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CONTROLLED RELEASE PELLETS: AN EFFECTIVE TOOL IN CHRONIC THERAPY

R. Santosh Kumar, Mattaparthi Sahiti

GITAM Institute of Pharmacy, GITAM University, Rushikonda, Visakhapatnam-45.

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ABSTRACT

Multiparticulate drug delivery systems like pellets, granules, micro particles, minitablets etc., prove to be promising and highly flexible systems with ease of formulating with different drug release kinetics. In present era, pelletization technologies are gaining much attention as they represent an efficient pathway for manufacture of oral drug delivery systems. Pelletization is an agglomeration process that converts fine powders or granules of bulk drugs and excipients into small, free flowing semi-spherical units. Pellets, being multiparticulate systems, are widely used due to the technological as well as therapeutic advantages over single-unit dosage forms. The present review focus on advantages, disadvantages, formation of pellet growth, different pelletization techniques, characterization, marketed pellets products and also outlines recent developments in the pharmaceutical approaches that have been used to prepare pelletized dosage forms with different techniques emphasizing on the recent research work done in the area of pelletization.

Corresponding author
R. Santosh Kumar
GITAM Institute of Pharmacy,
GITAM University,
Rushikonda, Visakhapatnam-45.
radasantosh@rediffmail.com

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INTRODUCTION

Over the past 30 years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled release drug delivery systems. The attractiveness of these dosage forms is due to awareness to toxicity and ineffectiveness of drugs when administered or applied by conventional method in the form of tablets, capsules, injectables, ointments etc. Usually conventional dosage form produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. These factors as well as factors such as repetitive dosing and unpredictable absorption led to the concept of controlled drug delivery systems.

The term "sustained release" is known to have existed in the medical and pharmaceutical literature of many decades. It has been constantly used to describe a pharmaceutical dosage form formulated to retard the release of a therapeutic agent such that its appearance in the systemic circulation is delayed and/or prolonged and its plasma profile is sustained in duration. The onset of its pharmacological action is often delayed and the duration of its therapeutic effect is sustained.[1] Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. In these systems, the dosage of the drug substances is divided on a plurality of subunit typically consisting of thousands of spherical particles with diameter of 0.05 to 2.00 mm. Thus multi-particulate dosage forms are pharmaceutical formulations in which the active substance is present as a number of small independent subunits. Multiparticulate systems show better reproducible pharmacokinetic behavior than conventional (monolithic) formulations. Some other studies were done to investigate pharmacokinetics of sustained release dosage forms prepared using ion exchange resins. Drug safety may also be increased by using multiparticulate dosage forms, particularly for modified release systems.[2]

The concept of sustained or prolonged release of biologically active agents has been well-appreciated and rationalized for decades. In the field of pharmaceuticals, sustained release systems have been widely used in oral medication, since early 1950s.Perhaps the earliest examples are enteric-coated orally ingested tablets. Other slow release systems include encapsulated pellets or beads, sparingly soluble salts, complex system, drug embedded in matrix, ion exchange resins, and swelling hydro gels. Most of the early products can be classified under sustained delivery systems, which means the release of active agent is slower than any conventional formulation, but is significantly affected by an external environment.[3]

The goal in designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. So, controlled release dosage form is a dosage form that release one or more drugs continuously in a predetermined pattern for a fixed period of time, either systemically or to a specified target organ. Sustained release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery.

The Mebeverine Hydrochloride (Hcl) in tablet form of three times dose per a day the prior art may cause problems in patients with swallowing difficulty for adults and children. This drawback is avoided with the use of multiparticulate formulations, since they may be dispersed in liquids at the movement of the administration. The Sustained release multiparticulate formulations of Mebeverine Hydrochloride of the invention advantageously provide a better drug release at the gastrointestinal tract compared with single tablets formulations and the dosing frequency will be reduced. The Sustained release capsules will be used mainly to treat irritable bowel syndrome.[4, 5]

Modified Release Drug Delivery Systems [6]

Modified release delivery systems may be divided conveniently in to four categories.

A) Delayed release
B) Controlled release
   i) Sustained release
   ii) Extended release
C) Site specific targeting
D) Receptor targeting.

Delayed Release

These systems are those that use repetitive, intermittent dosing of a drug from one or more immediate release units incorporated into a single dosage form. Examples of delayed release systems include repeat action tablets and capsules and enteric-coated tablets where timed release is achieved by a barrier coating.

Controlled Release [7]

These systems include any drug delivery system that achieves slow release of drug over an extended period of time.

Sustained Release[8]

These systems also provide a slow release of drug over an extended period of time and also can provide some control, whether this be of a temporal or spatial nature, or both, of drug release in the body, or in other words, the system is successful at maintaining constant drug levels in the target tissue or cells.

Extended Release

Pharmaceutical dosage forms that release the drug slower than normal manner at predetermined rate and is necessarily to reduce the dosage frequency by two folds.

Site Specific Targeting

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is adjacent to or in the diseased organ or tissue.

Receptor Targeting

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is the particular receptor for a drug within an organ or tissue. Site specific targeting and receptor targeting systems satisfy the spatial aspect of drug delivery and are also considered to be controlled drug delivery systems.

Controlled Release Drug Delivery Systems

Most conventional drug products, such as tablets and capsules, are formulated to release the active drug immediately after administration to obtain rapid and complete systemic drug absorption. In recent years, various modified drug products have been developed to release the active drug from the product at a controlled rate. The controlled release drug delivery systems provide a therapeutic amount of drug to the proper site in the body to achieve and then maintain the desired drug concentration.

An ideal dosage regimen in therapy of any disease is the one which immediately attains the desired therapeutic concentration of the drug in plasma or at the site of action and maintains it constant for the entire duration of treatment. This is usually achieved by repeated administration of a drug in a suitable amount (dose) and at a particular frequency. The fluctuations in plasma concentration of the drug following its repeated administration are shown is Fig.No.1.1.

