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Formulation Development and Evaluation of Acyclovir Orally Disintegrating Tablets

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ABSTRACT

Orally disintegrating systems have an edge amongst the oral drug delivery systems due to the highest component of compliance they enjoy in patients especially the geriatrics and pediatrics. In addition, patients suffering from dysphagia, motion sickness, repeated emesis and mental disorders prefer these medications because they cannot swallow large quantity of water. Further, drugs exhibiting satisfactory absorption from the oral mucosa or intended for immediate pharmacological action can be advantageously formulated in these dosage forms. However, the requirements of formulating these dosage forms with mechanical strength sufficient to withstand the rigors of handling and capable of disintegrating within a few seconds on contact with saliva are inextricable. Therefore, research in developing orally disintegrating systems has been aimed at investigating different excipients as well as techniques to meet these challenges. 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 and wet granulation techniques after incorporating superdisintegrants croscarmellose sodium and sodium starch glycolate. Seven formulations were prepared. Tablet containing sodium starch glycolate showed excellent in vitro dispersion time and drug release as compared to other formulation. After study of seven formulations DT3 showed short dispersion time with maximum drug release in 10 min. It is concluded that fast disintegrating acyclovir tablets could be prepared by direct compression using superdisintegrants.

Keywords: Acyclovir, ODT, Superdisintegrants.

INTRODUCTION

A vast variety of pharmaceutical research is directed at developing new dosage forms for oral administration. Most of these efforts have focused on either formulating novel drug delivery systems or increasing the patient compliance. Among the dosage forms developed for facilitating ease of medication, the orally disintegrating systems have been the favorite of product development scientists (Mohd Yasir, 2011). Due to decline in swallowing ability with age, a great many elder patients complain that it is difficult for them to take some currently used dosage forms such as tablets, capsules or powders.

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For this reason tablets which can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Rapidly dissolving or disintegrating tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people.

Orodispersible tablets (ODT) are oral solid dosage forms that disintegrate in the oral cavity in easy swallow residue. Orodispersible tablets are also known as "Mouth dissolving tablets", "Orally disintegrating tablets", "Melt- in- mouth", "Fast dissolving drug delivery", "Rapimelts tablets", "Porous tablets", "Quick dissolving tablets" etc. Recently ODT terminology has been approved by United States Pharmacopoeia, British Pharmacopoeia, and Centre for Drug Evaluation and Research (CDER) (Ghosh & Ghosh, 2011).

The benefits of formulating dispersible tablets are (Dinesh Kumar et al., 2011):

1. To aid the administration of drugs to patients who experience swallowing difficulties.
2. To improve the overall clinical performance of drugs by reducing the incidence of non-compliance.
3. To affect rapid release of medication.
4. To provide the advantage of a liquid medication in the form of a solid preparations.
5. Adaptable and amenable to existing processing and packaging high speed machinery.
6. Cost- effective, lower production, packaging and distribution costs compared to current commercially available products.
7. As with granules and effervescent tablets, dispersible tablets offer the patient a dosage form that is both potable and easy to swallow.

This dosage form is useful for (Shaikh et al., 2010) –

1. Geriatric patients mainly suffering from conditions like hand tremors and dysphasia.
2. Pediatric patients who are unable to swallow easily because their central nervous system and internal muscles are not developed completely.
3. Traveling patients suffering from motion sickness and diarrhea that do not have easy access to water.
4. Patients with persistent nausea for a long period of time are unable to swallow. Especially cancer patients after taking their chemotherapy are too nauseous to swallow the H2 blockers, which are prescribed in order to avoid gastric ulceration.
5. Mentally challenged patients, bedridden patients and psychiatric patients.

