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Formulation Development and Evaluation of Acyclovir Orally Disintegrating Tablets

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ABSTRACT

The Mouth Dissolving Drug Delivery Systems was an advancement that came into existence in the early 1970's and combats over the use of the conventional tablets, syrups, capsules which are the other oral drug delivery systems. Orally disintegrating dosage forms can address the pharmaceutical needs of the paediatric and geriatric patient group having difficulties in swallowing the conventional solid oral dosage forms. Orally disintegrating dosage forms also have the advantage of self medication, pain avoidance hence better patient compliance. Taste masking of bitter drugs is an important parameter. Orally disintegrating dosage forms may have an added advantage of bypassing first pass metabolism. 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 techniques after incorporating superdisintegrants croscarmellose sodium , sodium starch glycolate and Crossprovidone . Eight formulations were prepared. Tablet containing sodium starch glycolate and croscarmellose sodium showed excellent in vitro dispersion time and drug release as compared to other formulation. After study of eight formulations F8 showed short dispersion time with maximum drug release in 25 min. It is concluded that fast disintegrating acyclovir tablets could be prepared by direct compression using superdisintegrants.

Keywords: Acyclovir, ODT, Superdisintegrants

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INTRODUCTION

Oral drug delivery is the more advisable route for drug administration among all the routes used for drug delivery. Various types of dosage forms are prepared for administration of drug via oral route. Solid dosage forms are popular because of ease of administration, self medication, accurate dosage, pain avoidance and most importantly the patient compliance[1.] Buccal dosage forms are most commonly used dosage forms.[2] Most common dosage form is a tablet which can be defined as a unit of a solid dosage form made by compaction of medicaments. There are many types of tablets for the delayed rate or controlled rate of drug release. In this formulation the main drawback is dysphagia i.e having difficulty in swallowing. Dysphagia occurs in children due to undeveloped muscular and nervous system, geriatric patients suffering from Parkinson's disease, bedridden &mentally ill patients.[3]

To overcome these problems mouth dissolved tablets are the best choice of formulation. These tablet contents get disintegrated or dissolved in buccal cavity avoiding water consumption. This is a newer dosage form that gets dissolved in saliva in very few seconds. These tablets are also known as melt in mouth tablet (MMT), Fast melting tablet(FMT), Fast dissolving tablet(FDT), Orally Disintegrated tablet(ODT), Rapidly Disintegrated tablet(RDT).[7]

Advantages of Mouth Dissolving Tablets

- ODTs offer all the advantages of liquid dosage forms and solid dosage forms and.[4]
- Minimal or no residue remains in mouth after administration.[3]
- Rapid drug therapy intervention.[7]
- Good mouth feel property helps to change the perception of medication.[2]
- Administration of drug is possible to paediatric, geriatric & psychiatric patients.[6]
- Achieve increased bioavailability/rapid absorption through pre-gastric absorption.[6]
- Convenient for administration and patient compliant for disabled, for busy people and travellers , who do not always have access to water and bedridden patients .[5]
- The risk of chocking during oral administration of conventional formulations due to physical obstruction is avoided, thus providing batter safety.[7]
- Beneficial in cases such as suede episodes of allergic attack or coughing, motion sickness where a rapid onset of action required.[5]
- An increased bioavailability, specifically in cases of insoluble and hydrophobic drugs, due to quick disintegration and dissolution of these tablets.[3]
- Suitable for sustained/controlled release actives.[9]

- In condition of pain their Fast disintegration also impose a placebo effect before the medicine's effect actually begins and patient get relief quickly.[3]

Limitations of Mouth Dissolving Tablets:

- The tablets usually not have sufficient mechanical strength. Hence, careful handling is required.[5]
- FDT requires special packaging for safety of stable product and properly stabilization .[10]
- The tablets may leave unpleasant taste in mouth if not formulated properly.[3]
- Drugs with relatively larger doses are difficult to formulate into MDT.[3]
- 1.[3]
- The mechanical strength of the fast dissolving tablets is not so much then the traditional tablets. Many products are very light weight requiring them to be individually packaged. Patients were advised not to push these tablets through the foil film, but the peel the film back to release the fast-dissolving tablet.[11]

