

A COMPREHENSIVE REVIEW ON SUSTAIN EXTENDED RELEASE MULTIUNIT PARTICULATE ORAL DRUG DELIVERY SYSTEMS

Debjit Bhowmik*, Chiranjib.B, Sobharam Sahu, Chaya Sahu

Rajiv Gandhi college of pharmacy, Nautanwa

Maharajganj, Uttar Pradesh

Email-debjit_cr@yahoo.com

INTRODUCTION

The term 'Sustained Release' is known to have existed in the medical and pharmaceutical literature for many decades. Sustain release has been constantly used to retard the release of therapeutic agent such that its appearance in the circulation is delayed and/or prolonged and its plasma profile is sustained in duration. The onset of its pharmacological action is often delayed and duration of therapeutic action is sustained.

The object of sustain release of drug, in a general way is to modify the normal behaviour of drug molecule in a physiological environment. It can lead to the following.

- ❖ Sustaining drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with minimization of desirable side effects.
- ❖ Localization of drug action by spatial placement of a controlled release system usually rate controlled adjacent to or in the diseased tissue of organ.
- ❖ Targeting drug action by using carriers of chemical derivatives to deliver drug to particular target cell type.

Initially the ultimate criterion for a sustain release tablet is to achieve a blood level and the drug comparable to that of liquid product administered every 4 hrs. To this end prolong release dosage forms are designed to release the drug so as to provide a drug level within the therapeutic range for 8 to 12, with a single dose rather than a dose every 4 hrs. No prolonged drug forms have without disadvantages. Since gastrointestinal tract is not uniform. In certain individuals if drug release in higher concentration very fastly, they experience toxic or exaggerated response. If drug release was more slowly then not receive

proper benefit of response was seen. This is especially true for older people whose gastrointestinal tract is less active than that of the younger. Also liberation is slow, there is danger of accumulation of the drug after several days resulting in high blood levels and a delayed exaggerated response.

Multi Unit Particulate System offers several advantages such as

- ❖ Improve GIT absorption.
- ❖ Minimize local irritation.
- ❖ Offers high degree of flexibility.
- ❖ Reduces dose dumping.
- ❖ Reduces inter and intra subject variability.

SUSTAINED RELEASE DRUG DELIVERY SYSTEM:-

The ideal object of drug delivery system points to the two aspects, most namely spatial placement and temporal delivery of drug. Spatial placement release to targeting of a drug to a specific organ or tissue, while temporal delivery refers to controlling the rate of drug delivery to the target tissue. An approximately designed sustained release drug delivery system can be a major advance towards solving these two problems. It is for their reason that the science and technology responsible for development of Sustained Release pharmaceuticals have been and continue to be focus of a great deal of attention in both industrial and academic laboratories. The fact that coupled with the intrinsic inability of conventional dosage forms to achieve spatial placement is a compelling matter for investigation of Sustained Release drug delivery system³.

Sustained Release drug Therapy: -

Conventional dosage forms include Solutions, Suspension, Capsules, Tablet, Emulsion, Aerosols, Foams and Suppositories, which can be considered to release their ingredients into an absorption pool immediately. This is illustrated in the following simple kinetic scheme.

kr

ka

imagine the ideal drug delivery system, two pre-requisites would be requested. First it would be a single dose for the duration of treatment whatever it may be for day or weeks as with infection or lifetime of the patient, as in hypertension or diabetes. Second it should deliver active entity directly to the site of action, there by minimizing of eliminating side effects.

Many terms used to refer to therapeutic systems of controlled and sustained release have been used to describe terms such as “Timed release” and “Prolonged release” gives excellent manufacture identification. Sustained release constitutes any dosage form that provides medication over an extended time. Controlled release however denotes that the system is able to provide actual therapeutic control.

Potential Advantages of Sustained Drug Therapy: -

All sustained release products share the common goal of improving drug therapy over that achieved with their non-sustained counterparts. This improvement of drug therapy is represented by several potential advantages of the Sustained Release system, as shown below.

1. Avoid patient compliance problems.
2. Employ less total drug.
 - Reduces dosing frequency.
 - Minimize or eliminate local side effects.
 - Minimize or eliminate systemic side effects.
3. Improve efficiency in treatment
 - Control condition most promptly.
 - Improve bioavailability of some drugs.
 - Make use of special effects, e.g.: sustained release.
 - A smoother therapeutic response over the dosage interval.
4. Economy

Because of the nature of its release kinetics a sustained release system should be able to utilize less total drug over the course of therapy than a conventional preparation. Unquestionably the most important reason for sustained drug therapy is improved efficiency in treatment i.e. optimized therapy. The result of obtaining constant drug blood level from a SR system is to promptly achieve and maintain the desired effect. Once daily SR formulation of shorter acting drug that provides a resistant therapeutic response at the end of the dosage interval can provide additional cover. Economy can be examined from two points of view. Although the initial unit cost of most sustain drug delivery system is usually greater than that of conventional dosage form because of the special nature of these products, the average cost of treatment over an extended time period may be less. Economy may also result from a decrease in nursing time/hospitalization, less cost work time, etc⁵.

Disadvantages: -

SR dosage forms have following disadvantages.

1. Unpredictable and often poor in vitro: in vivo correlation.
2. Dose dumping.
3. Reduce potential for dosage adjustment and increase potential for pass clearance and poor systemic availability in general.
4. For oral SR dosage forms an additional disadvantage that the effective drug release period is influenced and limited by G.I. residence time.

Release Rate and Dose Consideration: -

The objective in designing a sustained release system is to delivered drug at a rate necessary to achieve and maintain a constant drug level. This rate should be analogous to that achieved by continuous IV infusion where drug is provided at a constant rate equal to its rate of elimination. This implies that the rate of delivery must be independent of the amount of drug remaining in the dosage form and constant over time that is release from the dosage form should follow zero order kinetics. Shown by following equation.

$$kr^0 = \text{Rate In} = \text{Rate out} = ke. Cd. Vd$$

Where-

k_r^0 – Zero order rate constant for drug release.

k_e - First order rate constant for overall drug elimination.

C_d - Desirable drug level in the body.

V_d - Volume space in which drug is distributed/volume of distribution.

To achieve a therapeutic level promptly and sustaining the level for a given period of time, the dosage form generally consists of two parts, an initial priming dose, D_i , that release drug immediately and a maintenance or sustaining dose, D_m . The total dose, W , thus required for the system is –

$$W = D_i + D_m \quad (1)$$

For a system where the maintenance dose release drug by a zero order process for a specified period of time, the total dose is

$$W = D_i + K_r^0 T_d \quad (2)$$

Where K_r^0 is the zero order rates constant and T_d is the total time desired for sustained release form and dose.