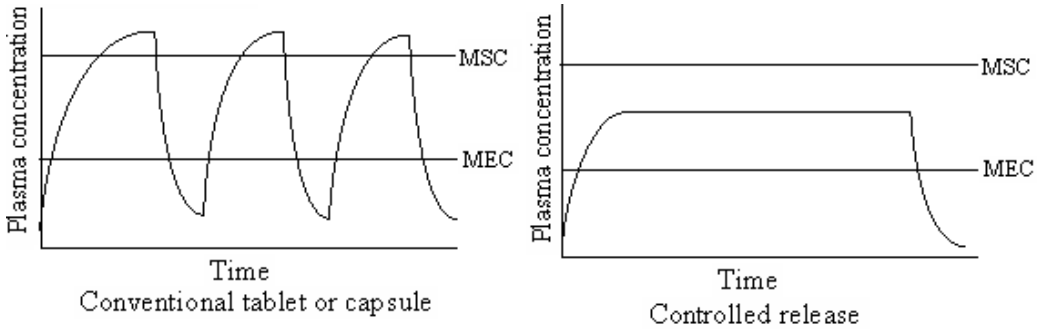

Fig No.1.1: Shows Comparative Blood Drug Level Profiles Obtained From Administration of Conventional And Controlled Released Dosage Forms.

The repeated administration of drugs has many disadvantages or limitations as follows

1. Poor patient compliance, increased chances of missing the dose of a drug with short half life for which frequent administration is necessary.
2. The unavoidable fluctuations in the drug concentration may lead to under medication or over medication as the C_{ss} values fall or rise beyond the therapeutic range.
3. The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index whenever over medication occurs.

As alternative approach to maintain the desired therapeutic plasma concentrations constantly for the entire duration of treatment is the design and use of controlled release dosage forms. Controlled release drug delivery systems are those dosage formulations designed to release an active ingredient at rates, which differ significantly from their corresponding conventional dosage forms. The controlled release drug delivery systems are aimed at controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of the drug to tissue. Drug release from these systems should be at a desired rate predictable and reproducible.

In general controlled delivery attempts to sustain drug action at a predetermined rate by maintaining a relatively constant effective drug level in the body with concomitant minimization of undesirable side effects associated with a saw tooth kinetic pattern.

1. Localize drug action by spatial placement of a controlled release system (usually rate-controlled) adjacent to or in the diseased tissue or organ.
2. Target drug action by using carriers or chemical derivatisation to deliver drugs to a particular ‘target’ cell type.

Advantages of Controlled Release Systems [7]

1. Maintenance of plasma drug concentration within an optimal therapeutic range for prolonged duration of treatment.
2. More consistent and prolonged therapeutic effect is observed.
3. Maximization of efficiency-dose relationship.
4. Reduction of adverse side effects.
5. Minimization of the need for frequent dose intake.
6. Enhancement of patient compliance.
7. Controlled administration of a therapeutic dose at a desirable delivery rate.

Disadvantages of Controlled Release Dosage Forms [7, 9]

1. Increased variability among dosage units.
2. Stability problems are observed.
3. Toxicity due to dose dumping occurs when more than usual fraction is being released.
4. Increased cost.
5. More rapid development of tolerance.
6. Need for additional patient education and counseling.

Selection of Drug Candidate for Controlled Release Dosage Forms

The physicochemical properties of the drug such as P^{ka}, partition coefficient, biological half-life, molecular weight, dose of the drug etc., have to be considered before selection.

Characteristics of Drug Suitable for Formulation as Controlled Release Products

1. Exhibit moderate rates of absorption and excretion.
1. Uniform absorption throughout the G.I tract.
2. Administered in relatively small doses.
3. Possess good margin of safety.
4. Used for treatment of chronic therapy.

Characteristics of Drug Unsuitable for Controlled Release

1. Not effectively absorbed in the lower intestine (Riboflavin).
2. Absorbed and excreted rapidly i.e. short biological half-lives, less than one hour (Penicillin G, Furosemide).
3. Long biological half-lives greater than 12 hours (Diazepam, Phenytoin).
4. Large doses required, 1gm (Sulphonamides)
5. Drugs with low therapeutic index (Phenobarbital, Digoxin).
6. Precise dosage titrated to individuals required (anticoagulants, cardiac glycosides).
7. No clear advantage for sustained release formulation (Griseofulvin).

Factors Influencing the Design and Performance of Sustained Release Products

The design of controlled - release delivery system is subjected to several variables of considerable importance. Among these are, the properties of the drug, the route of drug delivery, the type of delivery, the disease being treated and length of the therapy have major importance.

Physicochemical Properties of Drug

- Aqueous solubility
- Partition coefficient and Molecular size
- Drug stability
- Protein binding.

Biological Factors [10]

- Absorption of drug
- Distribution
- Elimination
- Duration of action
- Margin of safety
- Side effects
- Circadian rhythm
- Diseased state.

Physiological Factors [10, 11]

- Prolonged drug of absorption
- Variability in G.I.T emptying & motility
- G.I.T blood flow.

Pharmacokinetic Factors

- Dose dumping.
- First pass metabolism.
- Variability of urinary pH effect on drug elimination.
- Enzyme induction/inhibition upon multiple dosing.

Pharmacological Factors

Changes in drug effect upon multiple dosing (sensitivity / tolerance).

Physicochemical Properties of Drug

Aqueous Solubility

Since drugs must be in solution before they can be absorbed, compounds with very low aqueous solubility usually suffer oral bioavailability problems because of limited G.I transit time of the un-dissolved drug particles and limited solubility at the absorption site. The choice of mechanism for oral sustained controlled release systems is limited by aqueous solubility of the drug. Diffusion systems will be poor choices for slightly soluble drugs since the driving force for diffusion; the concentration in aqueous solution will be low. Such drugs may be effectively incorporated in matrix system. Aqueous solubility limits the loading efficiency of drugs into a variety of carriers such as liposome's, erythrocytes and other micro particles.

Partition Coefficient and Molecular Size

Partition coefficient and molecular size influence not only the permeation of a drug across biological membranes but also diffusion across or through a rate controlled membrane or matrix. The ability of a drug to diffuse through the membranes, its so-called diffusivity, is related to its molecular size by the equation.

$$\mathbf{Log\ D = S_v\ logV + K_v = S_m logM + K}$$

Where D is diffusivity, M is molecular weight, V is molecular volume and S_v, S_m, K_v and K_m are constants in a particular system. Generally denser medium, lesser diffusivity.