Desired Criteria for MDDS

Mouth Dissolving Tablets should

- Not require water to swallow, but it should disintegrate or dissolve in the mouth in matter of seconds.[6]
- Effective taste masking methods should be adopted for bitter taste drugs[4]
- Be portable without fragility concern.[4]
- Have a pleasing mouth feel.[2]
- Leave minimal or no residue in the mouth after oral administration.[3]
- Exhibits low sensitivity to environmental conditions as temperature and humidity .[2]
- Be able to be manufactured in a simple conventional manner within low cost. [12]

MATERIALS AND METHOD

Acyclovir was obtained as gift sample from Torrent Pharmaceutical Ltd. Sodium Starch Glycolate and Microcrystalline cellulose were obtained as gift sample from Arihant Trading Co., Mumbai; Sodium saccharine from Ranbaxy research lab, Gurgaon. All other excipients used were of analytical grade.

Preformulation studies

Determination of melting point

Solubility

Analytical Method for Identification of Acyclovir

1. λ max determination by UV spectroscopy
2. Fourier transformed infrared spectrophotometry
3. Differential Scanning Calorimetry (DSC)

λmax determination by UV spectroscopy

Preparation of stock and working standard solutions

1 mg of Acyclovir was accurately weighed and transferred to a 10 ml volumetric flask containing 3 ml of distilled water and sonicate for 20 minutes. This was further diluted up to the mark with distilled water to obtain drug concentration of 100 µg/ml. From this solution, 1ml was further diluted using same solvent to obtain drug concentration of 10 µg/ml as a working standard solution.

Preparation of calibration curve

Appropriate dilutions were made from stock standard solution to obtain solutions of concentration of 4, 6, 8, 10, 12, 14 and16 µg/ml, respectively. These solutions were scanned at249 nm& Absorbance was notes down. The calibration curve was plotted between Absorbance values against concentration.[16]

FT-IR spectral analysis (Drug & Drug excipient Compatibility study):[17]

FTIR spectroscopy was performed on Fourier transformed infrared spectrophotometer (Jasco International). The pellets of drug and potassium bromide were prepared by compressing the powders at 20 psi for 10 min on KBr press and the spectra were scanned in the wave number range of 4000- 600 cm-1. FTIR study was carried on Acyclovir.

The FTIR Spectrum of Pure acyclovir showed peaks

Wave number	
3563.81 cm-1	O-H stretching
3444.24 cm-1	N-H stretching
2927.94 cm-1	aliphatic C-H stretching anti symmetric
2856.06 cm-1	aliphatic C-H stretching symmetric
1714.41 cm-1	C=O stretching
1608.63 cm-1	O-H deformation
1482.99 cm-1	aliphatic C-H deformation
1143.8 cm-1	C-O stretching

DSC studies:

DSC thermo gram of acyclovir is presented in In case of Acyclovir two endothermic peaks were observed one at 1970C, which corresponds to melting process and the other at 2360C due to thermal decomposition. Thus from IR spectra studies and DSC thermo grams we can draw a conclusion that the drug remains in its normal form without undergoing any interaction with the

polymers.[17]

Formulation of tablets by direct compression method

All the ingredients mentioned in Table 1 were first passed through sieve no 60 and dried for one hour at 60oC and weighed accurately. The drug was mixed with dicalcium phosphate (DCP), Mg .stearate , Sodium saccharine and silicon dioxide.

For formulation F1 The drug was mixed with Sodium starch glycolate , in case of formulation F2 the drug was mixed with crosscarmellose sodium , in case of formulation F3 the drug was mixed with Crosspovidone, in case of formulation F4 the drug was mixed with Sodium starch gylcolate, crossprovidone , in case of formulation F5 the drug was mixed with Sodium starch gylcolate, crosscarmalose sodium , in case of formulation F6 the drug was mixed with crosscarmalose sodium, crossprovidone , in case of formulation F7 the drug was mixed with Sodium starch gylcolate, crossprovidone, crosscarmalose sodium. The addition was done in geometric proportions and mixing was done for 15 minutes to ensure uniform distribution. All other ingredients were added to respective formulations as shown in Table 1. Tablet weight and hardness was adjusted to 400mg and5-7 kg/cm2, respectively and tablets were punched using single punch machine.