Acyclovir [9-(2-hydroxyethoxymethyl) guanine], a synthetic purine nucleoside analog derived from guanine, is the most widely used antiviral agent. It is effective in the treatment of herpes simplex virus (HSV), mainly HSV-1 and HSV-2 and varicella zoster virus. According to the biopharmaceutical classification system, acyclovir is categorized as a class - III drug

i.e. having high solubility and less permeability. The pharmacokinetic parameters of acyclovir, following oral administration, are generally highly variable. It has an average plasma half-life of about 3 hours in adults with normal renal function. Its absorption in the GIT is slow, variable and incomplete. The bioavailability of acyclovir after oral administration ranges from 10-30%. Approximately 80% of an oral dose is never absorbed and excreted through feces. Also the frequency of administration of acyclovir is high, being 200mg five times a day up to 400mg five times a day depending upon the type of infection (Dias et al., 2009).

MATERIAL AND METHOD

Material

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.

Method

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 60°C and weighed accurately. Drug was mixed with microcrystalline cellulose (MCC) in case of formulation DT1. In formulation DT2, the drug was mixed with dicalcium phosphate (DCP), MCC and Ac-di-sol. The drug was mixed with DCP in case of formulation DT3 and with DCP, Ac-di-sol in case of formulation DT4. In all above formulations, 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 and 5-7 kg/cm², respectively and tablets were punched using single punch machine in a room where humidity was controlled with the help of dehumidifier which was kept on 45 min prior to punching of tablets.

Table. 1: Composition of tablets prepared by direct compression.

Sr. No.	Ingredients	DT1 (mg)	DT2 (mg)	DT3 (mg)	DT4 (mg)
1	Acyclovir	200	200	200	200
2	Dicalcium Phosphate Dihydrate	-	125	175	165
3	Microcrystalline Cellulose (Avicel) pH102	110	56	-	-
4	Croscarmellose Sodium (Ac-di-sol)	-	15	-	30
5	Magnesium Stearate	2	2	2	3
6	Fumed Silicon Dioxide (Aerosil)	2	2	2	2
7	Sodium Starch Glycolate (Primogel)	6	-	21	-
8	Pregelatinised Starch (Pregel)	80	-	-	-
	Tablet Weight	400	400	400	400

Formulation of tablets by wet granulation method

Acyclovir, MCC, Primogel, Sodium saccharine and DCP were weighed accurately and mixed in geometric proportions as shown in Table 2. Starch paste (10%) was prepared and added to powder mixture as a binder to prepare a wet mass. Granules were prepared by passing the mass through sieve no. 16. Granules were dried at 60°C for 2 hours. Granules were then mixed with Talc, Magnesium stearate and Aerosil as shown in Table 2. Granules were evaluated as described in "Evaluation of powder blend and granules" and then compressed into tablet using single stroke tablet compression machine.

Table 2: Composition of tablets prepared by wet granulation.

Sr. No	Ingredients	WT1 (mg)	WT2 (mg)	WT3 (mg)
1	Acyclovir	200	200	200
2	Microcrystalline Cellulose (Avicel) pH102	-	25	25
3	Sodium Starch Glycolate (Primogel)	145	125	-
4	Starch (as binder)	30	50	40
5	Saccharin Sodium	24	24	25
6	Talc	25	2	-
7	Magnesium Stearate	3	2	-
8	Fumed Silicon Dioxide (Aerosil)	3	2	2
9	Dicalcium Phosphate	-	-	138
	Total Weight	430	430	430

Evaluation of powder blend and granules (Khinchi et al, 2011; Patil, 2011)

The powder blend obtained in direct compression and the granules obtained from wet granulation were evaluated for angle of repose, bulk density, tapped density, % compressibility and flow rate.

Angle of Repose

Angle of repose (θ) was determined using funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. The radius of the heap (r) was measured and angle of repose was calculated.

$$\tan \theta = h/r$$

Where θ is the angle of repose

Bulk Density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A suitable amount of powder or granules from each formulation, previously lightly shaken to break agglomerates formed, was introduced into a 10 ml measuring cylinder. After initial volume was observed, the cylinder was allowed to fall under its own weight on to a hard surface from a height of 2.5cm at 2 seconds intervals. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using following formula.