Drug Stability

The stability of a drug in the environment to which it is exposed is another physicochemical factor to be considered in the design of controlled systems. Drugs that are unstable in the stomach can be placed in a slowly soluble form or have their release delayed until they reach the small intestine.

Protein Binding

It is well known that many drugs bind to plasma proteins with a concomitant influence on the duration of drug action. Since blood proteins are for the most re-circulated and not eliminated, drug protein binding can serve as depot for drug producing a prolonged release profile, especially if a high degree of drug binding occurs. Quaternary ammonium compounds bind too much in the G.I tract. +Drugs bound much may increase absorption, if the bound drug acts as depot.

Biological Factors [10]

The design of controlled products should be based on a comprehensive picture of drug disposition. This would entail a complete examination of the ADME characteristics of a drug following multiple dosing. In the following discussion, it is assumed that the level of drug in blood or body tissue parallels biological activity of the drug.

Absorption

To maintain constant blood or tissue level of drug, it must be uniformly released from the controlled released system and then uniformly absorbed. The fraction of the drug absorbed from a single non-controlled dose or drug can sometimes be quite low for a variety of reasons such as drug degradation due to solvo lysis or metabolism, binding of drugs to proteins, physical loss or perhaps site or dose dependent absorption. If the drug was erratically absorbed, as might occur in a route of administration with variable absorptive surface, such as G.I.T, design of a controlled release product would be more difficult or prohibitive with respect to the oral route, it is well known that the absorptive character of the different segments of the G.I tract varies which in turn can influence the rate and amount of absorption of certain drugs. The oral anticoagulant Dicoumarol, the quaternary ammonium compounds and the amino glycosides such as Gentamycin are examples of such drugs.

Distribution

The distribution into tissues can be an important factor in the overall drug eliminate kinetics since it not only lowers the concentration of circulating drug but it also can be rate limiting in its equilibration with blood and extra cellular fluids. In general, the bound portion of drug can be considered inactive and unable to cross membranes. At high binding one sees prolonged drug action. The apparent volume of distribution of a drug is frequently used to describe the magnitude of distribution, including binding, within the body. The total apparent volume of distribution for a drug at steady state can be calculated from the following equation.

$$V_{dss} = [(k_{12}+k_{21})/k_{21}] V_p$$

Where V_{dss} is the apparent volume e of distribution at steady state

K_{12} is the constant for the distribution of drug from the central to peripheral compartment.

K_{21} is the constant for the distribution of drug from the peripheral to central compartment

V_p is the volume of central compartment.

Metabolism

Metabolism of a drug can either inactivate an active drug or convert an inactive drug to an active metabolite. Metabolic alteration of a drug can occur in a variety of tissues some of which are richer in enzymes than others. For example, the organ most responsible for metabolism is the liver and thus the greatest metabolic conversion occurs after a drug has been absorbed into the general circulation. Clearly for optimal bioavailability, the route of administration may be dictated by the drugs metabolic pattern. Metabolism of a drug will be reflected in the elimination rate constant of a drug or by the appearance of a metabolite. It is possible to incorporate this pharmacokinetic property into the design of controlled release product, provided that the rate and extent of metabolism are predictable and that the rate constant(s) for the process are not too large. Undoubtedly, complex metabolic patterns would make the design much more difficult, particularly when biological activity is wholly or partly due to a metabolite, as is the case in Isosorbide 2,5-dinitrate.

Duration of Action

The biological half-life and hence duration of action of a drug obviously play a major role in the process of considering a drug for controlled release. Factors influencing the biological half-life of a drug include its elimination, metabolism and distribution patterns. Drugs with short half-lives require frequent dosing in order to minimize fluctuations in blood levels accompanying conventional oral dosage regimens. Therefore controlled release dosage forms would appear very desirable for such drugs. Basic pharmacokinetic principles suggest that for a given steady state drug concentration, the zero order rate of release of a drug from its dosage form is directly proportional to its rate of elimination. Thus for a drug with a very short half-life, the desired rate of release will be quite large. This large rate of release in turn will lead to a prohibitively large dose, so that the upper limit imposed on the size of the tablet, capsule or other dosage forms may be exceeded. The numerical value of biological half-life (4hours) was quoted to make a drug a good candidate for controlled release.

Side Effects

It is believed that for some drugs, the incident of side effects is a function of plasma concentration. Theoretically, the incidence of side effects can be minimized by controlling the concentration at which the drug exists in plasma at any given time, and hence controlled release formulations appear to offer a solution to this problem. The technique of controlled release has been more widely used to lower the incidence of G.I side effects than that of systemic side effects and appears to produce more satisfactory results. It is postulated that by slowing the rate at which the drugs are released, the likelihood of G.I irritation will be reduced due to a smaller amount of drug exposed to the G.I mucosa at given time.

Mean Residence Time

The mean residence time of a drug molecule in the body is corresponding to 63.2% elimination from the body and is calculated from AUC and AUMC i.e. area under the first movement curve.

Dosage Form Index

Dosage form index is the peak ($C_{ss\ max}$) and through ($C_{ss\ min}$) values within the dosage intervals.

Oral Sustained Release Drug Delivery Systems [12, 13, 14]

Oral ingestion is traditionally preferred route of drug administration, providing a convenient method of effectively achieving both local and systemic effects. In conventional oral drug delivery systems, there is very little control over release of drug. The effective concentration at the target site can be achieved by intermittent administration of grossly excessive doses, which in most situations, often results in constantly changing, unpredictable and often sub or supra therapeutic plasma concentrations leaving the marked side effects.

An ideal oral drug delivery system should steadily deliver a measurable and reproducible amount of drug to the target site over a prolonged period. Controlled release (CR) delivery system provide a uniform concentration /amount of the drug at the absorption site and thus, after absorption allow maintenance of plasma concentrations within a therapeutic range, which minimizes side effects and also reduces the frequency of administration.

CR products are formulations that release active drug compounds into the body gradually and predictably over a 12-24 hr period and that can be taken once or twice a day. Typically these products provide numerous benefits compared with immediate release drugs, greater effectiveness in the treatment of chronic conditions, reduced side effects, greater convenience and higher levels of patient compliance due to a simplified dosing schedule. Because of the above advantages, such systems form the major segment of the drug delivery market.

