

DESIGN OF MULTI UNIT PARTICULATE SYSTEM CONTAINING ANTIRETRO VIRAL DRUGS

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ABSTRACT

MUPS (Multi Unit Particulate System) of Didanosine were formulated using drug layering technique and were further compressed into tablets by using various excipients and polymers such as Micro crystalline cellulose in optimized amount to reduce the rupture of the enteric coating layer of MUPS. The Multi Unit Particulate System was prepared by drug layering onto the non pareil seeds followed by enteric coating. The prepared MUPS were found intact in simulated gastric fluid and released at intestinal pH. The controlled release of acid labile Didanosine from MUPS was influenced by the proportion of diluents added in tablet formulation to provide cushioning effect to MUPS. The release data evaluated by dissolution technique showed no release of drug at gastric pH and 100% release at intestinal pH.

Key words: *Didanosine; Microcrystalline cellulose; Multi Unit Particulate System.*

INTRODUCTION

Solid dosage forms are widely prevalent, they hold a high potential as they serve to be most convenient for the administration of drugs. These have been developed into a wide range of formulations from conventional dosage forms for immediate release of the drug to controlled release dosage forms for the constant rate of drug release. Oral route is the most convenient and commonly used method of drug delivery. More than 50% of drug delivery systems available in the market are oral drug delivery systems. They offer convenience and ease of administration, greater flexibility in dosage forms have been used widely for decades mainly due to their convenience of administration and their suitability for delivery of drugs for systemic effects. The most commonly used pharmaceutical solid dosage forms today include granules, pellets, tablets and capsules.¹

Enteric coated dosage forms

Enteric coated dosage forms are designed to resist the acidic environment of the stomach and to disintegrate in the higher pH environment of the intestinal fluid. Polymers for enteric coating can be applied to solid dosage forms (granules, pellets or tablets) from aqueous latex or pseudo latex dispersions, aqueous solutions of alkali salts or organic solvent solutions. Medication that causes incompatibilities in the stomach or irritates the gastric mucosa or provokes nausea and sickness can be coated with enteric films to pass the acid environment of the stomach unchanged and release the active drug only after entering the small intestine. Such coatings should also be used to protect acid sensitive drugs against aggressive gastric fluid.²

Multi Unit Particulate System

Multiparticulate systems are a plurality of granules or microspheres that can be loaded into either a capsule or tablets.²

Advantages of multi unit particulate system

- ☐ Multiparticulates can be divided simultaneously into desired doses without formulation and process changes.
- ☐ They can be blended simultaneously to deliver bioactive agents or particles with different release profiles at the same site or at different sites within the gastrointestinal tract.
- ☐ Multiparticulates disperse freely in the gastro intestinal tract.
- ☐ Maximize absorption.
- ☐ Minimize side effects.
- ☐ Reduce inter and inpatient variability.

Limitations of multi unit particulate system

- ☐ Multiparticulate system are quite complex in design and manufacture.
- ☐ Require specialized equipment.
- ☐ Increasing manufacturing cost.
- ☐ Variation in surface and coating thickness can also translate into incomplete release of the active agent.
- ☐ Multiparticulate systems also have difficulties in handling large active ingredient loads.

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Pellets

Traditionally, the word "Pellet" has been used to describe a variety of systematically produced, geometrically defined agglomerate obtained from diverse starting materials utilizing different processing conditions.³

Pelletization is an agglomeration process that converts fine powders or granules of bulk drugs and excipients into small, free flowing, spherical or semi spherical units, referred to as pellets. Pellets range in size, typically, between 0.5 to 1.5mm, though other sizes could be prepared depending on the processing technologies employed.⁴

