DESIGN AND EVALUATION OF MULTIPARTICULATE SYSTEMS PREPARED USING SIEVING-SPHERONISATION AND EXTRUSION-SPHERONISATION

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DESIGN AND EVALUATION OF MULTIPARTICULATE SYSTEMS PREPARED USING SIEVING-SPHERONISATION AND EXTRUSION-SPHERONISATION

BY

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Dedicated to my beloved father Abdul Karim ((late) and mother Aqila Karim

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LIST OF ABBREVIATIONS AND SYMBOLS

Abbreviation	Description
A	Frequency constant
AUC	Area under the curve
$AUC_{0-\infty}$	Area under the curve from zero to infinity
AUMC	Area under the movement plasma level time curve
BD	Becton Dickinson
BP	British Pharmacopoeia
°C	Degree Celsus
C	Concentration remaining
C_{max}	Peak plasma concentration
CDER.	Center for drug evaluation and research
CI	Confidence interval
d_i	Mean diameter of sieve fraction number i
d_{gw}	Geometric weight mean diameter
Eq	Equation
Ea	Activation energy
EMS	Error in mean square
FDA	Food and drug regulation authority
GERD	Gastroesophageal reflux disease
g/s	Gram per second
g/ml	Gram per milliliter

Abbreviation	Description
g	Gram
H	Distance between the tip of the funnel and the base
HPLC	High performance liquid chromatography
ICH	International committee of harmonization
∞	Infinity
Kg	Kilogram
K	Rate constant
LOD	Limit of detection
LOQ	Limit of quantification
Ln	Natural log
ml	Milliliter
mg	Milligram
µm	Micrometer
min	Minute
MRT	Mean residence time
MCC	Microcrystalline cellulose
MAE	Methacrylic acid/ethyl acrylate
µg	Microgram
ng/mL	Nanogram per milliliter
PEG	Polyethylene glycol
OTC	Over the counter
P_b	bulk density is the
P_p	tapped density

PVP	Polyvinylpyrrolidone

Abbreviation	**Description**
pH	Power of hydrogen ion concentration
P	Significant value, A model is statistically significant if $p<0.05$
R	Radius of the base of cone
R	Universal gas constant
%	Percentage
rpm	Revolution per minute
RSD	Relative standard deviation
SPSS	Statistical procedure for social science
SD	Standard deviation
Sg	Geometric standard deviation
SEM	Scanning electron microscope
T	Temperature
1/T).	Absolute temperature
T_{max}	Time for peak concentration
$t_{50\%}$	Time for 50 percent of drug release
$t_{75\%}$	Time for 75 percent of drug release
Ø	Angle of repose,
U S P	United State Pharmacopoeia
UV/VIS	Ultra violet/visible

UK	United Kingdom
USA	United State of America
Vs	Verses
WHO	World Health Organization
Vd	Volume of distribution
W_i	Weight of sieve fraction number i.

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REKA BENTUK DAN PENILAIAN SISTEM MULTIPARTIKEL YANG DISEDIAKAN DENGAN MENGGUNAKAN SFERONISASI TAPISAN DAN SFERONISASI EKSTRUSI

ABSTRAK

Dosej berbentuk pelet boleh disediakan melalui pelbagai kaedah yang biasanya memakan masa serta memerlukan tenaga kerja yang banyak. Kajian ini dijalankan untuk menilai kebolehlaksanaan penyediaan pelet bulat melalui tapisan jisim serbuk basah dan dikuti dengan proses sferonisasi. Kaedah ini dibandingkan dengan proses sferonisasi ekstrusi dari segi ciri-ciri fizikal and profil pelarutan *in-vitro* daripada rumusan yang dibangunkan. Pelet parasetamol pelepasan cepat terdiri daripada selulosa mikrohablur, laktos, krospovidon dan polivinil pirolidon-K90. Peratusan hasil pelet parasetamol yang terhasil melalui proses sferonisasi tapisan adalah lebih tinggi ($p< 0.05$) berbanding dengan yang terhasil melalui proses sferonisasi ekstrusi. Sebaliknya, sferonisasi ekstrusi menunjukkan kebolehaliran yang lebih baik ($p<0.05$) daripada sferonisasi tapisan. Walau bagaimanapun, tiada perbezaan yang signifikan ditemui dalam sifat fizikal yang lain bagi kedua-dua kaedah. Profil pelarutan didapati lebih tinggi dalam teknik sferonisasi tapisan. Kesamaan faktor menunjukkan bahawa profil pelarutan boleh dibandingkan dalam rumusan yang disediakan bagi kedua-dua kaedah dan mengikuti kinetik tertib pertama. Kadar pelepasan drug tidak bergantung pada pH dan juga kadar goncangan. Pelet bulat omeprazol yang mempunyai kadar pelepasan yang dikehendaki dibangunkan dengan menggunakan proses sferonisasi tapisan. Pelet yang mempunyai ciri-ciri yang dikehendaki diperoleh dengan menggunakan jumlah minimum selulosa mikrohablur (16%), laktos, polivinilpirolidon K30, polietilena glikol 6000 dan natrium