A number of techniques are used to achieve controlled release of drugs via the oral cavity. The majority of the oral controlled release systems relay on dissolution, diffusion or a combination of both mechanisms to generate slow release to drug to the G.I milieu.

- Dissolution controlled release
  Encapsulation dissolution control
  Matrix dissolution control
- Diffusion controlled release
  Reservoir devices
  Matrix devices
- Diffusion and dissolution systems
- Ion-exchange resins
- PH -independent formulations
- Osmotically controlled release
  1. Altered density formulation
  2. High density approach
- Low density approach (Floating systems)
- Swelling and expanding systems
- Bio adhesive systems
- Electrically stimulated release devices

Dissolution Controlled Release

Controlling the dissolution rate of drugs that are highly soluble can be done by preparing the appropriate salt or derivative by coating the drug with a slowly soluble material or by incorporating it into a tablet with a slowly soluble carrier.

Encapsulated Dissolution Systems

These systems can be prepared either by coating particles or granules of drug with varying thicknesses of slowly soluble polymers or by micro-encapsulation. Microcapsules are commonly filled into capsules. The commonly used coating materials include shellac, gelatin, Carnuba wax, ethyl cellulose, etc.

Matrix Dissolution Devices

These systems are prepared by compressing the tablet with a slowly soluble polymer carrier into tablet form. Wax matrices are prepared either by congealing or dispersion the drug - wax mixture in water. Matrix tablets are also prepared by direct compression of drug, polymer and excipients.

Diffusion Controlled Release

In these systems the release rate of drug is determined by its diffusion through a water insoluble polymer. There are basically two types of diffusion devices: reservoir devices, in which a core of drug is surrounded by a polymeric membrane, and matrix devices, in which dissolved or dispersed drug is distributed uniformly in an inert polymeric matrix.

Reservoir Devices

The methods used to develop reservoir type devices include micro-encapsulation of drug particles and press coating of tablets containing drug cores. In most cases particles coated by micro-encapsulation form a system in which the drug is contained in the coating film as well as in the core of the microcapsule drug release involves a combination of dissolution of diffusion with dissolution being the process that controls the release rate. If the encapsulating material is selected properly, diffusion will be the controlling process. The membrane barrier materials include polyvinyl acetate, ethyl and methyl celluloses, Hydroxypropylcellulose, waxes, etc.

Matrix Devices

The three major types of materials used in the preparation of matrix devices are insoluble plastics, hydrophilic polymers and fatty compounds. The most common method preparation is to mix the drug with the matrix material and then compress the mixture into tablets. In the case of wax matrices the drug is generally dispersed in the molten wax which is then congealed, granulated and compressed into tablets.

Diffusion and Dissolution Systems

In these systems the release rate of drug is determined by both the diffusion and dissolution mechanisms.

Osmotically Controlled Release [15]

Osmotic pressure can be employed as the driving force to generate a constant release of the drug. A tablet core consisting of an osmotically active drug or a drug with an osmotically active salt surrounded by a semi permeable membrane containing a small orifice is an osmotic delivery system. When the tablet is exposed to aqueous medium water will flow into the tablet and due to the osmotic pressure developed the contents are expelled out through the orifice.

Swelling and Expanding Systems [16]

These systems increase the residence time of the dosage form in the stomach. Particles greater than 10mm are unable to enter the duodenum and are retained in the stomach. But large particles pose problems during swallowing. The swelling systems incorporate hydro gels which are polymers that can swell up to 100 times their dry weight. The hydro gels used must be biodegradable.

Floating Systems

These systems are retained in the stomach and are suitable for drugs that are poorly soluble or unstable in the intestinal medium. The dosage form is made less dense than the gastric fluid so that it can float and stay in the absorptive region for longer periods of time.

Bioadhesive Systems [17]

Bioadhesive can be defined as any substance that can adhere to a biological membrane and remain there for an extended period of time. If the membrane substrate is then the polymer is referred to as mucoadhesive. The bioadhesives increase the residence time and contact time at the area of absorption and provide a high concentration gradient across the membrane.

Electrically Stimulated Release Devices

These are monolithic devices prepared by using polyelectrolyte gels which swell when; an external electrical stimulus is applied, causing a change in P^H The release could be modulated, by the current, giving a pulsate release profile.

Ion-Exchange Resins [18]

They are water insoluble cross linked polymers containing salt forming groups in repeating positions in the polymer chain. Drug is bound to the resin by prolonged exposure of resin to the drug solution. Drug release from the resin depends on the resin and the pH of the gastric system. Once the drug molecules are released by exchange with the ions in the gastrointestinal tract they diffuse out of the resin. The release rate can be modified by coating the drug resin complex to serve as a rate limiting barrier.

Pharmaceutical industry adopted the ion exchange technology to achieve sustained release of drugs. Keating listed the following advantages of adsorbing basic nitrogen containing drugs onto sulfuric acid Cation exchange resins and using them in dosage forms.

1. Prolonged availability, by releasing the drug from the complex for over 12 hours in the gastro -intestinal tract
2. Reduced toxicity by slowing drug adsorption.
3. Increased stability by protecting the drug from hydrolysis or other degradative changes in the GI tract.
4. Improved palatability.

Applications of Sustained Release Dosage Forms

Patient Compliance

Lack of compliance is generally observed with long term treatment of chronic disease, as success of drug therapy depends upon the ability of patient to comply with the regimen. Patient compliance is affected by a combination of several factors, like awareness of disease process, patient faith in therapy, his understanding of the need to adhere to a strict treatment schedule. And also the complexity of therapeutic regimens, the cost of therapy and magnitude of local and or systemic side effect of the dosage form. The problem of lack of patient compliance can be resolved to some extent by administering sustained release drug delivery system.

Reduced 'See- Saw' Fluctuation

Administration of a drug in a conventional dosage form [except via intravenous infusion at a constant rate] often results in 'see – saw' pattern of drug concentration in the systemic circulation and tissue compartments. The magnitudes of these fluctuations depend on drug kinetics such as the rate of absorption, distribution, elimination and dosing intervals. The 'see-saw' or 'peak and valley' pattern is more striking in case of drugs with biological half lives of less than four hours, since prescribed dosing intervals are rarely less than four hours. A well-designed sustained release drug delivery system can significantly reduce the frequency of drug dosing and also maintain a steady drug concentration in blood circulation and target tissue cells.