Table 1: Composition of tablets prepared by direct compression.

Sr no	Ingredient	F1	F2	F3	F4	F5	F6	F7	F8
1	Acyclovir	200	200	200	200	200	200	200	200
2	dicalcium phosphate	173	173	173	173	173	173	173	173
3	Mg .Sterate	2	2	2	2	2	2	2	2
4	silicon dioxide	2	2	2	2	2	2	2	2
5	Sodium starch gylcolate	21			10.5	10.5		7	10.5
6	crosscarmalose sodium		21			10.5	10.5	7	10.5
7	Crossprovidone			21	10.5		10.5	7	
8	Sodium saccharine	2	2	2	2	2	2	2	2

EVALUATION TEST FOR FAST DISSOLVING TABLET

Tablets from all the formulation were subjected to following quality control test.

PRE-COMPRESSION PARAMETERS

Evaluation of blend for the following parameters to be carried out before compression of MDT's

Untapped Bulk Density:

10 g powder place into 100 ml measuring cylinder. Volume occupied by the powder weight is noted without disturbing the cylinder and bulk density is calculated by the following equation:

Untapped Bulk Density = Mass of bulk drug / Volume of bulk drug [3]

Tapped Bulk Density:

10 g powder place into 100 ml measuring cylinder. The cylinder is then subject to a fixed number of taps (~100 times) until the powder bed volume goes to the minimum level. Record the final volume and calculate the tap density by following equation:

Tapped Bulk Density = Mass of bulk drug/ Volume of bulk drug on tapping [3]

Compressibility:

It is an important measure obtained from bulk density and is

Defined as,

C=. Pb-Pu/Pb x100

Where Pb=tapped density of powder

Pu=bulked density of powder

If the particle bed is more compressible the blend will be less flow able and flowing materials.

Table 3: Relationship between % compressibility and flow ability

% Compressibility Flow ability

% compressibility	Flow ability
5 – 12	Excellent
12 – 16	Good
18 – 21	Fair Passable
23 – 35	Poor
33 – 38	Very Poor
< 40	Very Poor

Hausner Ratio: [3]

Hausner of the drug is found out using the following formula:

Hausner Ratio = Bulk Density / Tapped Density

Angle of repose:[1]

The frictional force of a powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the pile's surface of the powder & the horizontal plane. If more powder is added to the pile, It slides down the sides of the pile until the friction of the particles producing a surface angle, which is in equilibrium with the force of gravitation.

The angle of repose was determined by the funnel method suggested by Newman. Angle of repose is determined by the Formula

$\text{Tan}_{\theta} = h/r$

Therefore $_{\theta} = \text{Tan}^{-1}2h/r$

Where $_{\theta}$ = Angle of repose

h = height of the cone

r= Radius of the cone base

Angle of Repose less than 30 ° shows the free flowing of the material.

Table 2: Angle of Repose as an Indication of Powder Flow

Sr. No.	Angle of Repose (θ)	Type of Flow Properties
1	< 20	Excellent
2	20 – 30	Good
3	30 – 34	Passable
4	> 34	Very Poor

POST-COMPRESSION PARAMETERS

General Appearance:

The general appearance of a tablet is its visual identity and overall "elegance" is essential for consumer acceptance.[1]

Size and Shape:

The size and shape of the tablet could be dimensionally described, monitored and controlled.[1]

Hardness

A significant strength of MDT is difficult to achieve due to the specialized processes and ingredients used in the manufacturing. The limit of hardness for the MDT is usually kept in a lower range to facilitate rapid disintegration in the mouth. The hardness of the tablet can be measured using conventional hardness test.[4, 9]

Weight variation:[1]

Select 20 tablets randomly from the lot and weigh individually to check for weight variation. Weight variation specification as per I.P. is shown as follows

Limits for the weight variation of tablets:

Average weight of tablet % deviation

Average weight of tablet	% deviation
80mg or less	±10
More than 80 mg but less than 250 mg	±7.5
250mg or more	±5

Tablet thickness:

Tablet thickness is an important parameter in reproducing appearance and also in counting by using filling. Some filling equipment utilizes the same or uniform thickness of the tablets as a counting mechanism. Ten tablets are taken and thickness is measured by micrometer.[1]