Pellets are of great interest to the pharmaceutical industry for a variety of reasons. Pelletized products not only offer flexibility in dosage form design and development, but are also utilized to improve the safety and efficacy of bioactive agents. However, the single most important factor responsible for the proliferation of the pelletized products is the popularity of controlled release technology in the delivery of drugs.⁵ When the pellets containing the active ingredient are administered in vivo in the form of suspensions, capsules or disintegrating tablets, they offer significant therapeutic advantages over single unit dosage forms. Because pellets disperse freely in the gastrointestinal tract, they invariably maximize drug absorption, reduce peak plasma fluctuations and minimize potential side effects without appreciably lowering drug bioavailability. Pellets also reduce variations in gastric emptying rates and overall transit times. Thus, intra and inter subject variability of plasma profiles, which are common with single unit regimens, are minimized.⁵ Another advantage of pellets over single unit dosage forms is that high local concentrations of bioactive agents, which may inherently be irritative or anesthetic, can be avoided. When formulated as modified release dosage forms, pellets are less susceptible to dose dumping than the reservoir type, single unit formulations.⁵

Compaction of Multiparticulate oral Dosage forms

The design and development of multiparticulate dosage formulations in the form of compressed tablets rather than hard gelatin capsules are becoming increasingly important.⁶

Advantages of tablet dosage forms

- ☐ Reduced cost
- ☐ Reduced liability to tampering
- ☐ Less prone to difficulties in esophageal transport than capsules
- ☐ Can be divided into two equal halves thus improving patient compliance in ingestion.

When a multiparticulate dosage product is developed in the form of a tablet, it is often desirable to produce

compacts that disintegrate into many subunits soon after ingestion, to attain more uniform concentrations of active substances in the fact that the coated subunits in the formulation must withstand the process of compaction without being damaged, since, for e.g. the existence of a crack in the coating may have undesirable effects on the drug release properties of that subunit. The type and amount of coating agent, the size of the subunits, selection of the external additives, and the rate and magnitude of the pressure applied must be considered carefully to maintain the desired drug release properties of that subunit.⁷

Particle rearrangement during compaction

Prior to the penetration of the upper punch into the die, the particles flow with respect to each other, with the finer particles entering the voids between the larger ones, resulting in a closer packing arrangement. At this stage, the energy involved in the process is due to interparticulate friction, which define the number of contact points (i.e. potential binding areas) between the particles, are governed primarily by the density, size, size distribution, shape and surface properties of the individual particle as well as by the process variables, such as the rate of flow, and the relationship between the die cavity diameter and particle diameter. The packing characteristics of spherical, cubical, needlelike or filamentous particle are different.⁷

Deformation of particles

As the upper punch penetrates the die containing the powder bed, initially, there are essentially only points of contact between the particles. Utilizing the punches, application of an external force to the bed results in forces being transmitted through these interparticulate points of contact, where the stress is developed and local deformation of the material occurs. If there is any energy loss, it would be due to interparticulate and die wall friction as well as deformation of particles. The deformation will feature one or a combination of the following: elastic, plastic and /or fragmentation. The type of deformation depends on the rate and magnitude of the applied force as well as the duration of the locally induced stress and physical properties of the material.⁸

Factors affecting multiparticulate tablet dosage form⁸

- ☐ **Selection of external additives:** It is of importance in the design of multiparticulate tablets such as diluents, since these additives are expected to prevent the occurrence in the coated subunits.
- ☐ **Compatibility of additives:** The compatibility of external additives with the subunits in terms of particle size is also very critical since, non uniform size distribution can cause segregation, resulting in many tableting problems, such as weight variation and poor content uniformity. To minimize

the occurrence of such problems, placebo microspheres, with good compaction and cushioning properties, can be used as diluents if the size of the active microspheres is much larger than that of the external powder additives.

- **Size of subunits:** Small active subunits also improve the content uniformity of low dose drugs. The size and shape, as well as surface properties, of micro spherical particles may differ from those of their powder form. This may also cause a change in their deformation mechanisms. For example microcrystalline cellulose, which deforms primarily by plastic deformation, can produce pellets that exhibit elastic and/or brittle fragmentation.
- **Mechanism of compaction:** Any undesirable change in the mechanism of compaction may cause a reduction in the mechanical strength of the ejected compacts and/or can alter the drug release characteristics.
- **Amount of lubricant:** Since the surface area of the spherical particles will be minimum as compared to other shapes, microspherical multiparticulate formulations may require only a very small amount of and mixing time with the lubricant must also be carefully considered.
- **The type and amount of coating:** It is important that the coated subunits in the formulation be able to withstand the process of compaction without being damaged.⁸

Research Envisaged

The use of Anti retroviral drugs has tremendously increased in the past decade. In the present study, Anti retroviral drugs i.e. Didanosine, Stavudine and Nevirapine have been selected as the model drugs on the basis of its pharmaceutical and pharmacokinetic considerations for the formation of Multi Unit Particulate System in tablet dosage form.