Reduced Total Dose

Sustained release drug delivery systems have repeatedly been shown to use less amount of total drug to treat a diseased condition. By reducing the total amount of drug, decrease in systemic or local side effects are observed. This would also lead to greater economy.

Improved Efficiency in Treatment

Optimal therapy of a disease requires an efficient delivery of active drugs to the tissues, organs that need treatment. Very often doses far in excess to those required in the cells have to be administered in order to achieve the necessary therapeutically effective concentration. This unfortunately may lead to undesirable, toxicological and immunological effects in non-target tissue. A sustained release dosage forms leads to better management of the acute or chronic disease condition.

Challenges

Dose Dumping

Dose dumping is a phenomenon where by relatively large quantities of drug in a sustained release formulation is rapidly released, introducing potential toxic quantities of the drug into the systemic circulation. Dose dumping can lead to fatalities in case of potent drug, which have a narrow therapeutic index e.g. Phenobarbital.

Limited Choice of Selecting Desired Dose In The Unit

In conventional dosage forms, dose adjustments are much simpler e.g. tablet can be divided into two fractions. In case of sustained release dosage forms, this appears to be much more complicated. Sustained release property may get lost, if dosage form is fractured.

Poor *In Vitro* – In Vivo Correlation

In sustained release dosage form, the rate of drug release is deliberately reduced to achieve drug release possibly over a large region of gastrointestinal tract. Here the so 'Absorption window' becomes important and may give rise to unsatisfactory drug absorption in vivo despite excellent in-vitro release characteristics.

Patient Variation

The time period required for absorption of drug released from the dosage form may vary among individuals. Co-administration of other drugs presence or absence of food and residence time in gastrointestinal tract is different among patients. This also gives rise to variation in clinical response among the patient.

Other applications

Sustained Drug Delivery

As mentioned earlier, drug absorption from oral controlled release (CR) dosage forms is often limited by the short GRT available for absorption. However, HBS type dosage forms can retain in the stomach for several hours and therefore, significantly prolong the GRT of numerous drugs. These special dosage forms are light, relatively large in size, and do not easily pass through pylorus, which has an opening of approx. 0.1– 1.9 cm.

Site Specific Drug Delivery

A floating dosage form is a feasible approach especially for drugs which have limited absorption sites in upper small intestine. The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug. This reduces side effects that are caused by the drug in the blood circulation. In addition the prolonged gastric availability from a site directed delivery system may also reduce the dosing frequency. The eradication of Helicobacter pylori requires the administration of various medicaments several times a day, which often results in poor patient compliance. More reliable therapy can be achieved by using GRDDS. Floating alginate beads have been used for the sustained release of Amoxicillin trihydrate. Thus, it can be expected that the topical delivery of antibiotic through a FDDS may result in complete removal of the organisms in the fundal area due to bactericidal drug levels being reached in this area, and might lead to better treatment of peptic ulcer.

Pellets

Pellets have been used to describe a variety of systematically produced, geometrically defined agglomerate obtained from diverse starting materials utilizing different processing conditions. They contain multiples of free-flowing, spherical or semi-spherical solid units which are smaller in size (0.5mm to 1.5mm), and are intended mostly for oral administration. [19, 20, 21] The small sterile masses which are obtained from the compression of implants or sterile cylinders are termed as pellets in pharmacy. [22, 23]

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

Pellets are small spherical free flowing units with improved flow properties and flexibility in formulation development and manufacture. Their size and shape allow their administration as injections and also for oral drug delivery [24].

History of Pellets

Although various industries have routinely utilized pelletization processes since the turn of the 20th century in order to manufacture particles with defined sizes and shapes, it was only in the early 1950's, in response to a desire to sustain the release of drugs over an extended period of time, that the pharmaceutical industry developed a keen interest in the technology. In 1949, pharmaceutical scientists at Smith Kline & French (SKF) realised the potential of candy seeds in developing sustained-release preparations and began the development of tiny drug pellets that could be loaded into capsules. In time, extensive research was conducted to develop pelletization techniques and major resources were allocated towards exploring methods that were faster, cheaper and more efficient, both in terms of formulation and processing equipment[25].The trend is expected to continue in the foreseeable future. Also, the role of pellets, especially of spheroids, in oral dosage form design and development has increased substantially during recent decades. Currently, pellets containing the active ingredients are administered in the form of suspensions, capsules or tablets, a great number of these kinds of pharmaceutical products being available on the market.

Also, pelletization is used in various industries, such as agriculture (fertilizers and herbicides), mineral processing (iron ore pelletization), food and detergent industry.

Reasons for Pelletization

The pharmaceutical industry has developed a great interest in pelletization due to a variety of reasons [26]

- Prevention of segregation of co-agglomerated components, resulting in an improvement of the uniformity of the content;
- Prevention of dust formation, resulting in an improvement of the process safety, as fine powders can cause dust explosions and the respiration of fines can cause health problems;
- Increasing bulk density and decreasing bulk volume;
- The defined shape and weight improves the appearance of the product;
- Improvement of the handling properties, due to the free-flowing properties;
- Improvement of the hardness and friability of pellets;
- Controlled release application of pellets due to the ideal low surface area-to-volume ratio that provides an ideal shape for the application of film coatings.

All these aspects can be considered as technological advantages of pelletization.

Advantages of Pellets [27, 28, 29, 30, 31, 32]

- Pellets are non-dusting.
- Do not require measuring.
- Takes up less space because they are compressed.
- The ingredients that make up a pellet do not separate during transit and storage.
- Pellets also allow the separation of incompatible ingredients with in different layers of the pellet body.
- They can be divided in to desired dosage strength without process or formulation changes.
- When pellets containing the active ingredients are in the form of suspension, capsule, or disintegrating tablet, they offer significant therapeutic advantages over single dosage forms [33, 34, 35].
- They can also be blended to deliver incompatible bioactive agents.
- Pellets offer higher degree of flexibility in the design and development of oral dosage form like suspension, sachet, tablet and capsule. [36, 37, 38]

Disadvantages of Pellets [39]

- Involves capsule filling which can increase the costs or tableting which destroy film coatings on the pellets.
- Dosing by volume rather than number and splitting into single dose units as required.
- The size of pellet varies from formulation to formulation but usually lies between 1 to 2 mm.
- The production of Pellets is quite an expensive process which requires highly specialized equipment and trained personnel.
- The control of production process is very difficult (e.g. the amount of water added and time is critical for the quality of pellets as over-wetting can occur very easily).