LBD= weight of the powder or granules / volume of the packing.

TBD= weight of the powder or granules / tapped volume of the packing.

Compressibility Index

Compressibility index of the powder was determined by Carr's compressibility index.

$$\text{Carr's Index (\%)} = \frac{(\text{TBD} - \text{LBD})}{\text{TBD}} \times 100$$

Hausner's Ratio

Hausner's ratio is a measure of frictional force existing in moving powder mass. It is calculated by following formula.

Hausner's ratio = Tapped density / Bulk density

Flow rate

Resistance to movement of particles, especially for granular powders with little cohesiveness is assessed by determining the flow rate. It is defined as the quantity of material that flows out in known period of time.

Glass funnel was fixed with a clamp so that the stem of the funnel was exactly perpendicular to the horizontal surface. Granules weighing 30gm were allowed to flow out through the funnel. Time taken for granules to flow out completely was noted and the flow rate was calculated as grams of granules divided by time in seconds.

Evaluation of Tablets (Bhardwaj, 2010)

Appearance

The general appearance of the tablets was evaluated with respect to the attributes such as tablet size, shape, color, presence or absence of odour, taste, surface texture and physical flows

Hardness

The force required to break a tablet in a diametric compression i.e. Hardness or tablet crushing strength was measured using Monsanto tablet hardness tester. The hardness was measured in terms of kg/cm².

Thickness

Thickness of tablet was measured by using vernier calipers. Three tablets were selected at random from each batch and average thickness in mm was reported.

Weight variation

Twenty tablets from each batch were selected at a random and average weight was determined. Then individual tablets were weighed and was compared with average weight.

Friability

Friability of the tablet determined using Roche friabilator. It subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25rpm and dropping a tablet at height of 6 inches in each revolution. Preweighed sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were de-dusted using a soft muslin cloth and reweighed.

The % friability (F) is given by the formula.

$$F = \frac{W_{\text{initial}} - W_{\text{final}}}{W_{\text{initial}}} \times 100$$

Where, W_{initial} is total weight of tablets before subjecting to the test

W_{final} is total weight of tablets after subjecting to the test

In vitro disintegration time

The test was performed using disintegration apparatus. A tablet was placed in each of the six tubes of the apparatus and one perforated plastic disc was added to each tube. The time in seconds taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was noted.

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).

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.

Dissolution studies

The dissolution profile of Acyclovir tablet was determined using USP XXII type 2 apparatus. 900ml of distilled

water maintained at a temperature of $37 \pm 0.5^\circ\text{C}$ was used as dissolution medium. Paddles were rotated at a speed of 100rpm. Aliquots of 5ml were withdrawn at specific intervals of 0.5, 1, 2, 4, 6, 8, 10 min and same volume was replaced with distilled water. Absorbance was measured at 249nm. Percent cumulative drug release was plotted against time in minutes to obtain dissolution profile.

RESULTS AND DISCUSSION

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 are shown in Table 3.

Table. 3: Flow properties of powder blend (DT 1-4) and granules (WT 1-3).

Formulation	Angle of repose	Loose bulk density (gm/cc)	Tapped bulk density (gm/cc)	Percent Compressibility	Hausner's ratio	Flow rate
DT1	34.15	0.687	0.753	8.76	1.096	1.2
DT2	32.26	0.459	0.528	18.068	1.15	1.06
DT3	30.12	0.573	0.618	7.281	1.078	1.12
DT4	34.15	0.525	0.563	6.749	1.072	1.01
WT1	32.25	0.59	0.624	10.85	1.121	1.15
WT2	34.16	0.59	0.619	10.08	1.112	1.03
WT3	30.02	0.62	0.692	7.096	1.076	1.21

The results of angle of repose, percent compressibility and Hausner's ratio ranged between 30.02 to 34.15; 6.74 to 18.06 and 1.072 to 1.15, respectively. Also flow rate of powder blends and granules ranged from 1.01 to 1.21. Percent compressibility of all the granules and powder blends, except DT2 was found to be less than 15 which indicate excellent flow properties.