Friability: [1]

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability

%Friability =(loss in weight / Initial weight)x 100

Disintegration Test:

It was determined using a disintegration test apparatus. This test was carried out at 37 ± 2°C in distilled water.[13]

Dissolution Test:

In vitro dissolution studies for all the fabricated tablets was carried out by using USP Type II apparatus (USP XXIII Dissolution Test Apparatus) at 100 rpm in 900 ml of water, maintained at 37±0.5°C.[13]

Wetting Time and Water Absorption Ratio:

Five circular tissue papers of 10 cm diameter were placed in a petridish with a 10-cm diameter.10 milliliters of PH 7.4 phosphate buffer solution is added to petridish. A tablet was kept on paper and time required for complete wetting was measured.

To measure the water absorption ratio the weight of the tablet before keeping in the petridish is noted down (W b) and the wetted tablet was taken and reweighed (W a). The water absorption ratio, R can be then determined according to the equation:[4]

$R = 100 (W a – W b)/W b$

In vitro dispersion time

In vitro dispersion time was measured by dropping a tablet in a 10 ml measuring cylinder containing 6ml of buffer solution simulating saliva fluid (pH6.8).[13]

Assay (% Drug content)

20 tablets were powdered and powder equivalent to 100mg of Acyclovir was weighed. To it, 60ml of 0.1M sodium hydroxide was added and powder was dispersed. Volume was made up to 100ml with 0.1M sodium hydroxide and filtered. To 15ml of filtrate 50ml of water and 5.8ml of 2M HCl was added. Volume was made up to 100ml with distilled water. To 5ml of above solution sufficient 0.1M HCl was added to produce 50ml. Absorbance of this solution was measured at wavelength of 255.4nm and %drug content was calculated.[13]

Stability study

Stability study of mouth dissolving tablets is done according to ICH guidelines for accelerated studies after suitable packaging at following conditions:

40 ± 1°C

50 ± 1°C

37 ± 1°C and RH 75% ± 5%

Tablets are withdrawn at specified time period and analyzed for various parameters like visual defects, hardness, friability, disintegration, dissolution etc.[15]