The drug in blood level or tissue level versus time profile is the ideal goal of a Sustained Release which is achieved by use of a maintenance dose that release drug by zero order kinetics. To maintain drug blood level within the therapeutic range over the entire time course of therapy, most Sustained Release drug delivery system and like conventional dosage forms, administered as multiple rather than single dose. For those Sustained Release systems utilizing the release kinetics other than zero order the multiple dosing is more complex.

Classification:-

Sustained Release drug delivery system can be classified into following categories.

- A. Rate programmed drug development system
- B. Activation modulated drug development system.
- C. Feed base modulated drug development system.
- D. Site targeting drug development system.

All categories consist of the following common structure features

- i. Drug reservoir compartment.
- ii. Rate-controlling elements.
- iii. Energy source.

DESIGN OF ORAL SUSTAINED RELEASE DOSAGE FORMS:

The oral route of administration received the most attention for Sustained Release system. Patient acceptance and flexibility of oral route is quite enough. It is safe route of administration compared to most parenteral routes. The present section will focus on the basic principle involved in conception and development of new approach to oral Sustained Release drug delivery system. The following classification of such system is chosen because it includes not only the conceptual approach of design, but also same element of physiology of the sustained release system as well.

1. Continuous release system:
 - a. Dissolution control
 - b. Diffusion control
 - c. Dissolution and Diffusion control
 - d. Ion exchange resin
 - e. Osmotically controlled devices
 - f. Slow dissolving salts and complexes
 - g. pH independent formulation
2. Delayed –transit and Continuous Release System:
 - a. Density-based system
 - b. Size-based system
 - c. Bio-adhesive system
3. Delayed-release System:

- a. Intestinal release
- b. Colonic release

MECHANISM OF DRUG RELEASE:

Sustained release dosage forms are often classified according to the mechanism of drug release. The following are the most common means used to achieve a slow controlled release of the drug from dosage forms;

- Dissolution control
- Drug transport control by diffusion
- Erosion control
- Drug transport control by convective flow (for example, osmotic pumping)
- Ion-Exchange control

Dissolution controlled release systems

In dissolution controlled extended release systems the rate of dissolution in the gastrointestinal juices of the drug or another ingredients is the release controlling process. Sparingly water-soluble drug can form a preparation of a dissolution controlled extended release type. Reduced drug solubility can be accomplished by preparing poorly soluble salts or derivatives of the drug. An alternative means to achieve extended release based on dissolution is to incorporate the drug in a slowly dissolving carrier.

Dissolution controlled extended release systems can also be obtained by covering drug particles with a slowly dissolving coating. The release of the drug from such units occurs in two steps,

- 1) The liquid that surrounds the release unit dissolves the coating (rate limiting dissolution step).
- 2) The solid drug is exposed to the liquid and subsequently dissolves

Sustained release oral products employing dissolution as the rate-limiting step are in principle the simplest to prepare. A drug with a slow dissolution rate is inherently sustained. Some example of these drugs includes digoxin, griseofulvin, and salicylamide. Others, such as aluminum aspirin, ferrous sulfate, and benzphetamine paomate, produce

such forms when in contact with the absorption pool contents. Steroids have been reports to undergo transformation into less soluble polymorphs during dissolution in the absorption pool.

For those drugs with high water solubility and therefore high dissolution rate, can decrease solubility through appropriate salt of derivative formation. Unfortunately, forms such as these do not meet the criterion of constant availability rate because their surface area decreases with time. Nevertheless, sustained drug release can be achieved by coating drug particles or granules with materials of varying thickness or by dispersing them in a polymeric matrix.

The basic principle of dissolution control is “If the dissolution process is diffusion layer controlled, where the rate of diffusion from the solid surface through an unstirred liquid film to the bulk solution is rate limiting” the flux J is given by:

$$J = -D(dc/dx) \quad (3)$$

Where D is the diffusion coefficient and dc/dx is the concentration gradient from the solid surface to the bulk solution. The flux can also be defined as the flow rate to material (dm/dt) through a unit area (A), thus equation becomes:

$$J = (1/A)dm/dt \quad (4)$$

If the concentration gradient is linear and the thickness of the diffusion layer is h,

$$dc/dx = (C_b - C_s)/h \quad (5)$$

Where C_s is the concentration at the solid surface and C_b is the concentration in the bulk solution. By combining the above equation, the flow rate of material is given by

$$dm/dt = -(DA/h)(C_b - C_s) = kA(C_s - C_b) \quad (6)$$

Where k is the intrinsic dissolution rate constant.

The above equation predicts constant dissolution rate. If the surface area, diffusion co-efficient, diffusion layer thickness, and concentration difference are kept constant. However, as dissolution proceeds parameters like the surface area especially, may change.

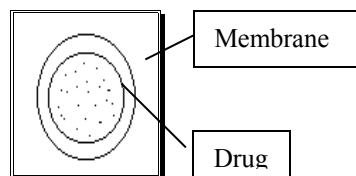


Figure No:-1 Dissolution control of drug release via thickness and dissolution rate of the membrane barrier coat.

Most suitable dosage forms for this mechanism is compressed tablets containing coated particles. E.g. Ethyl cellulose, Nylon, Acrylic resins. Release depends on drug solubility and pore structure membrane. Constant release resulted when gastrointestinal fluid passes through barrier to dissolve drug.

Diffusion Controlled Release:

There are basically two types of diffusion controlled systems which have been developed over the past two decades: reservoir devices and matrix devices. In diffusion controlled extended release systems the transport by diffusion of dissolved drug in pores filled with gastric or intestinal juice or in a solid (normally polymer) phase is the release controlling process.

Depending on the part of the release unit in which the drug diffusion takes place, diffusion controlled release systems are divided into matrix systems (also referred to as monolithic systems) and reservoir systems. The release unit can be tablet or a nearly spherical particle of about 1 mm in diameter (a granule or a milisphere). In both cases the release unit should stay more or less intact during course of the release process.

In matrix systems diffusion occurs in pores located within the bulk of the release unit, and in reservoir systems diffusion takes place in a thin water-insoluble film or membrane, often about 5-20 μm thick, which surrounds the release unit. Diffusion through the membrane can occur in pores filled with fluid or in the solid phase that forms the membrane.

Drug is release from a diffusion controlled release unit in two steps-

1. The Liquid that surrounds the dosage form penetrates the release unit and dissolves the drug. A concentration gradient of dissolved drug is thus established between the interior and the exterior of the release unit.
2. The dissolved drug will diffuse in the pores of the release unit or the surrounding membrane and thus be released, or, alternatively, the dissolved drug will partition into the membrane surrounding the dose unit and diffuse in the membrane.

A dissolution step is thus normally involved in the release process but the diffusion step is the rate controlling step. The rate at which diffusion will occur depends on four variables:

- The concentration gradients over the diffusion distance.
- The area.
- The distance over which diffusion occurs.
- The diffusion co-efficient of the drug in the diffusion medium.