lauril sulfat. Pelet yang disediakan melalui proses sferonisasi tapisan menunjukkan peratusan hasil yang lebih tinggi secara signifikan berbanding dengan yang disediakan melalui proses sferonisasi ekstrusi. Sistem pelepasan tertunda omeprazol dibangunkan melalui Kollicoat 30DP, dengan menggunakan sistem semburan bawah lapisan terapung (bottom spray fluidized bed). Tahap penyalutan sebanyak 17.5 % dapat menghalang pelepasan drug kurang daripada 10% pada pH 1 untuk 2 jam pertama dan pada pelepasan pH 6.8 adalah 80 hingga 84% dalam 45 minit, mengikut kinetik pelepasan tertib pertama. Dalam kajian kestabilan dipecutkan, kedua-dua drug mematuhi degradasi tertib sifar. Hayat simpanan dijangka untuk parasetamol and omeprazol adalah 24.42 dan 21.00 bulan masing-masing pada 25°C. Pelet omeprazol bersalut yang disediakan melalui sferonisasi tapisan dan drug rujukan (Zimor® 20mg) dinilai untuk kebiosetaraan, menggunakan arnab dalam reka bentuk bersilang, dan kedua-dua rumusan didapati setara. Kesimpulannnya, dosej berbentuk pelet boleh dirumuskan melalui tapisan dan diikuti dengan kaedah sferonisasi yang ringkas, mudah, cepat dan lebih ekonomi dibandingkan dengan proses sferonisasi ekstrusi.

DESIGN AND EVALUATION OF MULTIPARTICULATE SYSTEMS PREPARED USING SIEVING-SPHERONISATION AND EXTRUSION-SPHERONISATION

ABSTRACT

Pelletised dosage forms can be prepared by different methods which, in general, are time consuming and labor intensive. The current study was carried out to assess the feasibility of preparing spherical pellets by sieving the wet powder mass followed by spheronisation. This method was compared with extrusion-spheronisation process in terms of physical characteristics and *in-vitro* dissolution profile of the developed formulations. The fast release paracetamol pellets were comprised of, microcrystalline cellulose, lactose, crospovidone and polyvinyl pyrrolidone-K90. The percentage yield of paracetamol pellets produced by sieving-spheronisation was higher ($p<0.05$) in comparison with that produced by extrusion-spheronisation. The extrusion-spheronisation showed better flowability ($p<0.05$) than sieving-spheronisation. However, no significant difference was found in other physical properties of two methods. The dissolution profile was slightly higher in sieving-spheronisation technique, the similarity factors showed that dissolution profiles can be considered comparable in the formulations prepared by two methods and followed first order kinetics. The rate of drug release was essentially independent of pH and agitation rate. Omeprazole spherical pellets with required release rate were developed using sieving-spheronisation process. Pellets with desired characteristics were obtained with minimum amount of microcrystalline cellulose (16%), lactose, polyvinylpyrrolidone K30, polyethylene glycol 6000 and sodium lauryl sulfate. Pellets prepared by sieving-spheronisation

showed significantly higher ($p<0.05$) percentage yield as compared to that of extrusion-spheronisation. Omeprazole delay release system was developed by Kollicoat 30DP, using bottom spray fluidised bed system. Coating level of 17.5 % prevented the drug release less than 10% at pH 1 for initial 2 hours and at pH 6.8 release was 80 to 84% within 45 minutes, following the first order release kinetics. In accelerated stability studies, both drugs followed the zero order degradation. The estimated shelf life of paracetamol and omeprazole was 24.42 and 21.00 months respectively at 25 ºC. Coated omeprazole pellets prepared by sieving-spheronisation and the reference drug (Zimor® 20mg) were evaluated for bioequivalence, using rabbits in cross-over design, and both formulations were found to be equivalent.

In conclusion, the pelletised dosage forms can be formulated through sieving followed by spheronisation method, which is simple, easy, less time consuming and economical as compared to extrusion-spheronisation process.

CHAPTER 1

GENERAL INTRODUCTION

1.1 Pelletisation

Pelletisation is an agglomeration process that converts fine powders or granules of bulk drugs and excipients into small, free flowing, spherical units known as pellets (Ghebre-Sellassie and Knoch, 2002; Sawicki and Lunio, 2005). The size range of pellets is usually from 0.50 to1.50 mm. However, other sizes could also be prepared, depending on the processing technologies employed (Kristensen and Schaefar, 1987; Ghebre-Sellassie, 1989).

1.1.1 Historical review of pelletisation

The concept of multiple-unit formulations for controlled release applications was introduced in the early 1949. Pellets-based extended release products initially employed in the form of pills produced by traditional pill making machine. The process of pelletisation was revived in early 1950s as a result of the introduction and launch of a controlled release product known as spansule capsule by Smith Kline and French (SKF) which was an overwhelming success. This was the beginning of the age of oral controlled drug delivery system (Ghebre-Sellassie, 1989). Pills of different release profiles were combined in predetermined portions and encapsulated into hard gelatin capsules to produce sustained-release oral dosage forms. However, the number of pills that could be filled into a single capsule was limited and the duration of release could not be extended beyond a few hours. The manufacturing process of the pills was difficult, labor-intensive and required experienced personnel. This problem was solved to some extent as the processing equipments got more sophisticated and tableting machines were capable to produce thousands of tablets

within minutes. However, in spite of the advancements in reducing processing time and perfecting the technology that led to the production of mini tablets suitable for encapsulation, the approach did not alleviate the size limitation encountered during the development of pills-based sustained release products. However, in 1951, a report on the manufacturing process of seeds revolutionised the production of pelletised products (Cimicata, 1951). The process utilised the standard coating pans and involved successive layering of powder and binder on sugar granules until spherical seeds of desired size were obtained. Although the process was complicated and required days to be completed, it spearheaded a new era and provided the basis for development of future pelletisation methods. The pelletisation technology was refined and perfected by SKF and was applied to a number of its products (Blyth, 1956; Rees *et al.*, 1960; Heimlich and MacDonnell, 1964).