Challenges of research envisaged

- MUPS in tablet dosage form shows the rupturing of the enteric coating layer during compression.
- Didanosine is acid labile hence given in enteric coated form.
- Didanosine has pH dependent solubility.

Usually MUPS are marketed as capsule of any and tablets of low strength drugs formulations. For Antiretroviral drugs, it's effective to go for combination therapy. Didanosine enteric coated pellets prepared by drug layering onto the sugar beads and to avoid rupturing of these pellets during compression it was proposed to select a suitable polymer and coating on to the drug loaded pellets, also the selection of the excipients providing elasticity to the blend for compression.^{9,10}

EXPERIMENTAL

Step -1 Micronization of Didanosine

Didanosine was micronized in Cadmach Air Jet mill, micronization was repeated twice to obtain very fine micronized drug.

Step-2 Drug Layering on Sugar Beads

The drug layering and coating was performed in Glatt, type GPCG-1 fluidized bed coater with Wurster insert.

Equipment Information

Name: GLATT GmbH
Type: GPCG-1
Operation Pressure: 0.79bar
Fan Capacity: 2.2KW
RPM: 2900n
Voltage: 3 x 415V
Cycles: 50Hz
Heating Capacity, electric: 4KW

Process Parameters Setting

Supply air pressure: 6psibar
Operating air pressure: 6psibar
Atomisation pressure
Preselection: 2psibar
Output: 2psibar
Spray Nozzle purging air: 2psibar

Temperature Settings

Inlet air: 51°C
Exhaust air: 36°C
Product: 38°C
Exhaust air flap: 0.5bar
Wurster insert diameter: 6inches
Spray nozzle dia: 1mm
Peristaltic pump rate: 13-14 RPM

The formula for the drug layering of Didanosine on NP seeds is shown below in Table 1

Table 1 : Formula for drug layering on NP Seeds

Ingredients	mg/tab
NP Seeds (#40/60)	100
Didanosine (20µ)	125
HPMC (5cps)	25
SSG	5
P. water	q.s (15.5% w/w dispersion)
IPA	40mL

Procedure

- HPMC E5 and SSG were dispersed in purified water and with stirring Didanosine was dispersed into the above. IPA was added to defoam the solution. The above dispersion was coated onto the NP seeds in GLATT GPCG-1.

Drug layering process

A fluidized bed granulator equipped with a 6 inch Wurster (bottom spray) insert was loaded with sugar beads. The dispersion was then sprayed on the beads moving in the apparatus. When the spraying process was completed, the drug layered beads were dried by further supplying dry air of 35°C for about 5-10min. The coated beads were then allowed to cool in the apparatus by supplying dry air at 20-25°C for about 10-15min.

Spray Rate: 20-25RPM
Bed temperature: 34-36°C

Step – 3 Enteric coating of pellets

The formula for enteric coating on the drug loaded pellets is shown below in Table 2

Table 2 : Formula for enteric coating

Ingredients	mg/tab
Drug loaded pellets	255
Eudragit L 30 D 55	212.5
Propylene Glycol	42.5
P. water	q.s (20% w/w dispersion)
Sodium Hydroxide (5% w/v solution)	q.s to 5.0pH

Procedure

- Eudragit L 30 D 55 dispersion was stirred and water was added to it. Added Propylene Glycol and stirred. pH was adjusted with sodium hydroxide 5% w/v solution to 5.0. The drug layered pellets were coated with Prepared Eudragit L 30 D 55 solution.¹⁰