Some of these variables are used to modulate the release rate in the formulation.

a) Reservoir system

In a reservoir system the diffusion occurs in a thin film surrounding the release unit.

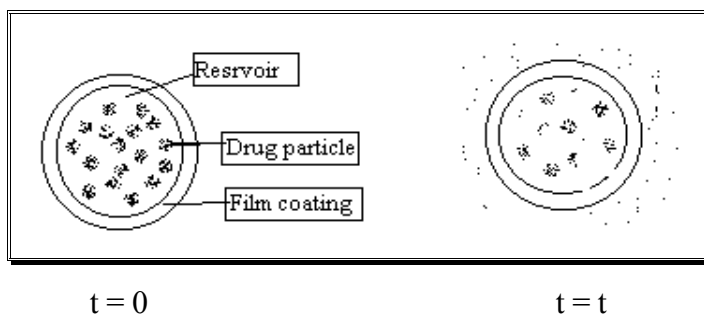


Figure No:-2 Schematic illustration of the mechanism of drug release from a diffusion based reservoir tablet (t = time)

This film is normally formed from a high molecular weight polymer. The diffusion distance will be constant during the course of the release and, as long as a constant drug concentration gradient is maintained, the release rate will be constant, i.e. a zero order release. One possible process for the release of the drug from a reservoir system involves partition of the drug dissolved inside the release unit to the solid membrane, followed by transport by diffusion of the drug within the membrane. Finally, the drug will partition to the solution surrounding the release unit. The driving force for the release is the concentration gradient of dissolved drug over the membrane.

In this system, a water-insoluble polymeric material encases a core of drug. Drug will partition into the membrane and exchange with the fluid surrounding the particle or

tablet. Additional drug will enter in the membrane, diffuse to the periphery, and exchange with the surrounding media.

Coefficient, which is defined as the concentration of drug in the membrane over the concentration of drug in the core. If the partition coefficient is high, the core will be depleted of drug in a short time so that zero order release will be observed only over a short segment of the time course of drug release.

b) Matrix Devices

In a matrix system the drug is dispersed as solid particles within a porous matrix formed of a water insoluble polymer, such as polyvinyl chloride. Initially, drug particles located at the surface of the release unit will be dissolved and the drug released rapidly. Thereafter, drug particles at successively increasing distances from the surface of the release unit will be dissolved and released by diffusion in the pores to the exterior of the release unit. Thus, the diffusion distance of dissolved drug will increase as the release process proceeds. The drug release, in terms of the cumulative amount of drug (M) release from a matrix in which drug particles are suspended is proportional to the square root of time i.e. $M = kt^{1/2}$

The main formulation factors by which the release rate from a matrix system can be controlled are

- The amount of drug in the matrix,
- The porosity of the release unit, The length of the pores in the release unit (dependent on the size of the release unit and pore tortousity) and
- The solubility of the drug (which regulates the concentration gradient). The characteristics of the pore system can be affected by,

For example: - The addition of soluble excipients and by the compaction pressure during tableting.

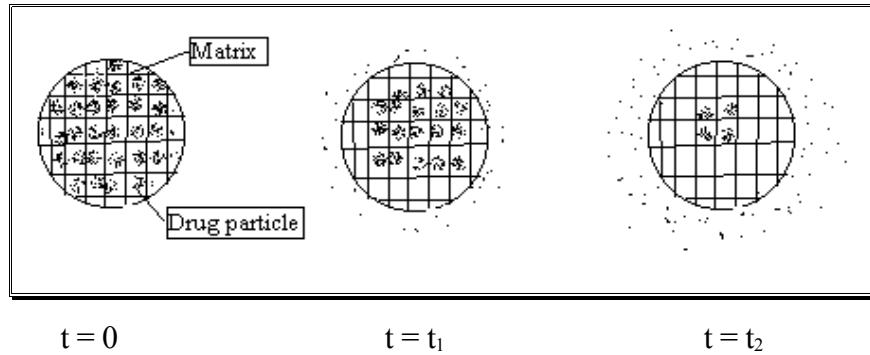


Figure No:-3 Schematic illustration of the mechanism of drug release from a diffusion based matrix tablet (t = time)

Erosion controlled release systems

In erosion controlled extended release systems that rate of drug release is controlled by the erosion of a matrix in which the drug is dispersed. The matrix is normally a type of dosage forms, i.e. the matrix is formed by an operation, and the system can thus be described as a single unit system. The erosion in its simplest form can be described as a continuous liberation of matrix material (both drug and excipients) from the surface of the dosage forms, i.e. surface erosion. The consequence will be a continuous reduction in dosage forms weight during the course of the release process.

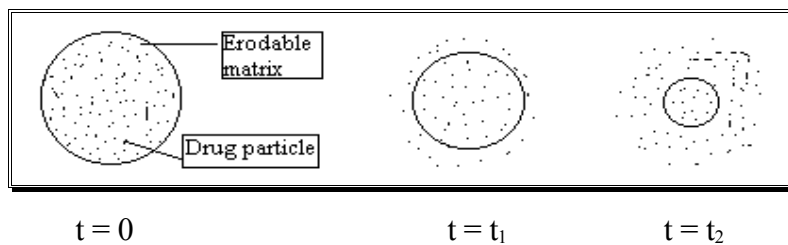


Figure No:-4 Schematic illustration of the mechanism of drug release from a erosion based matrix tablet (t = time)

Drug release from an erosion system can thus be described in two steps.

1. Matrix material, in which the drug is dissolved or dispersed, is liberated from the Surface of the dosage forms.
2. The drug is subsequently exposed to the gastrointestinal fluids and mixed with (if the drug is dissolved in the matrix) or dissolved in (if the drug is suspended in the matrix) the fluid.

The eroding matrix can be formed from different substances. One example is lipids or waxes, in which the drug is dispersed. Another example is polymers that gel in contact with water (Hydroxy ethyl cellulose). The gel will subsequently erode and release the drug dissolved or dispersed in the gel. Diffusion of the drug in the gel may occur in parallel.

Osmotic controlled release systems

Osmotic controlled oral drug delivery systems utilize osmotic pressure for controlled delivery of active agents. Drug delivery from these systems to a large extent is independent of the physiological factors of the gastrointestinal tract and these systems can be utilized for systemic as well as targeted delivery of drugs. The release of drug from osmotic systems is governed by various formulation factors such as solubility and osmotic pressure of the core component, size of the delivery orifice and nature of the rate controlling membrane. Drug release from this system is independent of pH and other physiological parameter to a large extent and it is possible to modulate the release characteristics.

MODIFIED ORAL DRUG RELEASE:

Modified release can be categorized into delayed release and extended, or prolonged, release. The primary aims of using delayed release are to protect the drug from an unfavourable environment in the gastrointestinal tract, to protect the gastrointestinal tract from high, local concentrations of an irritating drug compound, or to target a specific region of absorption or action.