In 1964, a new pelletisation technique called spray-congealing process that provided sustained-release pellets ranging in size between 0.25 to 2.00 mm was patented by SKF (Lauts and Robinson, 1964). At the same time, the marumeriser was introduced commercially. The marumeriser and variations of it were subsequently patented in the United States (Nakahara, 1966; Moriya, 1971). Basically the process involved extrusion of a wet mass of a mixture of active ingredients and excipients to produce cylindrical extrudates followed by spheronisation of the extrudates in the spheroniser or marumeriser. The pharmaceutical application of this process for the development of pellets was first published in early 1970s (Conine and Hadley, 1970; Woodruff and Nussle, 1972; Mailnowski, and Smith, 1975).

As the drug delivery systems became more refined, the role of pellets in dosage forms design and development increased. Now pellets are expected to continue to play a major role in the design and fabrication of solid dosage forms.

1.1.2 Advantages of pellets

In the last two decades, pellets have established their position due to several added advantages over single unit dosage forms (Bechgaard and Nielsen, 1978; Hellen *et al*., 1993). Pelletised products not only offer flexibility in dosage form design and development but also utilised to improve the drug safety and efficacy (Ghebre-Sellasssie, 1989). These multiple unit dosage form can be formulated in the form of capsules, tablets and suspensions (Conine and Hadlay, 1970; Jalal *et al*., 1972; Mailnowski and Smith, 1975; Bechgaard, 1982; Bechard and Leroux, 1992). They disperse freely in the gastrointestinal tract, maximise drug absorption, decrease local irritation in gastrointestinal tract caused by single unit dosage form and minimise chances of dose dumping without appreciably lowering drug bioavailability (Wilson and Washington, 1989; Tang *et al.,* 2005). Pelletised dosage forms also reduce variations in gastric emptying and overall transit time (Digenis, 1994). Pellets composed of different drug entities can be blended and formulated into a single dosage form. This allows the combined delivery of two or more bioactive agents which may or may not be chemically compatible, to the same site or to different sites within the gastrointestinal tract. In addition the pellets with different release rates of the same drug can be combined in a single dosage form (Ghebre Sellasssie, 1989; Wan and Lai, 1991).

Successful film coating can be applied onto the pellets due to their ideal spherical shape and a low surface area-to-volume ratio especially for sustained release and acid resistant formulations (Rowe, 1985; Chambliss, 1992; Vertommen *et al.,* 1997). As pellets flow and pack freely with narrow particle size distribution, it is not difficult to obtain uniform and reproducible fill weights in tablets and capsules (Reynolds, 1970). Pellets, therefore, offer the possibility of achieving a more reliable source of drug and facilitating a lower dosage frequency (Bechgaard and Lodefoged, 1978). Additionally the pellets can be given to patients on nasogastric tube feeding who have the problem of swallowing tablets or capsules.

1.2 Manufacturing considerations of pelletisation

Pellets, according to Vuppala *et al.* (1997) should be spherical with a smooth surface (for subsequent film coating), narrow particle size range and contain the required ingredients within reasonable size limits. There are certain manufacturing constrictions that must be taken into account before the pelletisation process. Production of pellets generally involves an expensive process due to highly specialised equipments (Ghebre-Sellasssie, 1989; Noche *et al.,* 1994). Processing of a single batch may sometimes require a great deal of time to be completed resulting in a higher cost of production. Conversely, a short processing time mandates utilisation of efficient and unique equipments that require the allocation of substantial capital investment. Extruders, spheroniser and rotor granulators fall under this category. Formulation variables should be manipulated to accommodate the availability of the equipment and cost effectiveness of the pelletisation process. Another processing step that extremely impacts on the successful development of pelletisation product is coating of the drug pellets. Although the pellets could

conceivably be coated in any tablet coating machine, they generally require specialised coating equipment for optimum processing, whether the intention of the coating is for esthetics, identification or controlled release purposes. Therefore, accessibility to the relevant coating equipment should be assessed before a decision is made to develop pelletised products. The performance of the coated product is dictated by the surface morphology, shape, and composition of the core pellets. Drug pellets that possess optimum surface properties must be selected for coating (Woodruff and Nuessle, 1972; Ghebre-Sellassie, 1989).

Segregation is another factor that is important for the successful pelletisation process. Segregation occurs whenever a homogenous blend of pellets is subjected to any kind of vibration. It is induced by differences in size or density of pellets. Other factors that lead to segregation are static charges and surface morphology which may be generated during the blending process as a result of interparticulate friction (Ghebre-Sellassie, 1989). Another important variable, which affects the success of the pelletisation method, is the drug content of individual pellet. If the drug content of pellet is very high, it is extremely difficult to maintain content uniformity in the final dosage form, especially in case of potent drugs (Woodruff and Nuessle, 1972; Ghebre-Sellasssie, 1989).

Loss of a few pellets during the encapsulation process may lead to a significant loss in potency. Therefore it is imperative that pellets containing potent drugs should contain extremely low quantities of active drug and mixed with the bulk of inert excipients (Vuppala *et al.,* 1997; Ghebre-Sellassie, 1989).

1.3 Pelletisation methods

Pellets are currently a popular dosage form for oral application. They can be prepared by several pelletisation techniques (Haring *et al*., 2008). Comprehensive research has been focused on the improvement and optimization of the existing pelletisation skills as well as on the development of novel manufacturing approaches that use innovative formulations and processing equipments (Woodruff and Nuessle, 1972; Noche *et al.*, 1994).

The most commonly used pelletisation methods are layering and extrusion-spheronisation. Other pelletisation methods include spherical agglomeration or agitation or balling, compression, droplet formation, cryopelletisation and melt pelletisation (Ghbere-Sellasie and Knoch, 2002).