RESULTS AND DISCUSSION

λmax=249nm

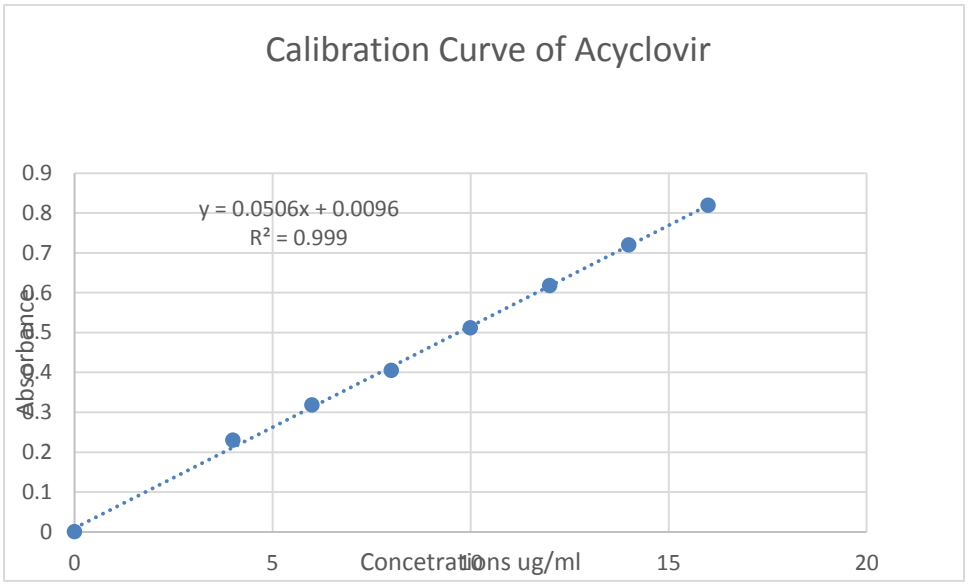

Figure 1: λmax determination by UV spectroscopy

FT-IR spectral analysis

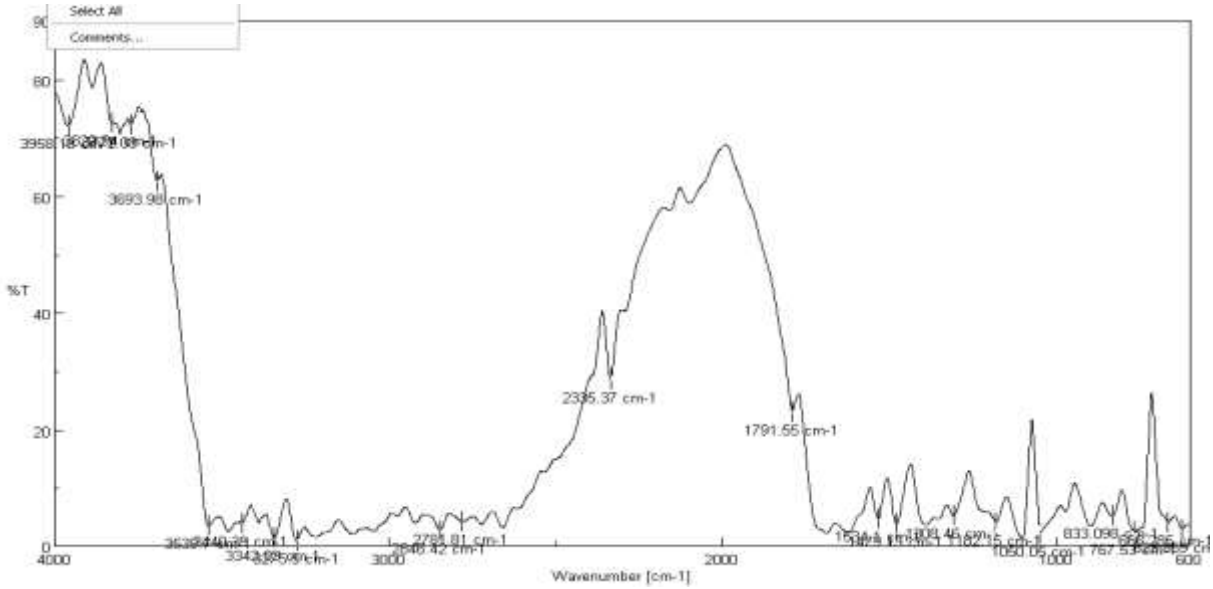

Figure 2: FT-IR spectra of Acyclovir

DSC studies

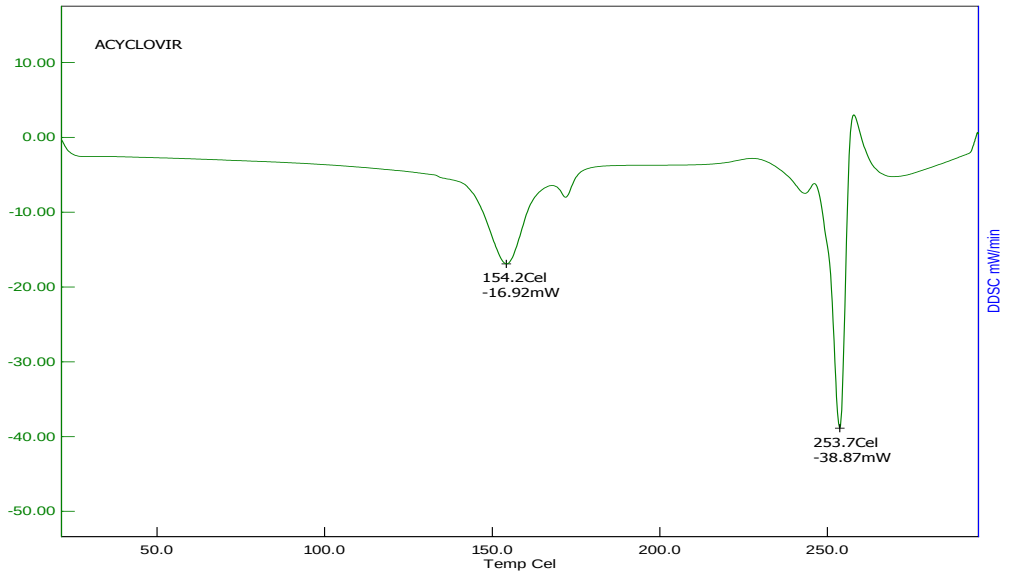

Figure 3: DSC of Acyclovir

Evaluation Test for Fast Dissolving Tablet

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

Table 1: Pre-compression Parameters

Formulation	Angle of repose	Loose bulk density (gm/cc)	Tapped bulk density (gm/cc)	Percent Compressibility	Hausner's ratio
F1	32.14±0.28	0.654±0.009	0.728±0.017	8.985±0.21	1.10±0.03
F2	31.33±0.24	0.586±0.025	0.623±0.023	10.65±0.14	1.16±0.06
F3	31.75±0.30	0.423±0.029	0.507±0.007	8.652±0.19	1.058±0.05
F4	34.37±0.17	0.625±0.008	0.694±0.020	6.256±0.08	1.2±0.04
F5	30.12±0.31	0.573±0.013	0.618±0.013	7.281±0.13	1.078±0.03
F6	30.87±0.26	0.565±0.024	0.623±0.025	15.263±0.20	1.065±0.02
F7	32.67±0.12	0.498±0.018	0.545±0.008	7.589±0.17	1.089±0.05
F8	30.15±0.34	0.572±0.013	0.618±0.012	7.283±0.13	1.078±0.03

Mean ± SD, n=3

Angle of repose

The results of angle of repose of drug powder was in range $30.12+0.31^0$ to $34.37+0.17^0$.

Untapped Bulk Density

The results untapped Bulk Density of drug powder was in range 0.423+0.029 gm/cc to 0.654+0.009gm/cc.

Tapped Bulk Density

The results tapped Bulk Density of drug powder was in range 0.507+0.007 gm/cc to 0.694+0.020 gm/cc.

Compressibility