Theory of Pellet Formation and Growth

- Nucleation
- Coalescence
- Layering
- Abrasion transfer.

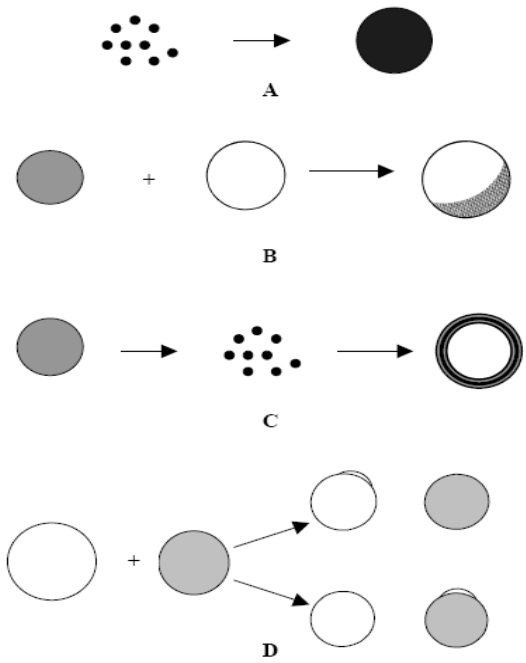

Fig No.1.2: Pellet Growth Mechanism. (A) Nucleation, (B) Coalescence, (C) Layering and (D) Abrasion Transfer.

Methods of Preparation of Pellets

The pellets can be prepared by the following methods

1. Drug layering
2. Extrusion and Spheronization.
3. Direct pelletization
4. Other Pelletization method
   - Globulation
   - Compression
   - Balling.
   - Spray congealing

Compaction and drug layering are the most widely used Pelletization techniques in pharmaceutical industry. Of 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 equipments, e.g.: High-shear mixer. Other methods of pelletization such as globulation, cryopelletization, balling and compression are also used in development of pharmaceutical pellets but in a limited scale [40, 41].

Pelletization by Drug Layering

Pelletization by layering is nothing but pellet build-up, layer by layer, around a given starting core. Pellet diameter may be between 0.6mm and 2.5mm.

Two types of layering are

a. Powder layering
b. Suspension or Solution layering

Powder[42, 43]

Powder layering involves the deposition of successive layers of dry powders of drugs and excipients on preformed nuclei or cores with the help of binding liquids. As powder layering involves simultaneous application of binding agents and dry powders, hence it requires specialized equipments like spheronizer. The primary requirement in this process is that the product container should be solid walls with no perforation to avoid powder lose beneath the product chute before the powder is picked off by the wet mass of pellets that is being layered.

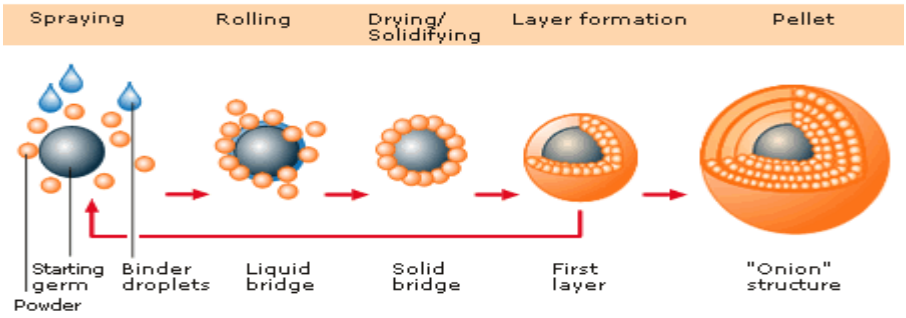

Figure No.1.3 Powder Layering Process.

Suspension or Solution layering [44]

Solution or suspension layering involves the deposition of successive layers of solution and/or suspensions of drug substances and binder over the starter non-pareal seeds, which is an inert material or crystals or granules of the same drug. In fact the coating process involved in general is applicable to solution or suspension layering technology. Consequently conventional coating pans, fluidized beds, centrifugal granulators, wurster coaters have been used successively to manufacture pellets by this method. The efficiency of the process and the quality of the pellets produced are in part related to the type of equipment used.

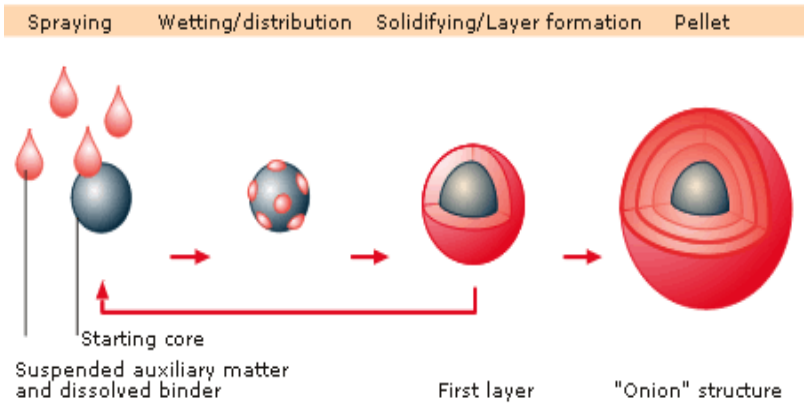

Fig. No.1.4 Suspension or Solution Layering Process.

With suitable additives pellets can be made into tablets or used to fill capsules. The round shape is ideal for uniform coating. Pellets are good for automatic dosing [45].

