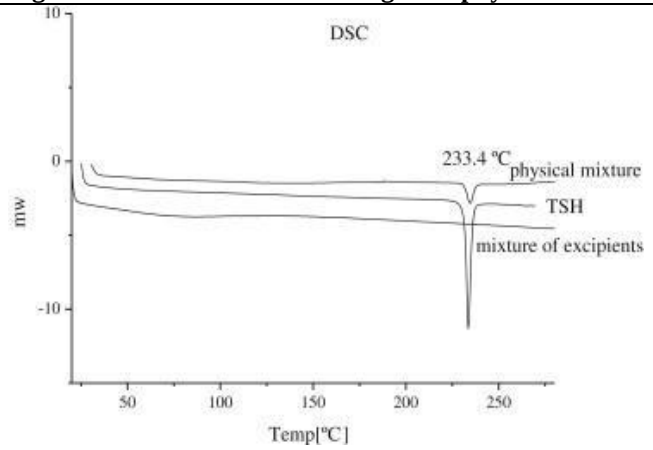
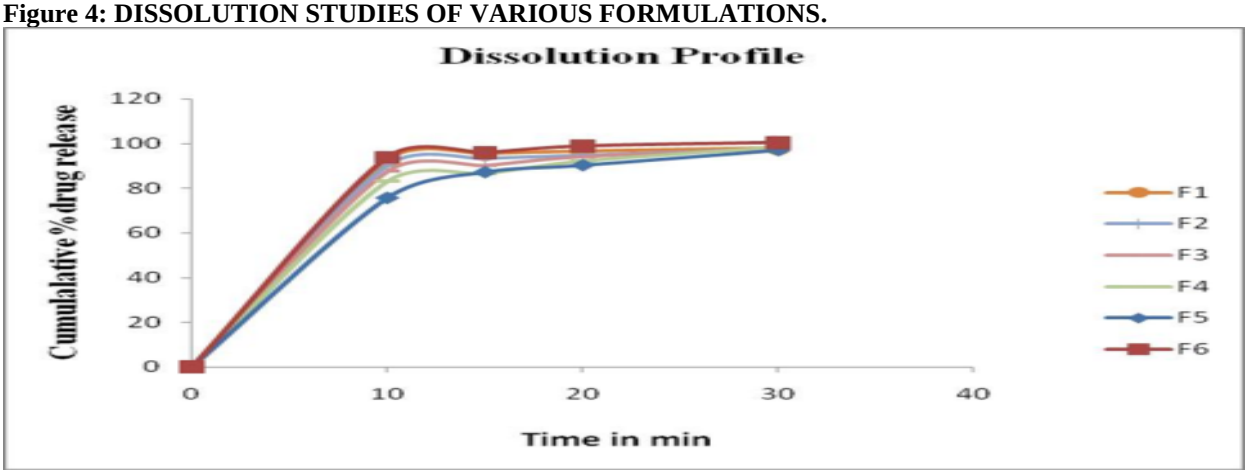


Figure 4: DISSOLUTION STUDIES OF VARIOUS FORMULATIONS.



Sample preparation:

One tablet was placed in each of six dissolution flasks containing 500 ml dissolution medium, previously maintained, taking care exclude air bubbles from the surface of each dosage unit and immediately operate the apparatus for 30 min. After completion of 10,15,20,30 min withdraws a portion of solution was withdrawn from the zone midway between the surface of the dissolution medium and top of the rotating blade, not less than 1 cm from vessel and filtered through 0.45 membrane filter. Separately equal volumes of diluents as blank (dissolution medium), standard preparation and sample preparations were kept into spectrometer and measure the absorbance. based on the absorbance we can calculate the %cumulative release of the drug.

RESULTS AND DISCUSSION

Standard curve absorbance values

The Active pharmaceutical ingredient were analyzed for the parameters such as bulkdensity, tapped density, hausners ratio, angle of repose and the results were found to be within the limits.

The blends were analyzed for the precompression studies. Bulk density and tapped density values range between 0.446-0.480 gm/cc and 0.539-0.637gm/cc and the values were found to be within limits. Hausner's ratio values for F1 to F6 range between1.16 to 1.19 and Angle of repose values within the limits

FTIR studies

FTIR spectrum of Adefovir was characterized with various peaks corresponding to various bonds like 1636.84 cm-1 for C=O stretching, 2931.53cm-1 for C—H stretching, 1221.13 cm-1 for --CH3, 3313.87 cm-1 for N—H stretching. Similarly corresponding peaks for the polymer, Polymer had been obtained and infers as 1109.52 cm-1 for C=O stretching, 2883.56 cm-1 for C—H stretching and 1339.81 cm-1 for O—H stretching. The peaks that correspond to C=O at 1641.21 of the drug had been shifted to 1625.17 cm-1and –CH3 at 1214.38 cm-1 had been shifted to 1219.07 cm-1 indicating that there are

strong bonds between drug and polymer but there was no other distinctive new peaks seen indicating that there is no chemical interaction between them.

Adefovir shows endothermic in DSC studies the standard melting point of the pure drug is 228ºc same was seen in DSC thermo gram in the presence of various excipients hence there is no interaction between drug and excipients.

- Visually examined tablets from each formulation.
- The total weight of each formulation was not maintained constant however the weight variation of the tablet was within the limits of 5%
- Tablets means thicknesses were almost uniform in all formulations and were found to be in the range of 2.5 to 2.9mm.
- Hardness of each formulation was analyzed for formulations F1 to F6. All formulations were found to have good hardness. So they were taken for further studies to measure hardness of tablets of each batch range between 4 to 6 kg/cm^2.
- Friability values were found to be less than 1% in all cases and considered to be satisfactory and the values 0.3 to 0.5%
- The prepared tablets were checked for assay as per USP specifications. All the formulations passed the test and the % of active ingredient ranges from 96 to 99%.
- All the tablets passed the pharmacopeial specifications for the disintegration of uncoated tablets within 15 min.

Invitro dissolution studies of formulations F1-F6 were carried out in0.01N HCL medium and % of drug release was calculated. All the formulations were kept for 30 min. it was found that all the formulations met the standard limits (80% drug release in 30 min). The dissolution profile of each formulation was compared with that of the standard product and found the formulation F6 had similar values of % drug release.

SUMMARY & CONCLUSION

Adefovir tablets were formulated by using direct compression method using lactose as diluent, MCC as binder, crospovidone as disintegrating agent and magnesium stearate as lubricant. The blend was compressed into tablets and was analyzed for the parameters such as average weight, thickness, hardness, friability and disintegration. Formulation containing Crospovidone (2mg) shows rapid rate of disintegration when compared with other formulations. The invitro dissolution profiles of F1 and F6 were found to have equivalent % of drug release with that of innovator product. But the disintegration time of F6 was relatively low (1 min 8 sec as compared to the F1 (1 min50sec) and concluded that F6 is better and similar to innovator product

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