Delayed release products are typically enteric-coated or targeted to the colon. Extended release products aim at releasing the drug continuously at a predetermined rate in order to increase the patient compliance.

This is expected since the frequency of administration is reduced and peaks are cut to prevent high concentrations, locally or systemically, which can cause undesirable side effects. Thus, the tissue concentrations are kept at a low but effective level over an extended time period.

There are numerous ways of achieving prolonged drug release, including the use of ion exchange resins, pH-independent formulations, prodrugs, barrier-coating, embedment in hydrophilic, plastic or slowly eroding matrixs, repeat action, polymer resin beads, drug complex formation, bioadhesives and local targeted systems. Of these, the ones most commonly used are barrier-coating, effectively giving a reservoir system where a polymer membrane surrounding the dosage regulates the drug release, and embedment in different types of matrixs resulting in homogeneous dosage systems through which the drug diffuses at a controlled rate.

Modified release dosage forms are available as single unit dose (non-divided preparations, e.g. matrix tablets) or multiple unit dose systems (divided preparations, e.g. granules or pellets).

SUSTAINED RELEASE MULTIPLE UNITS AND SINGLE UNITS DOSES :

A single unit dose, e.g. matrix tablet or tablet enclosed in a diffusion membrane, is a depot which releases a drug during the passage of the entire alimentary canal without disintegration. The empty core or shell is discharged. To retain a depot effect it is imperative that the dose unit is swallowed intact as dividing it would result in an unintended rapid drug release.

A multiple units dose consists of many mini depots, pellets, mini tablets or microencapsulated crystals contained in a capsule or in a tablet. These mini depots are dispersed and distributed throughout the gastrointestinal tract when the capsule or tablet disintegrates. A multiple units tablets may thus be divided at ingestion without loss of the depot effect, as the sub unit act as self-contained depots.

Attaining a reproducible therapeutic effect may be considerable as the effects of a single unit and a multiple unit dose are not equally dependent on physiologically function like gastric emptying and intestinal motility. In the case of sustained release single unit dose which having considerable dimensions (10-16mm in diameter) is unable to reach to the small intestine independently of gastric emptying. Accordingly the emptying of undisintegrated dosage forms from the stomach shows variations ranging from less than $\frac{1}{2}$ to more than 7 hours. As many drug shows optimum absorption in the upper small intestine a lasting detention of the dose in the stomach might imply a severely delayed absorption.

According to Heading et. al. The rate of absorption in man is directly related to the gastric emptying rate¹⁰.

If the drug release from the depot is pH-dependent e.g. low in acid environment, the release process will only get properly started when the depot is emptied into the intestine. Also in this case the bioavailability rate will depend closely on gastric emptying, and the reproducibility of the effect is rendered questionable. A particular disadvantage connected with the inclination of single- unit depots to be trapped in a narrow passage is constituted by the risk of local irritation or erosion when the released concentrates at the site of the trap. Application of the multiple units dose principle will essentially eliminate the dependence of the drug effect on gastric emptying, the mini depot being sufficiently small to make possible their passage through the pylorus even between its actual openings. As a result of this,

- 1) The drug may reach the site of optimum absorption in a reproducible fashion,
- 2) High local drug concentration is avoided since the mini depot are dispersed and distributed over large surfaces, reducing the risk of mucous irritation.

Table No :- 1 Characteristics :

Single unit dose	Multiple unit dose
a) Transport dependent on gastric emptying. b) Transport strongly influenced by intestinal motility and transit time of food. <ul style="list-style-type: none"> • Varying rate and extent of bioavailability. • Risk of accumulation of doses. • Risk of high local drug concentrations. • Risk of local irritation. c) Tablets non-dividable	a) Transport virtually independent of gastric emptying. b) Transport only moderately affected by intestinal motility and transit time of food. <ul style="list-style-type: none"> • Reproducible bioavailability. • No risk of accumulation of doses and its consequences. c) Tablets dividable.

PELLETS:

Pellets are agglomerates of fine powders or granules of bulk drugs and excipients. They consist of small, free-flowing, spherical or semi-spherical solid units, typically from about 0.5 mm to 1.5 mm, and are intended usually for oral administration¹¹. Implants of small, sterile cylinders formed by compression from medicated masses are also defined as pellets in pharmacy¹². Pellets can be prepared by many methods, the compaction and drug-layering techniques being the most widely used today. Regardless of which manufacturing process is used, pellets have to meet the following requirements.

(1) They should be near spherical and have a smooth surface, both considered optimum characteristics for subsequent film coating.

(2) The particle size range should be as narrow as possible. The optimum size of pellets for pharmaceutical use is considered to be between 600 and 1000 μm .

(3) The pellets should contain as much as possible of the active ingredient to keep the size of the final dosage form within reasonable limits.

In the last two decades, pellets have established their position for many reasons¹³. Pellets offer a great flexibility in pharmaceutical solid dosage form design and development. They flow freely and pack easily without significant difficulties, resulting in uniform and reproducible fill weight of capsules and tablets. Successful film coating can be applied onto pellets due to their ideal spherical shape and a low surface area to volume ratio¹⁴.

Pellets composed of different drugs can be blended and formulated in a single dosage form. This approach facilitates the delivery of two or more drugs, chemically compatible or incompatible, at the same sites or different sites in the gastrointestinal tract. Even pellets with different release rates of the same drug can be supplied in a single dosage form¹³.

The most important reason for the wide acceptance of multiple-unit products is the rapid increase in popularity of oral controlled-release dosage forms. Controlled-release oral solid dosage forms are usually intended either for delivery of the drug at a specific site within the gastrointestinal tract or to sustain the action of drugs over an extended period of

time. With pellets, the abovementioned goals can be obtained through the application of coating materials (mainly different polymers), providing the desired function¹⁴ or through the formulation of matrix pellets to provide the desired effect.

The advantage of multiple-unit products as a controlled-release dosage form is believed to be their behaviour in vivo because of their advantageous dispersion pattern in the gastrointestinal tract and their special size characteristics¹⁵. The transit time of a gastrointestinal drug delivery system along the gastrointestinal tract is the most limiting physiological factor in the development of a controlled-release gastrointestinal drug delivery system targeted to once-a-day medication. Gastro-intestinal transit time, greatly affects the bioavailability of a drug from an orally administered controlled-release preparation. Gastric transit of both single and multiple-unit solid dosage forms is prolonged in a fed stomach compared to a fasting one. Plastic spheres of 7 mm remained in the food-filled stomach even as food itself expelled steadily. Once the stomach had emptied, the spheres began to transit in clusters. It has been reported that pellets smaller than about 2.4 mm in diameter, are free from the digestive function of the stomach and the closing system of the pyloric sphincter to be emptied from the stomach. A maximum pellet diameter of 1.5 mm has been recommended for an optimal multiple-unit formulation clearly showed that the threshold size must be below 1 mm. According to there is no actual cut-off size for gastric emptying, but as the size of the pellets increase, predictable emptying from the fed stomach becomes uncertain and highly variable. However, it has been demonstrated that gastric emptying is not only dependent on the size but also on some other important factors, such as density of pellets, nature of food and inter-subject variation that both density and size of the pellets affect the gastrointestinal transit time. The higher density of the pellets prolonged the gastric transit time, while the larger size slightly prolonged the small gut transit time but not the gastric transit time. Controversial results have also been reported to the effect of pellets densities on the transit times through the gastrointestinal tract¹⁶.