Enteric Coating Process

A fluidized bed granulator equipped with a 6 inch Wurster insert was loaded with drug layered pellets. The solution was then sprayed on the pellets fluidizing in the equipment. When the spraying process was completed the enteric coated pellets were dried by further supplying dry air of 35°C for about 5-10min. The coated pellets were then allowed to cool in the apparatus by supplying dry air of 20-25°C for about 10-15min.¹⁰

Spray rate: 15-20RPM
Bed temp: 35-37°C

The enteric coated pellets prepared seemed to be uniform but little agglomeration were found in the pellets, so talc and aerosil-200 were mixed to the enteric coated pellets.

Talc: 2mg/tab
Aerosil 200: 2mg/tab

Step – 4 Addition of other Antiretroviral drugs

The other Antiretro viral drugs were added as granules along with the Didanosine pellets, the formula for preparation of granules is given in Table 3

Table 3 : Formula for Stavudine and Nevirapine granules

Ingredients	mg/tab
Stavudine	30
Nevirapine	200
Lactose	75
PVP K-30	3
P. water	q.s
Magnesium stearate	0.5
Aerosil	0.5

Procedure

Stavudine, Nevirapine, Lactose were sifted through #22 and mixed blend were granulated with 15% solution of PVP K-30. Added extra granular ingredients after sieving through #60.

The formula to prepare the tablet including Didanosine pellets and other anti retro viral drugs as granules is given in Table 4

Table 4 : Formula for Didanosine, Stavudine and Nevirapine tablets

Ingredients	mg/tab
Didanosine pellets enteric coated	576.23
Stavudine + Nevirapine granules	309.00
Avicel 102	709.77
Ac Di Sol	5

Procedure

Weighed Didanosine enteric coated pellets, Stavudine and Nevirapine granules and mixed. Avicel 102, Ac Di Sol passed through #60 and mixed. The above blend was compressed on 22.5 × 10.5mm, concave, caplet punch.

Results

The assay of enteric coated pellets is given in Table 5

Table 5 : Assay of enteric coated pellets (by HPLC)

Sample	% Assay
1	101.0
2	102.0
3	101.6
4	101.9
5	102.0
6	101.2
Average	101.6

The results of Acid resistance of Didanosine pellets is given in Table 6

Table 6 : Acid Resistance (by HPLC)

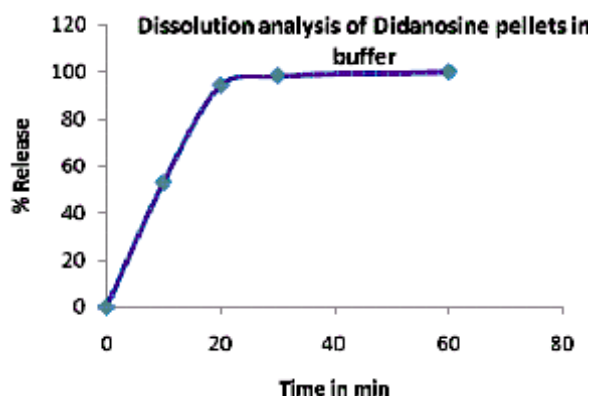
Sample	%Retained	% Released
1	98.0	3.6
2	96.0	5.6
3	94.0	7.6
4	95.0	6.6
5	99.0	2.6
6	96.0	5.6
Average	96.34	5.3

The results of Dissolution analysis of Didanosine pellets in buffer is given in Table 7

Table 7 : Dissolution Analysis for Didanosine pellets in 6.8 pH phosphate buffers after 2 hrs in 0.1N HCl (by HPLC)

Sample	% Release of Didanosine			
	10min	20 min	30 min	60 min
1	59.0	92.0	102.0	102.0
2	56.0	93.0	99.0	101.0
3	49.0	95.0	98.0	101.0
4	45.0	92.0	97.0	97.0
5	58.0	98.0	98.0	99.0
6	51.0	96.0	96.0	101.0
Average	53.0	94.3	98.3	100.0