1.3.1 Layering

In layering process, inert nonpareil or preformed drug nuclei are used for the deposition of successive layers of drug in solution, suspension or dry powder. The layering process can be further divided into solution or suspension layering and powder layering. In solution or suspension layering, the drug particles are either dissolved or suspended in binder solution to be sprayed onto the inert material or granules of the same drug. During the spraying and drying stage, liquid bridges that are convertible to solid bridges, are formed and the process is continued until the desired pellet size is achieved (Gamlen, 1985; Chambliss; 1992 and Vuppala *et al.*, 1997).

On the other hand powder layering is a growth mechanism that involves the

deposition of successive layers of dry powder of drug or excipients or both on the preformed nuclei with the help of binding solution. These nuclei, while they tumble in the rotating pan take the powder drug and form small particles adhered to each other and to nuclei due to the development of capillary forces of binding solution (Sherrington, 1969; Ghebre-Sellassie *et al*., 1985; Ghebre-Sellassie and Knoch, 2002).

1.3.2 Extrusion-spheronisation

The pelletisation process has improved significantly after the introduction of the extruders and spheronisation (Hicks and Freese, 1989; Varshosas *et al.,* 1997, Fekete *et al*., 1998; Basit *et al.,* 1999). It was invented in 1964 by Nakahara and introduced for the first time into the pharmaceutical industry by Rynold as well as Conine and Hadley. (1970). The process is lengthy and consists of five unit operations: (a) dry mixing, (b) preparation of wet mass, (c) extrusion or shaping of the wet mass into cylinders, (d) rounding (spheronisation) of particles in to spheres and (e) drying (Otsuka *et al.,* 1994). These phases are strongly related to each other and the quality of the final product (Newton, 1994).

Different types of extruders are available to prepare the extrudates of the wet mass. The selection of an extruder depends upon the characteristics of the extrudates and the nature of further processing steps required. The five main types of extruders commonly used are screw feed extruder, (Reynolds, 1970; Rowe, 1985), sieve extruders, basket extruders, roll extruders and ram extruders (Lindberg, 1988; Hicks and Freese, 1989; Ghebre-Sellassie and Knoch, 2002; Keleb *et al.*, 2002).

Beside the types of extruder, other factors affecting the extrusion process include extrusion screen, speed, and temperature. The effect of extrusion screen on the pellet and extrudates quality is characterised by two parameters, thickness and diameter of perforations. Changing one of these two parameters influences the quality of extrudates and of pellets Baert *et al*. (1993). The extrusion speed is important because the total output should be as high as possible for economical reasons but several authors reported that increase in the extrusion speed influenced the final pellet quality (Goodhart *et al.,* 1973; Pinto *et al.,* 1993). Harrison *et al*. (1985) showed that the surface impairments such as roughness and shark skinning became more pronounced with increasing extrusion speed. These surface defects of the extrudates lead to pellets of poor quality due to uneven breaking up of extrudates during the initial stages of spheronisation process, resulting in wide range of particle size distribution.

The extruder screen is also important to affect the final quality of pellet. The screen is characterised by two parameters, the thickness of the screen and diameter of the perforations. Changing one of these two parameters influences the quality of the extrudates and pellets. (Malinowski and Smith, 1975; Harrison *et al*., 1987; Chariot *et al*., 1987; Hellen *et al*., 1993; Hileman *et al.,* 1993).

The control of the extrusion temperature is an imperative feature not only when a thermolabile drug is processed but also in view of the moisture content. A rise in temperature during the extrusion cycle could dramatically alter the moisture content of the extrudates due to evaporation of the granulation liquid. This could lead to a difference in the quality of the extrudates produced at the beginning of a batch

and at the end of a batch (Fielden *et al.*, 1988). To avoid a rise in temperature during extrusion, the use of screw extruder with a cooling jacket around the barrel to keep the temperature of the given formulation between predetermined limits has been reported (Klenebudde and Linder, 1993).

A spheroniser is a device consisting of a grooved horizontal plate rotated with a stationary vertical hollow cylinder fitted with a door to allow the prepared spheronizer products. The plate has grooved surface to increase the friction force. Generally the diameter of the grooves is 1.5-2.0 times of the target pellet diameter. The diameter of the friction plate is approximately 20 cm for laboratory scale spheroniser and up to 1.0 m for production scale units (Ghebre-Sellassie and Knoch, 2002). In the spheronisation process the prepared extrudates are loaded on to the rotation plate of spheroniser and are transferred by the centrifugal force to the periphery of the spheroniser.

Extrudates during spheronisation process undergo through different stages to form round pellets. Initially they form cylinders with round edges, then dumbbells followed by elliptical particles and eventually perfect spheres (Rowe, 1985). Another pellet-forming mechanism was suggested by Baert and Remon. (1993) in which the initial cylindrical particles are deformed into a bent rope-shaped particle and then form a dumbbell and with the twisting action the dumbbell shape breaks into two spherical particles with a flat side having a hollow cavity. Eventually, the continued action in the spheroniser causes the particles to round off into spheres.

Pellet quality is dependent on spheroniser load, speed and time. Spheroniser load mainly affects the particle size distribution and the bulk and tap density of the final pellets (Vervaet *et al.,* 1995). The yield of pellets in a specific size range decreases with an increase in the spheroniser speed and at low spheroniser load and increase with extended spheronisation time at a higher spheroniser load (Newton *et al*., 1994). Barrau *et al* (1993) found that increasing spheroniser load led to a reduction in the roundness but enhancement in the hardness of pellets and the yield in the specific size range remained unchanged. Increasing the spheroniser load caused an increase in bulk and tap densities but a decrease in the size of pellets (Hellen *et al.,* 1993). The spheronisation speed affects the particle size, (Gandhi *et al*., 1999) hardness, friability (Bataille *et al*., 1993), roundness, porosity (Bianchini *et al*., 1992), bulk and tap densities (Hellen *et al.,* 1993), flowability and surface morphology of pellets (Malinowski and Smith, 1975).