Pelletization by Extrusion and Spheronization

The process involves first making the extrudes from the powder material and then converting the extrudes into beads using the spheronizer. The powder material could be any kind of powder (drug powder, ayurvedic powder, food ingredient powder, detergent powder, nuclear powder etc). Beads are as fine as 0.6mm[46].

Direct Pelletizing

Powder is mixed and moistened with a solvent or binder. The powder bed is set into a centrifugal motion. The impact and acceleration forces can occur. This process results in the formation of agglomerates, which become rounded out into uniform and dense pellets the speed of rotation has a direct influence on the density and size of the pellets. The moist pellets are subsequently dried in the fluid bed. If required, the system can be made inert for applications with organic solvents. [47]

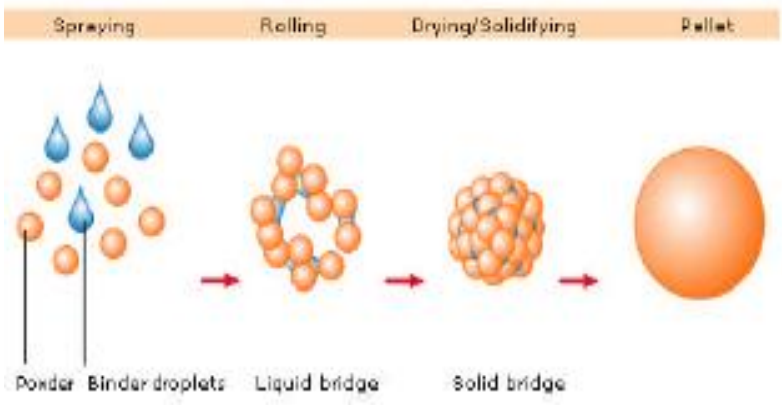

Fig No.1.6 Scheme of Different Stages In Direct Pelletization.

Other Pelletization 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.

Globulation or Droplet Formation

It consists of two related processes, spray drying and spray congealing. Spray drying is the process in which drugs in the suspension or solution without excipients 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.

Spray Congealing

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

It is one type of compaction technique for preparing pellets. Pellets of different sizes and shapes are prepared by compaction mixture or blends of active ingredients and excipients under pressure. The formulation and process variables controlling the quality of pellets prepared are similar to those used in tablet manufacturing [48].

Balling

The pelletization 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 amount of liquid.

Table No.1.1 Drugs That Can Be Formulated as Pellets.

S.NO.	Category	Examples of drugs	Dose Recommended for Pellet formulations
1	Anti-Rheumatoid NSAIDS Analgesics	Ketoprofen SR Pellets	100mg/200mg
		Diclofenac Sodium/Potassium SR Pellets.	100 mg
		Diclofenac Sodium /Potassium Enteric Coated Pellets.	50 mg
		Indomethacin Enteric Coated Pellet.	25mg/75mg
		Nimesulide SR Pellets.	100 mg/200mg
		Tramadol SR Pellets	100mg.
		Aspirin delayed release Pellets	75mg/150mg
		Ibuprofen SR Pellets	300mg
		Flurbiprofen SR Pellets	200mg
		Paracetamol Pellets	630-650mg
2	Antispasmodic:	Mebeverine SR Pellets	40%,70%,80%
		Oxybutynin SR Pellets	10mg
3	Anti-Hypertensive/Antiang	Diltiazem HCL SR Pellets (12 & 24 hours dosing as per USP)	90mg/120mg/180mg
			40mg
		Isosorbide Dinitrate SR Pellets	60 mg
		Isosorbide Dinitrate SR Pellets	20 mg

		Nifedipine SR Pellets	2.5mg
		Nitroglycerin SR Pellets	120mg/240mg
		Verapamil Pellets	250mg/200mg
		Dipyridamole Pellets	2.5mg-20mg
		Glipizide Pellets SR	
4	Antiallergics:	Chlorpheniramine Maleate SR Pellets	8mg
		Cetrizine	5mg/10mg
		Dihydrochloride Pellets	5mg
		Loratidine Pellets	5mg/10mg
5	Anti-Tussive. Expectorant	Pseudoephedrine HCl SR Pellets	120mg
	Decongestant:	Phenylepherine HCl SR Pellets	10mg-20mg
		Codeine SR Pellets	
6	Anorexiant,	Phenylpropanolamine HCl SR Pellets	50mg/75mg
	Sympathomimetics :		
	Hyperacidity, Ulcers:	Omeprazole Enteric Coated Pellets	20mg
		Lansoprazole Enteric Coated Pellets	15-30mg
		Esomeprazole Enteric Coated Pellets	40mg
		Domperidone Pellets	10, 20 ,40 %
7	Anti-adrenergic	Tamsulosin Pellets	400mg.
8	Antiasthamatics	Theophylline SR Pellets	100mg/200mg/300mg
		Salbutamol SR Pellets	8mg
		Terbutaline sulphate Pellets	20%w/w
9	Antimalarial:	Chloroquine Phosphate Enteric Coated Pellet	250 mg.
10	Antifungal:	Itraconazole Enteric Coated Pellets	100mg
11	Anti –Depressant / Anti-	Venlafaxine Pellets	37.5/75mg.
	Psychotic / Anti-Convulsants:	Fluoxetine SR Pellets	90mg.
		Amitriptyline SR Pellets.	150mg
		Phenytoin Sodium SR Pellets.	100-300mg
12	Anti-Bacterial:	Doxycycline Hyclate enteric Coated Pellets	100mg.
		Sodium Amino Salicylate Enteric Coated Pellets	85mg
		Erythromycin SR Pellets.	30mg
		CloxacillinNa flavoured dispersible Pellets	250mg
13	Anti-Diabetic:	Gliclazide SR Pellets	30mg.
		Glibenclamide Pellets SR	10mg
14	Anti-Gout:	Allopurinol Pellets.	100mg
15	Vitamin's & iron:	Folic Acid Pellets	0.5mg.
		Calcium Panthothenate / Vitamin B12 / Thiamine /	50mg/75mg/90mg/120mg
		Mononitrate /Pyridoxine HCL / Niacinamide / vitamin C /	220mg
		Chromium as a Chromium Picolinate immediate Release	15mg
		Pellets.	125mg
		Carbonyl Iron Pellets.	
		Vitamin E Acetate	
		Zinc sulphate monohydrate SR	
16	Anti cardiovascular Drugs	Enalapril maleate Pellets.	40mg

Note:- SR–SUSTAINEDRELEASE
TR–TIMERELEASE
CR –CONTROLLED RELEASE

Various Excipients Used In The Formulation of Pellets [49, 50, 51, 52, 53, 54, 55]

Formulation aid or excipients are added to pharmaceutical dosage forms mainly to produce satisfactory levels of the drug at the intended site, to impact favorable characteristics to the dosage form and facilitate the manufacture of the product. Since pellets are intended to be administered orally. The excipients used in the pellet dosage forms are typically the same as those used in tablet or capsule formulation. Excipients that may be included in pellet formulation include.