The results Compressibility of drug powder was in range 6.256+0.08 % to 15.263+0.20 % .

Hausner Ratio

The results Hausner Ratio of drug powder was in range 1.078+0.03 to 1.16+0.06.

Table 2: Post-compression Parameters

Formulation	Appearance	Thickness (mm)	Hardness (Kg/cm2)	Friability (%)	Diameter (mm)	Weight Variation(mg)
F1	+++	4.5±0.12	5.5±0.29	0.785±0.017	13.98±0.06	394.85±1.17
F2	+++	4.12±0.05	5.7±0.29	0.938±0.010	14.08±0.01	398.52±1.88
F3	+++	4.6±0.07	5.6±0.29	0.824±0.020	14.11±0.04	405.03±1.89
F4	+++	4.15±0.10	5.5±0.29	0.782±0.011	14.05±0.07	402.21±2.05
F5	+++	4.1±0.04	5.2±029	0.752±0.014	14.01±0.03	401.14±1.58
F6	+++	4.3±0.08	5.4±0.29	0.814±0.008	14.11±0.03	401.35±1.84
F7	+++	4.8±0.09	5.9±0.29	0.784±0.013	14.13±0.01	399.22±1.27
F8	+++	4.3±0.05	5.1±029	0.754±0.016	14.01±0.02	401.16±1.56

Mean ± SD, n=3 + Poor, ++ Acceptable, +++ Good

Thickness

The thickness of the tablet indicates that die fill was uniform .The thickness depends on the size of punch (9.6 mm) and the weight of the tablet (400 mg). The thickness of the batch F1-F7 was found to be 4.1+0.04 mm to 4.8+0.09 mm.

Hardness

Hardness of the tablet batch from F1-F7 was found to be 5.2+029 kg/cm^2 to 5.9+0.29 kg/cm^2.

Friability

Friability was found to be 0.782+0.011 % to 0.938+0.010 % of the batch from F1-F7 which is within the official requirement i.e not more then 1% .

Diameter

Diameter of the tablet batch from F1-F7 was found to be 13.98+0.06 mm to 14.13+0.01 mm.