The spheronisation process can take from 5 to 30 minutes, depending on different variables such as elasticity, plasticity, brittleness of material, plate speed, plate geometry, load and water content. Spheronisation time mainly affects the particle size distribution (Newton *et al.,* 1994), bulk and tap densities of pellets (Malinowski and Smith, 1975; Fielden *et al.,* 1992; Hasznos *et al*., 1992; Hellen *et al*., 1993).

Pellets can be dried at room temperature (Hasznos *et al*., 1992) or at elevated temperature in a fluidized bed dryer (Fielden *et al*., 1992; Newton *et al*., 1994; Baert and Remon, 1993; Yuen *et al.,* 1993), microwave or ordinary oven (Bataille *et al*., 1993; Govender and Dangor, 1997). Pellet quality is dependent on the type of the

drier used. Oven drying provides less porous and harder pellets with a more homogenous surface than those dried in the microwave oven (Bataille *et al.*, 1993). Studies on the pellets dried by tray drier and fluidized bed dryer raveled that the nature of drying has quantifiable effect on the dramatic crushing strength, elasticity, drug release and a qualitative effect on the surface characteristics of pellets (Dyer *et al*., 1994).

To prepare the wet mass for the extrusion-spheronisation process, different types of granulators are available. It is investigated that a great influence of granulation step on extrusion-spheronisation process on the pellets hardness and disintegration properties (Granderton and Hunter, 1971; Jalal *et al.,* 1972; Ghorab and Adeyeye, 2007). The most commonly used granulator is the planetary mixer (Herman *et al*., 1988; Harrison *et al.,* 1985). However, in many cases the use of higher shear mixer, sigma blade mixer (Elbers *et al.,* 1992; Ku *et al.,* 1993) and a continuous granulator have also been reported (Hellen *et al.,*1993). Nevertheless high shear mixers introduce a large amount of heat that may cause evaporation of the granulating liquid, therefore influencing the extrusion behavior of the wet mass. It can be avoided by cooling the granulation bowl (Pinto *et al.,* 1993).

1.3.3 Spherical agglomerations (agitation or balling)

Balling or agglomeration process has little application in pharmaceutical industry but has greater role in the ore and fertilizer industries. In balling, the finely divided particles are converted to pellets with the addition of appropriate quantities of liquid prior to or during their continuous rolling in drums, discs or mixers (Bhrany *et al*.,1962; Sastry and Fuerstenau, 1971; Ghebre-Sellassie and Knoch, 2002). It can

be divided in to two categories, liquid induced agglomeration and melt-induced agglomeration. In liquid induced agglomeration, liquid is added to the powder before or during the agitation step. As powders come in contact with the liquid phase, they form agglomerates or nuclei, which initially are bound together by liquid bridges which, on drying, are replaced by solid bridges. The formed nuclei collide with other nuclei and coalesce to form larger nuclei or pellets. The coalescence process continues until the bonding forces are overcome by breaking forces. At this junction, coalescence is replaced by layering, where the small particles are adhered to the large particles and the size is increased until pelletisation process is completed (Wan and Jeyabalan 1985).

Melt-induced agglomeration is similar to the liquid-induced agglomeration except that the binding material is melted in the former case. In melt-induced agglomeration, the pellets are formed with the help of congealed material without going through the formation of solvent-based liquid bridges (Schaefer *et al.*, 1990). The limitation of this technique is a wide particle size distribution due to the random nature of the formation of the nuclei (Chambliss, 1992; Kleinebudde, 1997).

1.3.4 Globulation (droplet formation)

Another process for the preparation of pellets is globulation in which hot melt solutions or suspensions are atomized and through evaporation, cooling or solidification pellets are generated (Sherrington and Oliver, 1981). This process can be subdivided into two relevant processes, spray drying and spray congealing (Ghebre-Sellassie and Knoch, 2002). During spray drying, the drug entities in solution or suspension forms are sprayed, with or without excipients into a hot-air

stream to generate highly spherical particles. This method is generally applied to improve the dissolution rate and bioavailability of poorly soluble drugs. In spray congealing method, drug is allowed to melt or dissolve in hot waxes or fatty acids. The hot mixture is then sprayed into an air chamber where the temperature is below the melting points of the formulation components to produce spherical congealed pellets (Ghebre-Sellassie and Knoch, 2002).

1.3.5 Compression

In pelletisation using the compaction process, the mixtures or blends of active ingredients and excipients are compacted under pressure to generate pellets of defined shape and size. In fact the pellets prepared are small tablets that are spherical in shape and easy to fill in capsules. The formulation and processing variables for the pellet production are similar to those employed in the manufacture of tablets (Ghebre-Sellasie, 1989).

1.3.6 Cryopelletisation

Cryopelletisation is a new freezing technique for conversion of aqueous solutions or suspensions into solid bead like particles by employing liquid nitrogen as the cooling medium (Ghebre-Sellasie and Knoch, 2002). This technique, first developed for the nutrition industry as well as for the lyophilization of viscous bacterial suspensions, can be used to produce drug loaded pellets in liquid nitrogen at 160°C. The amount of liquid nitrogen required depends on the solid content and temperature of solution or suspension. The pellets are then dried in conventional freeze dryers (Knoch, 1994).

The equipment used for cryopelletisation consists of a container fitted with perforated plates at the bottom. Below the plates at a predetermined distance, there is a reservoir of liquid nitrogen in which a conveyor belt with transport baffles is immersed. The perforated plates generate droplets that fall and freeze immediately as they come in contact with the liquid nitrogen. The frozen pellets are transported out of the nitrogen bath into a storage container at -60°C before drying (Knoch, 1994).