THEORY OF PELLET FORMATION AND GROWTH :

In order to judiciously select and optimise any pelletisation/granulation process, it is important to understand the fundamental mechanisms of granule formation and growth. Different theories have been postulated related to the mechanism of formation and growth of pellets. Some of these theories are derived from experimental results while others are confined to visual observations. Results obtained from the experiments with some form of tracer technique are regarded as acceptable and convincing. As the conventional granulation, the most thoroughly studied, most classified pelletization process, which involves a rotating drum, a pan or a disc, has been divided into three consecutive regions: nucleation, transition and ball growth. However, based on the experiments on the mechanism of pellet formation and growth, the following steps were proposed: nucleation, coalescence, layering and abrasion transfer.

Nucleation (Figure 5A) is a common stage in all pelletisation/granulation processes and occurs whenever a powder is wetted with liquid . The primary particles are drawn together to form three-phase air-water-liquid nuclei and are attached together by liquid bridges which are pendular in nature. The bonding strength is improved by reduction of particle size. The sizes of the primary particles, the moisture content, the viscosity of the binding particles, the wettability of the substrate and the processing conditions, such as tumbling and drying rates, influence the size, the rate and the extent of nuclear formation . Both the mass and the number of nuclei in the system change as a function of time, which is an important feature of nucleation .

Nucleation is followed by a transition phase, and the growth mechanisms affecting the transition region are coalescence and layering. Coalescence (Figure 5B) is defined as the formation of large-sized particles by random collision of well-formed nuclei, and the mechanism requires slight excess moisture on the nuclear surface. Although the number of nuclei is progressively reduced, the total mass of the system remains unchanged during this step. Layering (Figure 5C) is a slow growth mechanism and involves the successive addition of fragments and fines on an already formed nucleus. In the layering step, the number of particles remains the same, but the total mass in the system increases due to

increasing particle size as a function of time. The fragments or fine particles can be formed by particle size reduction.

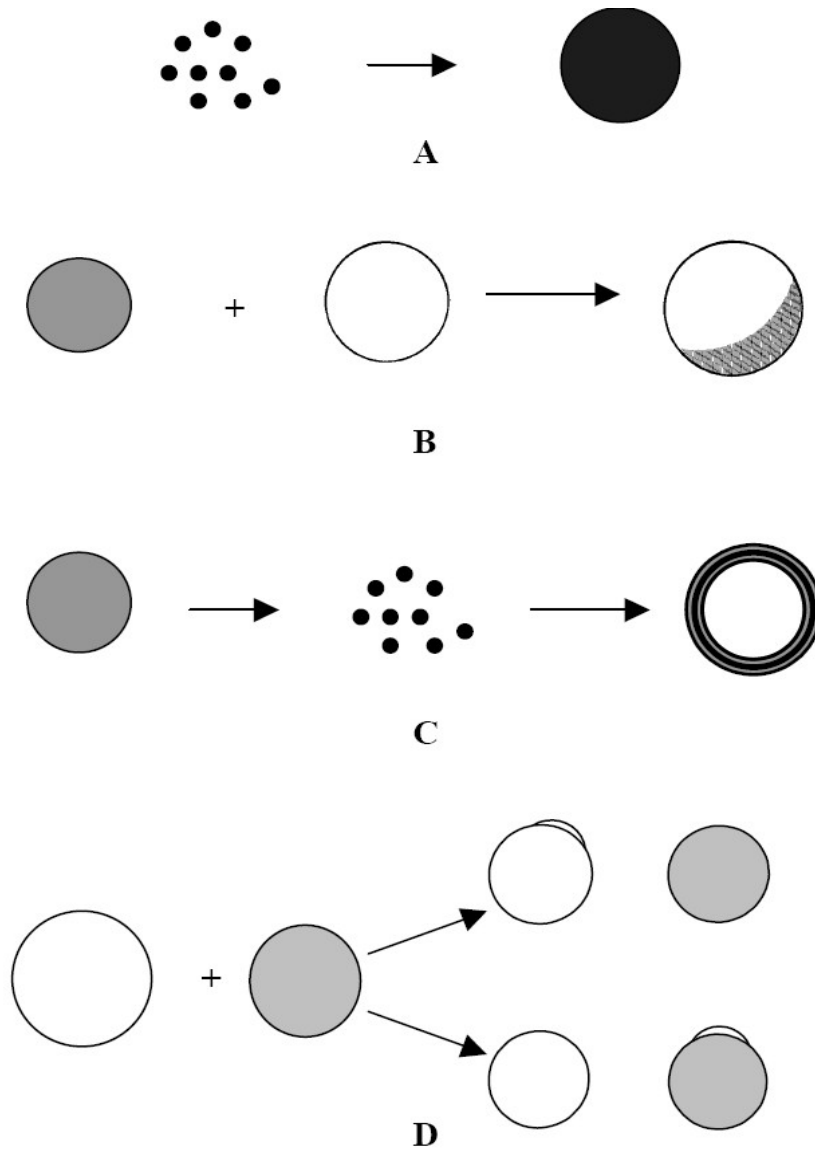


Figure No:-5 Pellet growth mechanisms. (A) Nucleation, (B) coalescence, (C) layering and (D) abrasion transfer¹³.

Large pellets pick up the fragments that are produced through size reduction. Production of fines and subsequent coalescence and layering continues until the number of

favourable collisions declines rapidly, thereby leading to a reduction in the rate of growth of the pellets. At this point the third phase, the ball growth region, is reached.

In the ball growth phase the main mechanism affecting the slow growth of agglomeration is the abrasion transfer (Figure 5D), which involves the transfer of materials from one granule formed to another without any preference in either direction. This situation does not result in a change in the total number or mass of the particles. The particles, however, undergo a continuous change in size as long as the conditions that lead to the transfer of material exist.

DESIRABLE PROPERTIES OF PELLETS:

- **Uncoated pellets:**
 - Uniform spherical shape,
 - Uniform size,
 - Good flow properties,
 - Reproducible packing,
 - High strength,
 - Low friability, Low dust,
 - Smooth surface,
 - Ease of coating.

- **Once coated:**
 - Maintain all of the above properties,
 - Have desired drug release characteristics.