The results of evaluation of Acyclovir tablets prepared by both direct compression (DT 1-4) and wet granulation (WT 1-3) are as shown in Table 4.

Table. 4: Results of evaluation of Acyclovir tablets prepared by direct compression (DT 1-4) and wet granulation (WT 1-3).

Formulation	Appearance	Thickness (mm)	Hardness (Kg/cm ²)	Friability (%)	Disintegration Time	Dispersion Time	Assay
DT1	White, odorless, circular in shape with smooth shining surface.	4.12	5.5	0.753	5min	5 min 4 sec	101.34
DT2	White, odorless, circular in shape with smooth shining surface.	4.15	5.7	0.945	3 min 10 sec	3 min 18 sec	100.51
DT3	White, odorless, circular in shape with smooth shining surface.	4.1	5.5	0.816	40sec	43 sec	101.89
DT4	White, odorless, circular in shape with smooth shining surface.	4.14	5.5	0.903	3 min 15 sec	3 min 20 sec	101.24
WT1	White, odorless, circular in shape with smooth shining surface.	4.14	5.5	0.825	9 min	9 min 42 sec	102.42
WT2	White, odorless, circular in shape with smooth shining surface.	4.16	6.5	0.843	7 min 40 sec	8 min 5 sec	101.53
WT3	White, odorless, circular in shape with smooth shining surface.	4.16	5.5	0.266	45 sec	47 sec	100.5
Marketed	White, odorless, circular in shape with smooth shining surface with line.	3.62	3	0.712	1 min 5 sec	1 min 10 sec	100.45

All the Acyclovir dispersible tablets, formulated by both direct compression and wet granulation, were white, odorless, circular in shape with smooth shining surface. Thickness and hardness of all the formulations ranged in between 3.62mm to 4.16mm and 3 kg/cm² to 6.5 kg/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. % drug content of all the formulations was found to be in the range of 99.36% to 102.42% which was acceptable. Also weight variation of all the formulation batches was found to be in the permissible limits of $\pm 5\%$ 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. Except for the tablet batch DT3, which was prepared by direct compression and WT3 which was prepared by wet granulation, all other tablets had disintegration time of more than 3 minutes. Disintegration time for tablets DT3 and WT3 was 40 sec and 45 sec, respectively. According to pharmacopoeial specifications, disintegration time of the fast disintegrating tablet should be less than 3 minutes, thus only formulation DT3 and WT3 passed the disintegration test and all other formulation were rejected for further evaluation. Dissolution profile of the batches DT3 and WT3 were studied and compared with the dissolution profile of marketed tablets (Fig. 1).

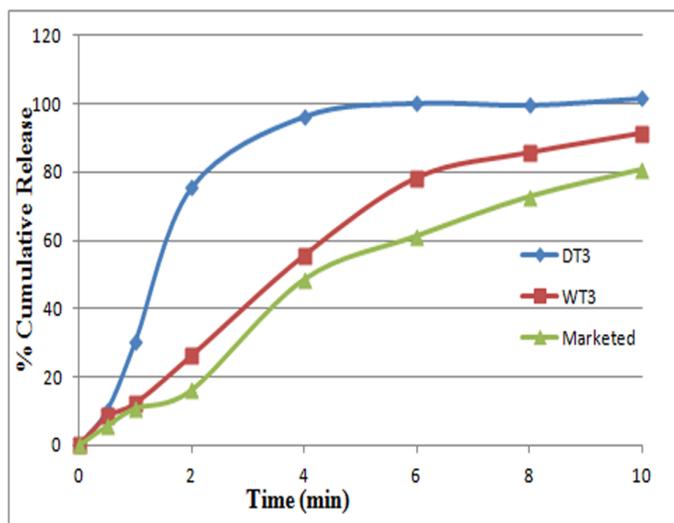


Fig. 1: Dissolution profile of Acyclovir tablets prepared by Direct Compression (batch DT3), Wet Granulation (WT3) and marketed tablets.