The most critical step in cryopelletisation is droplet formation, which is influenced not only by formulations related variables such as viscosity, surface tension and solid content. Solutions or suspensions suitable for cryopelletisation are those with high solid contents and low viscosities.

Another important property is the surface tension of the liquid formulation, which partly determines the pellet size. The addition of a surfactant to the formulation reduces the surface tension resulting in smaller particles (Knoch, 1994).

1.3.7 Melt pelletisation

Melt pelletisation is a process whereby a drug substance and excipients are converted into a molten or semi-molten state and subsequently shaped using appropriate equipment to provide solid spheres or pellets (Ghebre-Sellasie and Knoch, 2002). The process requires several pieces of equipment such as cutters, blenders, extruder and spheroniser. The drug substance is first blended with the appropriate pharmaceutical excipients, such as polymers and waxes and extruded at a predetermined temperature. The extrusion temperature must be high enough to melt at least one or more of the formulation components. The extrudates are cut into

uniform cylindrical segments. The segments are spheronised in a jacketed spheroniser to generate uniform size pellets. The spheronisation temperature needs to be high to partially soften the extrudates and facilitate deformation and eventual spheronisation (Ghbere-Sellasie *et al.,* 1993). The pellets produced are unique in that they are monosize, a property which is unmatched by any other pelletisation technique. The melt pelletisation technique in high shear mixer is a viable method to develop a sustained-release device (Grassi, 2003). However, the process is still in the developmental stage and additional work is needed before the process becomes a routinely used pelletisation technique.

1.3.8 Sieving-spheronisation process

In the present study the method adopted for the formulation of multiple unit dosage form was the sieving of wet mass followed by spheronisation. In this process various excipients can be used and formulation can be easily modified to suit a wide range of drug delivery applications. This process is simple, easy and in addition it is a continuous process and within a day several batches can be prepared with minimum wastage as compared to extrusion-spheronisation process.

1.4 Excipients of pellets

The selection of appropriate excipients is very important in the pelletisation. Drugs generally do not possess many of the required properties for the fabrication of dosage forms. Excipients are added to pharmaceutical dosage forms mainly to produce satisfactory delivery of the drug to the intended site, to impart favorable characteristics to the dosage form and to facilitate the manufacturing process. Using appropriate excipients, the extrusion mixture is formulated to produce a cohesive

plastic mass, which remains homogeneous during the process. It must maintain the flow during manufacturing and self-lubricating properties as it passes through the die. The resultant extrudates must remain non-adhesive to itself and retain a degree of rigidity so that the shape imposed by the die is retained (Conine and Hadley, 1970).

The excipients used in pellets dosage forms are the same as those in tablet or capsule formulations (Harris and Ghebre-Sellassie, 1989). The excipients that may be included in pellet formulations are soluble or insoluble fillers (Vecchio *et al*., 1994), pH adjusters, spheronisation enhancers, binders, disintegrants and surfactants (Bianchini, 1992).

Fillers are added in the pellet formulation to increase their bulk and to facilitate pellet formation. The commonly used fillers in pelletisation are microcrystalline cellulose (MCC), lactose and starch. In addition they are also incorporated in pellet formulation if bulk density of the drug is low, dicalcium phosphate or calcium sulphate could be included to adjust the density of the resulting pellets.

Microcrystalline cellulose is used extensively as the principal excipient in the production of pellets by extrusion-spheronisation (Reynolds, 1970). It acts as filler, diluent, extrusion aid, spheronising enhancer (Fielden and Newton, 1992) and binder (Reier and Shangraw, 1966; Malinowski and Smith, 1975). It functions as a molecular sponge to absorb water and aids in the binding and lubrication of moistened powder mass during extrusion (Fielden *et al*., 1988; Heng and Koo, 2001). It modifies the rheological properties of other ingredients in the mixture. It controls

the movement of water through the plastic mass and prevents phase separation when it is forced through the apertures during extrusion or subjected to centrifugal forces during spheronisation. Microcrystalline cellulose can be used with or without additional binding agents (Sienkiewics *et al.,* 1997). It has the property to be easily granulated with water to exhibit the elasticity required for extrusion-spheronisation (Miyake *et al*., 1973 a, b) and yields fairly soft free flowing granules and hard tablets that possess usually short disintegration time (Fox *et al*., 1963).

Lactose is another commonly used excipient (Rowe, 1985; Vervaet *et al*., 1995). It is a widely used binder (Van Kemp *et al*., 1986), diluent and filler (Harris and Ghebre-Sellassie, 1989b). It is also reported that lactose combined with microcrystalline cellulose exhibits the elasticity required for extrusion-spheronisation in the presence of water (Keleb *et al.,* 2002*).*

Binders play an important role in wet-granulation and drug-layering processes, affecting the physical, mechanical and release properties of the final product (Kokubo and Sumada 1996). Suitable binders are starch, gelatin, acacia, alginic acid, polyvinylpyrrolidone, carbomer, dextrin, guar gum, hydrogenated vegetable oil, glucose syrup, magnesium aluminum silicate, maltodextrin, polymethacrylates, zein, hydroxypropyl cellulose, hydroxypropyl methylcellulose and polyvinylpyrrolidone are the preferred binders.

Disintegrants are widely used during compaction and spheronisation when significant pressure is applied and the resulting pellets are dense. The disintegrants employed must be efficient in order to counteract both the effect of the binder and

the force of compression if the dosage form is intended to release the drug immediately. The high water absorptive properties of disintegrants may sometimes have a deleterious effect on pellets and should not be overlooked during formulation development. Pellets composed of moisture sensitive drugs could absorb moisture upon storage and cause instability of the product (Harris and Ghebre-Sellassie, 1989).