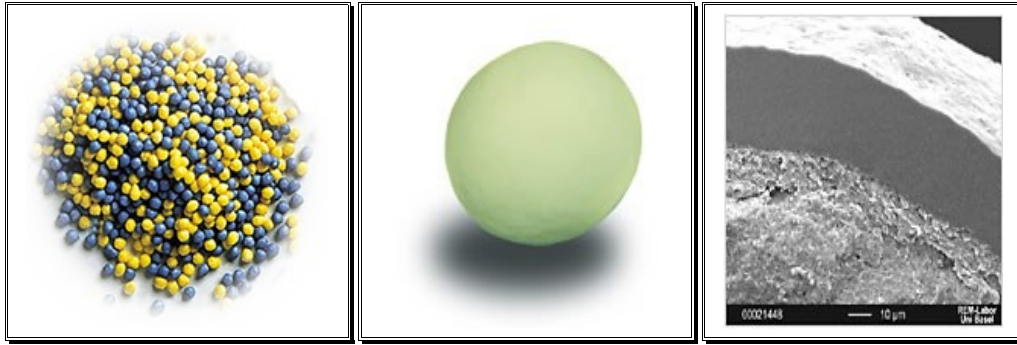


Figure No:-6 (a) Figure No:-7 (b) Figure No:-8 (c)
 (a) Pellets, (b) Perfect pellet, (c) Coated pellet.

Methods of preparing pellets :

Compaction and drug layering are the most widely used pelletisation techniques in pharmaceutical industry. In the compaction techniques, extrusion and spheronization is the most popular method. Recently, however, melt pelletization has been used frequently in making compaction pellets using a different type of equipment, e.g. a high-shear mixer. Other pelletization methods, such as globulation, balling and compression are also used in the development of pharmaceutical pellets although in a limited scale. Following of the mainly techniques used for the pelletization.

DIFFERENT PELLETIZATION TECHNIQUES :

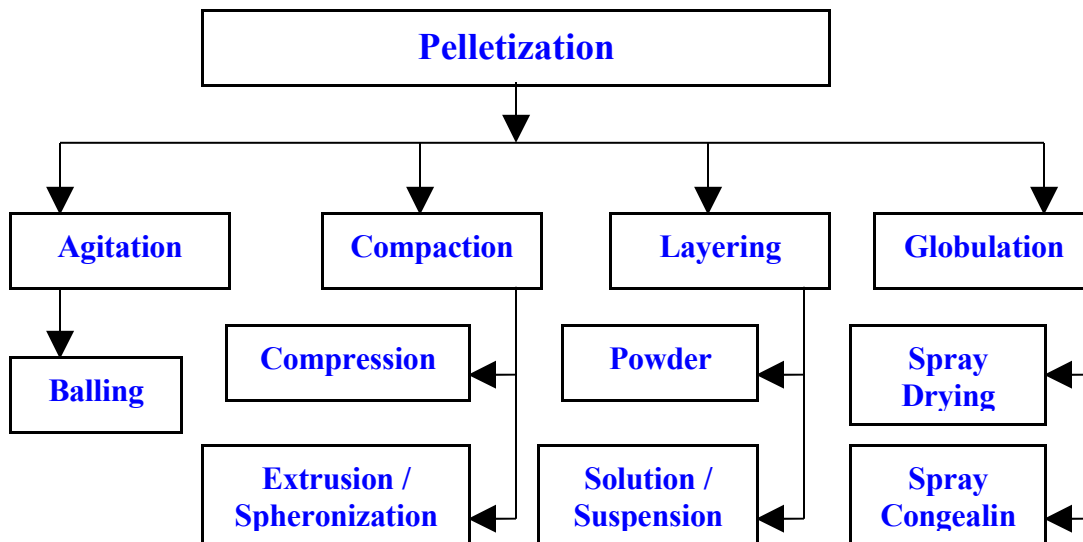


Figure No:-9

1. Extrusion-spheronization

Extrusion-spheronisation is a multiple-step compaction process comprising dry mixing of the ingredients with excipients, wet granulation of the mass, extrusion of the wetted mass, charging the extrudates into the spheroniser to produce a spherical shape, drying the wet pellets in a dryer and, finally, screening to achieve the required size distribution. The granulation step can be performed both in batch-type processors, including a conventional planetary mixer, and in vertical or horizontal high-shear and sigma-blade mixers, and in continuous mixers, and high-shear twin-screw mixer-extruders.

Table No :- 2 PHARMACEUTICAL EXTRUDERS

Sr.No.	Extruder	Examples
1	Screw fed extruders	Axial or End Plate, Dome, Radial
2	Gravity feed extruders	Cylinder Roll, Gear roll, Radial
3	Piston feed extruders	Ram

Extruders for the extrusion process (step) have been classified generally as screw, sieve and basket, roll and ram extruders. Based on the type of feed mechanism used to transport the mass towards the die, they have been broadly classified as screw, gravity or piston-type extruders. Most spheroniser have been designed based on a revolving grooved plate driven by a variable-speed drive unit at the base of a smooth-walled drum. The drum capacity, plate diameter and plate design may vary. In order to increase the capacity of the spheronisation stage, a continuously working spheroniser has been introduced.



Figure No:-10 (a)



Figure No:-11 (b)

(a) A Radial pattern with the grooves running from the center,

(b) A Graphical representation of the characteristic rope like formation in a spheronizer bowl during operation.

The process produces products ranging from barely-shaped, irregular particles like the conventional granulation, to very spherical particles with drastically different properties. Modifying the composition, the granulating fluid or the process conditions, can alter tableting characteristics. The main advantage over other methods of producing drug-loaded spheres or pellets is the capacity to produce spherical pellets of a uniform size and a high drug content up to 90%. Recently, different types of fluidised bed rotary processors have been developed more successfully for preparing compaction-type pellets such as the extrusion-spheronisation process in a one-step process. This technique has solved many problems related to the multi-step extrusion and spheronisation process; it consumes less time, requires lower labour costs and less space.