Weight Variation

Weight Variation of the tablet batch from F1-F7 was found to be 394.85+1.17 mg to 405.03+1.89 mg

Table 3: Post-compression Parameters

Formulation	Disintegration time(sec)	Dispersion time(sec)	Wetting Time(sec)	Water absorption ratio	Assay (%)
F1	49	56	64	52.75±1.43	101.54±0.68
F2	54	60	67	55.20±1.23	100.87±1.05
F3	57	62	66	49.58±1.35	101.24±0.53
F4	48	56	67	51.12±1.42	100.75±1.07
F5	43	48	60	49.25±1.27	101.89±0.37

F6	45	51	62	53.67±1.08	101.62±0.53
F7	51	59	63	54.87±1.12	101.11±0.72
F8	44	49	60	49.25±1.27	101.85±0.37

Mean ± SD, n=3

Disintegration time

Disintegration time of the tablet batch from F1-F7 was found to be 43 sec to 57 sec.

Dispersion time

Dispersion time of the tablet batch from F1-F7 was found to be 48 sec to 62 sec.

Wetting Time

Wetting Time of the tablet batch from F1-F7 was found to be 9 sec to 17 sec.

Water absorption ratio

Water absorption ratio of the tablet batch from F1-F7 was found to be

Assay

Assay of the tablet batch from F1-F7 was found to be 100.75+1.07 % to 101.89+0.37 %.

Dissolution studies

Table 4: Drug release profile of acyclovir in water by dissolution apparatus.

Time interval / Formulation	After 0 min(%)	After 5 min(%)	After 10 min(%)	After 15 min(%)	After 20 min(%)	After 25 min(%)
F1	0	58.65±0.42	75.50±0.27	84.92±0.34	89.00±0.28	93.04±0.13
F2	0	49.23±0.35	56.26±0.26	67.05±0.16	76.30±0.41	88.27±0.38
F3	0	57.85±0.21	69.28±0.32	75.79±0.19	88.82±0.26	91.88±0.16
F4	0	65.22±0.28	75.36±0.37	85.01±0.30	88.14±0.29	93.96±0.20
F5	0	60.52±0.22	71.95±0.17	84.25±0.24	90.87±0.30	99.16±0.10
F6	0	62.74±0.21	71.24±0.32	85.15±0.30	90.60±0.34	96.69±0.28
F7	0	63.80±0.36	79.52±0.24	83.25±0.25	89.04±0.23	94.85±0.30
F*8*	0	60.47±0.27	72.01±0.20	83.98±0.22	91.04±0.19	99.10±0.13

Mean ± SD, n=3

Total 7 formulations were formulated from F1-F7. The formulation F5 shows highest drug release 99.16±0.10 %. Formula F8 was the repetition of formula F5 to optimized the batch shows drug release 99.10±0.13 %

Table 5: Stability study (After 1 month)

Parameters	After 1 month
Thickness (mm)	4.12±0.03
Hardness (Kg/cm2)	5.19±0.24
Friability (%)	0.743±0.018
Diameter (mm)	14.01±0.03
Weight Variation (mg)	401.13±1.57
Disintegration time(sec)	42

Dispersion time(sec)	47
Wetting Time(sec)	60
Water absorption ratio	51.26±1.07
Assay (%)	101.85±0.36

Table 6: Dissolution study of optimize batch F5 (After 1 month)

Time interval	**After 1 moth (%)**
After 0 min(%)	0
After 5 min(%)	60.58±0.21
After 10 min(%)	72.09±0.25
After 15 min(%)	84.38±0.28
After2 0 min(%)	91.10±0.16
After 25 min(%)	99.18±0.11

CONCLUSION:

In the present study direct compression technique is used for their potential for the development of orally disintegrating tablets. From the results obtained it can be concluded that the direct compression serves to be a better method for this purpose Three types of superdisintegrants were used namely sodium starch glycolate and crosscaramellose sodium, cross povidone.in various combination .From the study that formulation of dispersible tablet using sodium starch glycolate and crosscaramellose sodium superdisintegrants used in combination gave best result. Hence for optimization formula F5 again formulated as F8, Which showed near about same result as of F5. Therefore in present study the mouth dissolved tablet prepared by the superdisintigrerants (sodium starch glycolate and crosscaramellose sodium) gave best results.

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