In pellet formulation the pH adjusters sometimes play an important role. Generally, acid labile compounds are protected from the acidic regions of the gastrointestinal tract through the application of an enteric film coat. Buffers may also be added to the core formulations to maintain the pH of the core in a favorable range for drug stability and to enhance dissolution rate of drug.

Spheronisation enhancers are used to facilitate the production of spherical pellets. These substances confer plasticity on the formulation and also impart binding strength and integrity. The extensively used spheronisation enhancers for spherical pellets are microcrystalline cellulose, polyvinylpyrrolidone and sodium lauryl sulphate (Kristensen, *et al.,* 1987). In addition crospovidone can also be used as a spheronisation aid to produce good spherical pellets without the need of a binder (Liew *et al.,* 2005).

The most commonly used granulating liquid is water, although in some cases the use of alcohol and water mixture in a ratio of 5:95 has also been reported (Milli and Schwarts, 1990). Water plays a vital role in pelletisation process. It acts as a binder, during wet mass preparation, a lubricant during extrusion and a plasticiser during spheronisation process (Hileman *et al.,* 1993; Wan *et al*., 1993; Vervaet *et al*.,

1995; Heng *et al*., 1996; Schmidt and Klenebudde, 1999). The use of different amounts of water as a granulating liquid alone or in combination with alcohol affects the hardness and particle size distribution of the final pellets. The amount and distribution of water during extrusion are critical for the success of the spheronisation process (Fielden *et al.,* 1993; Vervaet *et al*., 1995). An increase in water content was found to cause an increase in pellet size and decrease in porosity, friability, dissolution, compressibility, and increase in density. The physical properties of the pellets changed significantly as the ratio of the fluids was varied (Beart and Remon 1993; Vertommen *et al*., 1997; Umprayn *et al*., 1999; Korakianiti *et al*., 2000).

1.5 Characterisation of pellets

Satisfactory physical properties are important for the successful pellet production. Pellets should be characterised by pellet yield (%) particle size, flowability, friability density. and hardness.

1.5.1 Pellet yield (%)

The percentage yield is an important factor in pelletisation process. It shows the amount of pellets achieved from the wet mass after the pelletisation process. It can be determined mathematically using the following equation, (Eq),

$$\text{Yield}\,\% = \frac{\text{Weight of pellets}}{\text{Weight of powder ingredients fed initially}} \times 100 \qquad \text{Eq 1.1}$$

1.5.2 Particle size analysis

The size of the pellets can be determined using various parameters, particle size distribution, mean diameter, geometric mean diameter, interquartile range, mean particle size width and length (Woodruff and Nuessle, 1972; Goodhart *et al*., 1973; Malinowski and Smith, 1975; O'Connor and Schwarts, 1985; Milli and Schwarts, 1990; Wan *et al*., 1993). Particle size analysis is in most cases carried out by a simple sieve analysis (Fekete *et al*., 1998; Thoma and Siegler, 1998; Basit *et al*., 1999; Korakianiti *et al*., 2000; Anderson *et al.,* 2000; Larsen *et al.,* 2003; Chatchawalsaisin *et al*., 2005). This method is easy, inexpensive and rapid. Some authors reported a more advanced method, computer aided image analysis in determining pellet size (Fielden *et al*., 1992; Hellen *et al*., 1993).

1.5.3 Friability

It is necessary to attain acceptable friability of pellets to withstand handling, shipping, storage and coating. Pellets are placed and rotated in a friabilator for the predetermined time period at a specific rotation speed. The difference in pellet weight before and after the rotation is used to calculate the friability. The weight loss measured was then used to indicate its friability (Millili and Schwarets, 1990; Basit *et al*., 1999).

1.5.4 Density

The bulk and tap densities of pellets are determined to gain an idea of homogeneity of particle size distribution (O'Connor and Schwarts, 1989; Bianchini *et al*., 1992; Baert and Remon, 1993). They also indicate the extent of densification of pellets and not influenced by the diameter of pellets. Small size pellets have the

higher bulk densities because of smaller inter particle porosities (Thoma and Siegler, 1998). The true density could be measured by using a pycnometer (Sienkiewics *et al.,* 1997). While the bulk density of pellets could be calculated using a tap density tester and expressed in g/ml by determining the volume of pellets with a known weight in a 100 milliliter (ml) measuring cylinder, (Varshosas *et al*., 1997 and Umprayn *et al*., 1999). It can also be determined with a powder tester (Ando *et al*., 2007).

1.5.5 Flowability test

Flowability is the free flowing property of the pellets (Bataille *et al.,* 1993; Hellen *et al.,* 1993). The extent of inter-particle force is employed as an index of flow. Adequate flowability is essential to maintain a homogenous capsule filling and uniform tablet and capsule weight. A number of methods have been reported to assess the flowability of pellets. These include, percent compressibility index, vibrating spatula, hopper flow, avalanching method (Taylor *et al*., 2000), critical orifice diameter and angle of repose (Sienkiewics *et al*., 1997). Among all these methods the more commonly used are angle of repose and critical orifice diameter. Critical orifice diameter involves the use of a cylinder with a series of interchangeable base plate disc having orifices with different diameters. To calculate the angle of repose the pellets are poured carefully through the funnel until the apex of the conical pile just touches the tip of the funnel. (Umprayn *et al.,* 1999). The flowability can also be measured by a powder tester (Souto *et al*., 2005; Ando *et al.,* 2007).