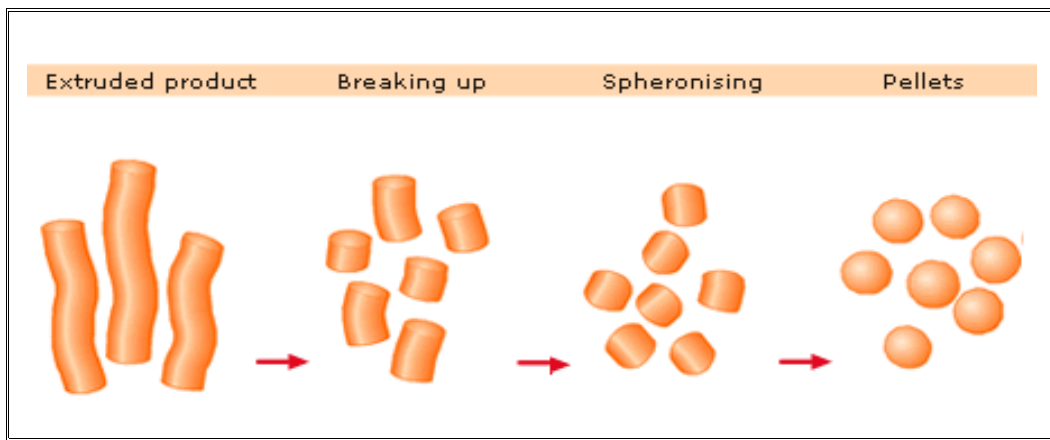


Figure No:-12

2. Drug layering

The layering process comprises the deposition of successive layers of drug entities from solution, suspension or dry powder on nuclei, which may be crystals, or granules of the same material or inert starter seeds. In solution/suspension layering, drug particles are dissolved or suspended in the binding liquid. In powder layering, complete dissolution does not occur, due to low liquid saturation, irrespective of the solubility of the active agent in the binding liquid. In powder drug layering, a binder solution is first sprayed onto the previously prepared inert seeds, followed by the addition of powder. Conventional pan

coaters have been used from the very beginning of the history of drug layering pelletization. From the economic point of view, however, use of conventional pan coaters is not very reasonable due to the higher labour costs and time consumption, and lower yield. An important disadvantage of pan coaters is the shortage of process control. More recently modified forms of pan coaters have been developed, which resolves many of the drawbacks related to the old system.

The problems of drug layering pelletisation by conventional pan coaters had lead to the development of two types of rotary granulators (fluidised-bed and centrifugal granulators) respectively. These devices offer many advantages including lower manufacturing costs, flexibility of operation and ease of automation. Centrifugal granulators can be used for manufacturing multiple-unit, immediate or controlled-release drug products for oral use. Through the use of these systems, initial beads can be prepared and subsequently drug-layered and coated in the same equipment, resulting in highly spherical multi-layered granules with adequate controlled-release characteristics.

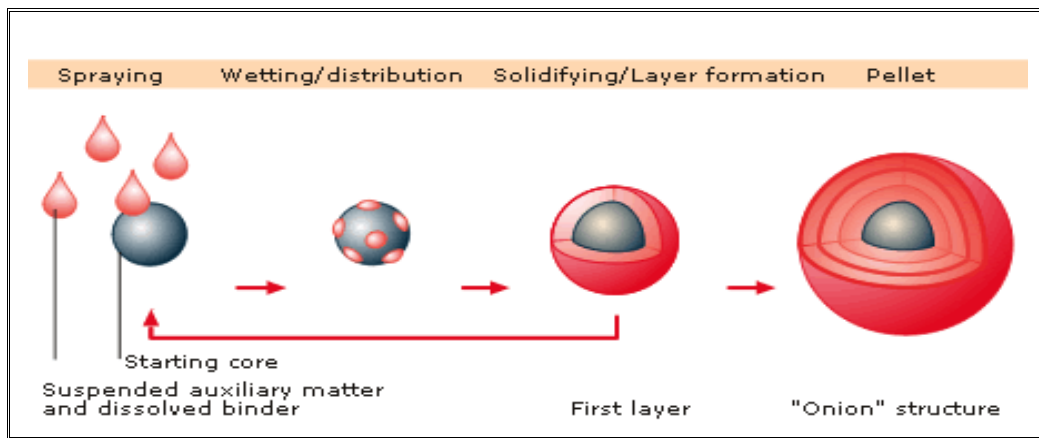


Figure No:-13

OTHER PELLETTIZATION METHODS:

Other pelletization methods such as globulation, agitation and compaction (compression) are also used, although in a limited scale, in the preparation of pharmaceutical pellets.

1. Globulation, or droplet consists of two related processes, spray drying and spray congealing. Spray drying is the process in which drugs in the suspension or

solution without excipient are sprayed into a hot stream to produce dry and more spherical particles. This process is commonly used for improving the dissolution rates, hence bioavailability of poorly soluble drugs.

2. Spray congealing is the process in which a drug is allowed to melt, disperse or dissolve in hot melts of gums, waxes or fatty acids, and is sprayed into an air chamber where the temperature is kept below the melting point of the formulation components, to produce spherical congealed pellets. Both immediate- and controlled-release pellets can be prepared in this process depending on the physicochemical properties of the ingredients and other formulation variables.

Compression is one type of compaction technique for preparing pellets. Pellets of Compacting mixtures or blends of active ingredients and excipients under pressure prepare definite sizes and shapes. The formulation and process variables controlling the quality of pellets prepared are similar to those used in tablet manufacturing.

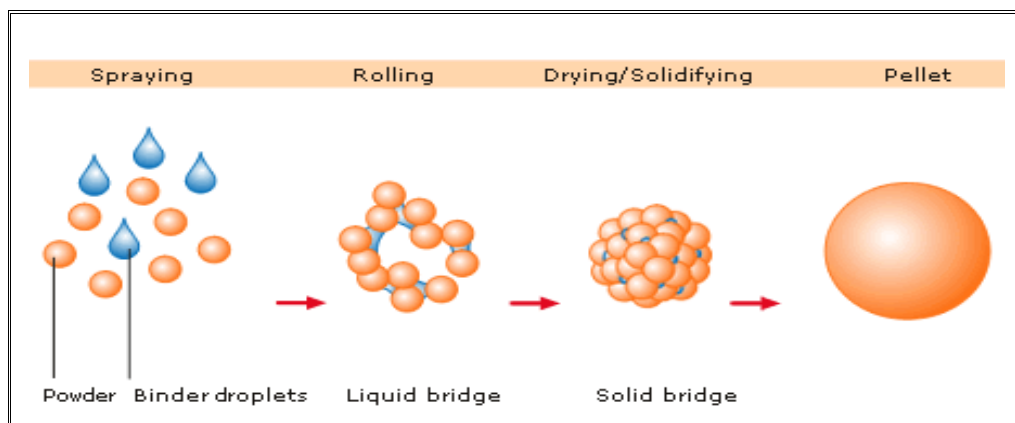


Figure No:-14

3. Balling is the pelletisation process in which pellets are formed by a continuous rolling and tumbling motion in pans, discs, drums or mixers. The process consists of conversion of finely divided particles into spherical particles upon the addition of appropriate amounts of liquid.

ADVANTAGES OF MULTI UNIT PARTICULATE ORAL DRUG DELIVERY SYSTEMS:

1. The palletized product can freely disperse in the gastrointestinal tract as a subunit, thus maximising drug absorption and reducing peak plasma fluctuation.
2. Potential side effects can be minimized without impairing drug bioavailability.
3. Local irritation derived from high local concentration of a drug from a single unit dose, can be avoided
4. They show more predictable gastric emptying and dispersion in gastrointestinal tract.
5. Reduced risk of dose dumping i.e failure of system leading to immediate release of the drug.
6. The pelletised products can improve the safety and efficacy of the active agent.
7. It reduces inter and intra subject variability.
8. It is helpful in achieving unique release pattern.
9. Simultaneous administration of two or more incompatible drugs.
10. It improves patient comfort and compliance.