Dissolution profile of Acyclovir tablet batch DT3 showed 100% drug release within 10 minutes while batch prepared by wet granulation and marketed tablets showed 91% and 80% drug release, respectively, at the end of 10 minutes. Successful tablet production depends on achievement of the right balance between brittle fracture and plastic behavior within the compression mixture, which, in turn, is dependent upon the compressional characteristics of the drug substance and the excipients. Theoretically, substances such as microcrystalline cellulose undergo plastic deformation while dicalcium diphosphate undergoes brittle fracture during direct compression. However, in

practice, most excipients and drugs get compacted by a combination of these mechanisms. The excipients could be ranked in descending order in terms of their brittleness: microcrystalline cellulose > spray-dried lactose > α -lactose > β -lactose > α -lactose monohydrate > dicalcium phosphate dehydrate (Goel *et al.*, 2008). The batch DT3 consists of sodium starch glycolate as superdisintegrant in greater proportion as compared to the other batches subjected to direct compression, 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 croscarmellose sodium which swells 4-6 folds in less than 10 sec in two dimensions. The mechanism of disintegration is mostly swelling in case of Sodium starch glycolate while swelling and wicking in case of croscarmellose sodium (Gupta *et al.*, 2010).

CONCLUSION

In the present study two techniques direct compression and wet granulation were evaluated 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. Two types of superdisintegrants were used namely sodium starch glycolate and croscarmellose 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.

REFERENCES

- Bhardwaj V, Bansal M, Sharma PK. Formulation and Evaluation of Fast Dissolving Tablets of Amlodipine Besylate Using Different Super Disintegrants and Camphor as Sublimating Agent. *Am-Euras. J. Sci. Res.* 2010; 5(4): 264-269.
- Dias RJ, Sakhare SS, Mali KK. Design and Development of Mucoadhesive Acyclovir Tablet. *Iranian Journal of Pharmaceutical Research.* 2009; 8(4): 231-239.
- Dinesh kumar V, Sharma I, Sharma V. A comprehensive review on fast dissolving tablet technology. *Journal of Applied Pharmaceutical Science.* 2011; 01(05): 50-58.
- Ghosh T, Ghosh A, Prasad D. A review on new generation orodispersible tablets and its future prospective. *Int j pharm pharm sci.* 2011; 3(1): 1-7.
- Goel H *et al.* Orally Disintegrating Systems: Innovations in Formulation and Technology. *Recent Patents on Drug Delivery & Formulation.* 2008; 2: 258-274.
- Gupta A *et al.* Recent Trends of Fast Dissolving Tablet - An Overview of Formulation Technology. *International Journal of Pharmaceutical & Biological Archives.* 2010; 1(1): 1-10.
- Khinchi MP *et al.* Design and development of Orally Disintegrating Tablets of Famotidine Prepared by Direct Compression Method Using Different Superdisintegrants. *Journal of Applied Pharmaceutical Science.* 2011; 01(01): 50-58.
- Mohd Yasir *et al.* Orally disintegrating tablets: formulation, preparation techniques and evaluation. *Journal of Applied Pharmaceutical Science.* 2011; 01(04): 35-45.
- Patil MG *et al.* Formulation and evaluation of orally disintegrating tablet containing tramadol hydrochloride by mass extrusion technique. *Journal of Applied Pharmaceutical Science.* 2011; 01(06): 178-181.
- Shaikh S, Khirsagara RV, Quazi A. Fast disintegrating tablets: An overview of formulation and technology. *Int J Pharmacy Pharm Sci* 2010; 2(3): 9-15.