The plot for Didanosine pellets % release Vs time is shown in Figure 1

Fig. 1 : Data plot of Didanosine pellets % release vs time (in min)

The combination tablet prepared were observed for physical parameters, which is summarized in Table 8

Table 8 : Observations for prepared tablet

Tests	Tab 1	Tab 1	Tab 1	Average
Weight (g)	1.602	1.598	1.611	1.604
Hardness (Kp)	12.20	12.90	12.60	12.57
DT (sec)	12.00	15.00	14.00	13.67
Thickness (mm)	9.44	9.47	9.29	9.40

The assay result of combination tablet is given in Table 9

Table 9 : Assay of combination tablet (by HPLC)

Sample	% Assay		
	DDI	STV	NEV
1	104.0	99.0	98.0
2	104.9	99.1	98.3
3	105.3	98.9	99.3
Average	104.7	99.0	98.6

The dissolution result of combination tablet is summarized in Table 10

Table 10 : Dissolution Analysis for Didanosine, Stavudine and Nevirapine tablets in 0.1N HCl

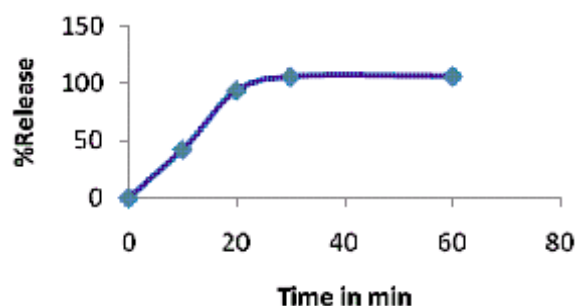
Sample	% Release in 1hr			% Release in 2hrs		
	DDI	STV	NEV	DDI	STV	NEV
1	0	92	99	0	95	100
2	2	91	100	1	96	98
3	1	89	96	0	99	99
4	0	95	89	2	97	102
5	-2	97	91	1	102	101
6	4	91	95	4	101	101
Average	0.83	92.5	95	1.33	98.33	100.16

The dissolution result of tablet in 6.8 pH phosphate buffer is given below in Table 11

Table 11 : Dissolution Analysis for Didanosine, Stavudine and Nevirapine tablets in 6.8 pH phosphate buffer after 2 hrs in 0.1N HCl

Sample	% Release of Didanosine			
	10min	20min	30min	60min
1	44.0	89.0	117.0	114.0
2	49.0	95.0	104.0	105.0
3	38.0	92.0	106.0	106.0
4	48.0	88.0	99.0	99.0
5	22.0	97.0	115.0	115.0
6	52.0	102.0	95.0	99.0
Average	42.17	93.83	106.0	106.33

The plot of Didanosine % release Vs time from tablet is shown in Figure 2

Dissolution analysis of DSN tablets in buffer**Fig. 2 :** Data plot of Didanosine % release vs time (in min) from tablet

MULTI UNIT PARTICULATE SYSTEM OF DIDANOSINE

The result of acid resistance of Didanosine pellets in combination tablet is given in Table 12

Table 12 : Acid Resistance of Didanosine

Sample	% Retained	% Released
1	98.0	7.0
2	103.0	2.0
3	87.0	18.0
4	74.0	31.0
5	78.0	27.0
6	86.0	19.0
Average	87.66	17.33

Discussion

Uniformly sized drug loaded pellets were obtained indicating that right amount of micronization and binder are available. Didanosine pellet showed 100% release in 60min.¹⁰ This satisfactory result obtained by in vitro dissolution analysis by HPLC method. Also the assay and acid resistance result was satisfactory. Didanosine, Stavudine and Nevirapine tablet showed 100% release in 30min. This satisfactory result obtained by in-vitro dissolution analysis.

Conclusions

From the above results and discussions, it can be said that polymer selection and its % coating onto the drug layered sugar beads has reduced the polymer wall rupturing during compression of pellets due to the elasticity generated in the pellets. Also, the cushioning effect due to Avicel 102 and its concentration optimization has helped in compressing the pellets in combination with other anti retro viral drugs without any coating rupture.

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