CONCLUSION

MUPS oral drug delivery system offers several advantages such as rapid absorption, reducing peak plasma fluctuation and ease of administration and termination of therapy. Hence in the present work pellets of drug were prepared with the objective of avoiding first pass metabolism and controlling the release of drug for prolonged period of time.

REFERENCE

Ashoka V Bhosle; Rahul V Tukawalw and sanjay D Sawant; Oral Novel Drug Delivery System; The Eastern Pharmacist; 2002;41-43.

6. M E Aulton; "Pharmaceutics" The Science of dosage form design; Churchill livingstone; 2nd edition; 2002; 414-418.

7. Joshep R Robinson; Vincet H Lee; Controlled drug delivery; 1987; Marcel dekker, 2nd edition; 376-391.

8. **R K Verma; D M Krishna; S Garg;** Formulation aspects in the development of osmotically controlled oral drug delivery systems; **J controlled release**; 2002(79); 7-27.
9. **Asa Tunon;** Preparation of tablet from reservoir compression behaviour & drug release, Uppasala University, 2003, 15-16
10. **R C Heading; J Nimmo; L F Prescott and P, Tohill; By J Pharmaceutics.;** 1973;47;415.
11. **Gajdos, B.,** Rotary granulators - Evaluation of process technology for pellet production using factorial design. *Drugs Made Ger.* 27, 30-36,1984.
12. **Cox, P.H. and Spanjers, F.**The preparation of sterile implants by compression. *Pharm. Weekblad* 105, 1970, 681-684.
13. **Ghebre-Sellassie, I.,** Pellets: A general overview. In Ghebre-Sellassie, I (ed.), *Pharmaceutical Pelletization Technology.* Marcel Dekker, Inc., New York, USA, Vol. 37, 1989, pp. 1-13.
14. **Ghebre-Sellassie, I., Gordon, R., Fawzi, M.B. and Nesbitt, R.U.,** Evaluation of a high-speed pelletization process and equipment. *Drug Dev. Ind. Pharm.* 11, 1985, 1523-1541
15. **Peh, K.-K. and Yuen K-H.,** Development and in vitro evaluation of a novel Multiparticulate matrix controlled release formulation of theophylline. *Drug Dev. Ind. Pharm.* 21 (13), 1995, 1545-1555.
16. **Bechgaard, H., Christensen, F. N., Davis, F. N., Davis, S. S., Hardy, J. G., Taylor, M. J., Whilley, D. R., Wilson, C. G.,** Gastrointestinal transit of pellet systems in ileostomy subjects and the effect of density. *J. Pharm. Pharmacol.* 37(10), 1985, 718-21.
17. **Sastry, K., V., S. and Fuerstenau, D., W.,** Kinetic and process analysis of the agglomeration of particulate materials by green pelletization, in *Agglomeration 77,* (K. V. S. Sastry, ed.), AIME, 1973, pp.381-402.
18. **Claudio Nastruzzi, Rita Cortesi, Elisabetta Esposito, Alberto Genovesi,** Influence of Formulation and Process Parameters on Pellet Production by Powder Layering Technique, *AAPS PharmSciTech.* 2000; 1(2): article 9.

- 19. L. Hanysova, M. Vaclavkova, J. Dohnal and J. Klimes**, Stability of Ramipril in the solvents of different pH, *Journal of Pharmaceutical and Biomedical Analysis*, Volume 37, Issue 5 , 29 April 2005, Pages 1179-1183.
- 20. Raluca-Ioana Stefan, Jacobus F. van Staden, Camelia Bala and Hassan Y. Aboul-Enein**, On-line assay of the S-enantiomers of enalapril, Ramipril and pentopril using a sequential injection analysis / amperometric biosensor system, *Journal of Pharmaceutical and Biomedical Analysis*, Volume 36, Issue 4 , 19 November 2004, Pages 889-892.
- 21. Fukumori, Y.;** Coating of multiparticulates using polymeric dispersions - formulation and process considerations, in Ghebre-Sellassie (ed.), *Multiparticulate oral drug delivery*, MarcelDekker, Inc., New York, (1994), 79 – 111.
- 22. Otilia May Yue KOO and Paul Wan Sia Heng** Dept. of Pharmacy, National university of Singapore, *Chem. Pharm. Bull.* 49(11) 1383-1387 (2001)
- 23. H. Steckel, F. Mindermann-Nogly** Production of chitosan pellets by extrusion/spheronization, *European Journal of Pharmaceutics and Biopharmaceutics* 57 (2004) 107–114
- 24. P.B. Deasy , M.F.L. Law** Use of extrusion-spheronization to develop an improved oral dosage form of indomethacin, *International Journal of Pharmaceutics* 148 (1997) 201- 209
- 25. Garg SK, Islam AS, Kumar N, Sehgal M, Bhargava VK** Effect of 'Mentat' on the pharmacokinetics of single and multiple doses o phenytoin in rabbits. *47(2)* 104-107(1999)
- 26. G. Tomer, F. Podczeck, J.M. Newton** The influence of model drugs on the preparation of pellets by extrusion“‘—”2a) spheronization: II spheronization parameters, *International Journal of Pharmaceutics* 231 (2002) 107–119
- 27. Delphine Blanque, Hilke Sternagel , Fridrun Podczeck, J. Michael Newton** Some factors influencing the formation and in vitro drug release from matrix pellets prepared by extrusion/spheronization, *International Journal of Pharmaceutics* 119 (1995) 203-211
- 28. Consuelo Souto, Alberto Rodríguez, Silvia Parajes and Ramón Martínez -Pacheco** A comparative study of the utility of two superdisintegrants in microcrystalline cellulose

pellets prepared by extrusion–spheronization, European journal of Pharmaceutics and Biopharmaceutics 61 (1-2) 2005, 94-99

29. A.Dashevskya, K. Kolterb, R. Bumpier pH-independent release of a basic drug from pellets coated with the extended release polymer dispersion Kollicoat SR 30 D and the enteric polymer dispersion Kollicoat MAE 30 DP, European Journal of Pharmaceutics and Biopharmaceutics 58 (2004) 45–49

30. Michelle F.L Law and Patrick B Deasy Use of hydrophilic polymers with microcrystalline cellulose to improve extrusion–spheronization, European journal of Pharmaceutics and Biopharmaceutics, 45(1), 57-65 (1998)

31. Reena Singh, S. S. Poddar, and Amit Chivate Sintering of Wax for Controlling Release From Pellets, AAPS PharmSciTech. 2007; 8(3): Article