1.5.6 Hardness

The hardness of pellets can be correlated with the friability (Reynolds, 1970) or can be measured directly (Bataille *et al*., 1993; Sousa *et al.,* 1996). Otherwise it is

measured as the force required to break the pellet of well-known diameter using a diametrical crushing force of a tablet strength tester (Sousa *et al.,* 1996; Lundquist *et al*., 1997). It can be measured as the water required to crush a pellet, where a light plastic container was placed on the pellet and a load was applied by allowing a constant rate of flow of water into the container (Wan and Jeyabalan, 1985). The more advanced technique to measure the hardness of pellets is using texture analyser (Schmidt and Kleinebudde, 1999; Steckle and Mindermann, 2004).

1.6 *In-vitro* evaluation

The oral route remains the preferred route of drug administration due to its convenience, good patient compliance and low medicine production costs. After oral administration a drug must be absorbed into the systemic circulation and dissolved in the gastric fluids. Dissolution is an official test used by pharmacopeias to quantify the amount and extent of drug release from solid oral dosage forms including immediate-sustained release tablets, pellets and capsules (Siwart *et al.,* 2003; Wong *et al*., 2006).

Dissolution test is used during the development of dosage form for evaluating the quality of the tablets or capsules and as an evaluation for comparing new or generic formulations with an existing one. More recently, dissolution has become important in testing drug release of dosage forms such as powders, chewable tablets, buccal and sublingual tablets, chewing gums, soft gelatin capsules, suppositories, transdermal patches, aerosols and semisolids (Siewart *et al*., 2003).

Dissolution provides useful information about the factors that could affect the drug release behavior of the controlled release formulations, which include lot to lot uniformity, processing variables and stability determination during various stages of the development process (Siwart *et al.*, 2003).

It is imperative that *in-vitro* dissolution test should reflect the conditions in gastrointestinal tract. However, this may not always be possible due to the changing environment of food status in the gastrointestinal tract. Some of the attributes essential for a good *in-vitro* dissolution system is the reproducible output and associated in some way with *in-vivo* study. The system should be quite sensitive and flexible in discriminating between *in-vitro* variables that may yield differences *in-vivo* (Costa and Lobo, 20001).

The important factors that should be considered in the dissolution tests are the types of dissolution apparatus, size and shape of dissolution vessels, volume of medium, mixing speed of dissolution medium, temperature and duration of the test. However, various dissolution devices have been developed (Banaker, 1991). Generally, dissolution systems can be distinguished as the stirred vessel and the open flow compartment system (Nelson and Muller, 1979). The official *in-vitro* dissolution methods in the US Pharmacopoeia (1999) for testing oral controlled release dosage forms are rotating basket (Wan and Lai, 1991; Ghol and Amin, 1999) and paddle methods (Khan *et al.,* 2000; Cerea *et al*., 2004; Franceschinis *et al.,* 2004). The percentage drug dissolved in dissolution media is quantified using spectrophotometer or high performance liquid chromatography method (Turkoglu *et al.*, 2004).

The dissolution medium can be buffered at various pH values along the gastrointestinal tract. This is helpful to determine the dependence of drug release at various sections of gastrointestinal tract. The release kinetics of controlled products can be tested with the mathematical models, zero-order, and first-order kinetics, Higuchi and cube root of time release. The development of dosage form usually begins with *in-vitro* studies and only when *in-vitro* dissolution tests have proven successful, further evaluation on human or animals can be proceeded (Costa and Lobo, 2001; Dokoumetszidis and Macheras, 2006).

1.7 Assessment of similarity and dissimilarity factors for drug dissolution profiles

Several methods have been proposed for the comparison of dissolution profile. Shah, (1998) proposed multivariate analysis of variance methods to test for the difference between two dissolution profiles. Tsong *et al*. (1996) used multivariate distance between two dissolution data sets for dissolution profile comparison. On the other hand Chow. (1997) proposed dissolution difference measurement and similarity testing based on parameters after fitting a one-degree auto regression time series model. Moore and Flanner (1996) proposed a simple model–independent approach using mathematical indices to define the difference factor (f1) and similarity factor (f_2) to compare dissolution profiles. This approach has been recommended by FDA for comparison of two dissolution profiles. The similarity factor (f_2) and different factor (f1) can be calculated by following equation;

$$f1 = \frac{\sum[R_t - T_t]}{\sum R_t} \times 100 \qquad \text{Equation 1.2}$$

$$f2 = 50 \times \mathrm{Log}\left[\frac{1}{\sqrt{1+\frac{1}{n}\sum(R_t - T_t)^2}} \times 100\right] \qquad \text{Equation 1.3}$$

The R_t and T_t are the percentages of drugs dissolved a each time point for the reference and test preparations respectively; n is the number of time points considered. f_1 factor calculates the percentage difference between the two curves at each time interval, and it describes the relative error between the two dissolution profiles. The percentage is zero when the reference and test formulations are identical. f_2 factor is a logarithmic reciprocal square root transformation of the sum of squared error and is the measurement of the similarity in the percentage of dissolution between the curves. Generally the f_1 value is ≤ 15 and f_2 value is ≥ 50; it means that the average difference is not more than 10% at the sampling time points. This ensures equivalence of the profiles and hence the performance of the test and the reference formulations (Moore and Flanner, 1996; Shah, 1998).

1.8 Influence of physiological factors on *in-vivo* performance

In considering an oral dosage form design, it is helpful to have an idea of the disposition of the dosage form within the gastrointestinal tract as well as to have information concerning its distribution and release characteristics. A variety of physiological conditions on the gastrointestinal tract can affect the performance of the administered dosage form. The human gastrointestinal tract can be divided into three major sections, namely, stomach, small intestine and colon. These sections differ in terms of anatomical and physiological characteristics (Youngberg *et al*., 1987).