Fillers

Fillers are water soluble or insoluble substances that are incorporated into pellet formulations, mainly to add bulk. Selection of filler should be based on the intended overall properties of the pellets. Some of the fillers used in pellets depending on the desired dose, the physical properties of drug, and manufacturing process involved, the amount of filler in the formulation can be as high as 99% or as low as 1%. If the filler component is the main ingredient of pellet formulation, its proportion essentially determine the properties of the pellets. It its apparent, therefore in some cases; the presence of filler in formulation may supersede the intended diluents function and contribute largely to the rate and extent of drug availability from pellets.

Two factors that impact heavily on the selection of filler are physicochemical and pharmacological inertness. The physicochemical stability of the filler also figures the stability of the pellets.

Example: Lactose, Manitol, Microcrystalline cellulose, Directly compressible starch.

Binder

Binder is adhesive materials that are incorporated in pellets formulation to bind powder and maintain pellet integrity. They are essential components of pellet formulations, regardless of the manufacturing process. Ex. Poly Vinyl Pyrrolidone (PVP), Cellulose derivatives like hydroxyl propyl methyl cellulose (HPMC), Ethyl cellulose.

Lubricants

Lubricants are substances that are incorporated in pellet formulations to reduce the coefficient of friction between individual particles or between the particles and the surface of processing equipment. Ex. Stearic acid, Talc, Polyethylene glycol.

Separating Agent

Separating agents are materials that absorb on surfaces and promote the separation of pellets into distinct units during a pelletization process. Pellets can develop surface charge during manufacturing and may tend to attract one another.

Disintegrants

Disintegrants are substances which in the presence of liquid, promote the disruption of solid dosage form, such as tablet, pellets, granules, capsules plugs or any other agglomerated materials to regenerate the primary particles that were originally compacted or agglomerated to produce the dosage form. Ex. Starch, PVP, Alginate, Cellulose derivative.

P^H Adjuster

P^H adjusters are substances that are incorporated in pellet formulation to influence the microenvironment of drug molecules for a variety of reasons. Generally, acid liable compounds are protected from acidic regions of the gastrointestinal tract through the application of an enteric film coat. Buffer systems may also be added to the core formulation to maintain the P^H of the core in the favorable range for drug stability. Ex. Acetate buffer, Phosphate buffer.

Surfactants

Surfactants are used in pellet formulation mainly for the same reasons that they are used in any other solid dosage form. They are employed to improve wet ability and enhance dissolution rates of poorly soluble and hydrophobic drugs. In most pelletization process, the initial formulation and subsequent growth of pellets depends, to some extent, on the liquid bridges that hold the primary particles together. Therefore it is important that the liquid (water in most cases) wet the particles effectively. That is, by lowering the surface tension of the binding liquid, surfactants tends to weaken the liquid bridges and make the forming pellets friable. Ex. Sodium lauryl sulphate, Ethylene glycol distearate, Sorbitan-tristerate.

Spheronization Enhancers

Spheronization enhancers are formulation aids that facilitate the production of spherical pellets, mainly during spheronization the balling. These substances not only confer plasticity that are essential for pellet strength and integrity. Ex.MCC, sodium CMC

Glidants

Flow characteristics play an important role during powder layering. Because the process require a well controlled powder feed rate to the binder solution, it is imperative that the powder does not adhere to the slides of the hopper and form bridges or rat holes. Ex. Silica derivatives, Talc, Corn starch. Ex. Talc, starch, Mg stearate

Release Modifiers

Release modifiers control the release kinetics of the drugs for sustained/controlled release from the pellets. These are applied on the pellet surface only after the application of Barrier coat which acts as a sealant. Release modifiers are usually applied on pellet surface using Fluidized bed coater. Ex. Ethylcellulose, carnauba wax, shellac.

Table No.1.2 Overview of Various Excipients With Examples.

Filler	MCC, starch, sucrose, lactose, mannitol
Binder	Gelatin, HPC, HPMC, MC, PVP, sucrose, starch
Lubricant	Calcium stearate, glycerin, PEG, Mg. stearate
Separating agent	Kaolin, talc, silicon dioxide
Disintegrant	Alginates, croscarmellose sodium
pH adjuster	Citrate, phosphate, meglumine.
Surfactant	Polysorbate, SLS
Spheronization enhancer	MCC , sodium CMC
Glidant	Talc, starch, Mg stearate.
Release modifier	Ethyl cellulose, carnauba wax, shellac.

Table No.1.3 Recent Literature on Pelletiztion.

S. no.	Drug	Category	Reason for formulating into pellets	Method used for formulation of pellets	Excipients used	Results	Reference no.
1	Ambroxol Hcl	Mucolytic agent	To investigate the effect of Ammonio Methacrylate Copolymer Dispersion TypeA and Ammonio Methacrylate Copolymer Dispersion Type B (Eudragit RS 30D) combination in different weight ratios on the release kinetics of Ambroxol Hydrochloride from coated pellets	Extrusion-Spheronisation process	Eudragit-RL-30D, EudragitRS-30D	Coating polymers Eudragit RL 30D and Eudragit RS 30D can be used as effective rate retarding polymers for controlled release of AmbroxolHcl pellets	56
2	Ambroxol Hcl	Mucolytic agent	To develop and characterize sustained release pellets of AmbroxolHCl using Ethyl cellulose 7cps and Ethyl cellulose 50cps.	Wruster process	Ethylcellulose 7 cps, Ethylcellulose 50cps	AmbroxolHcl pellets can be prepared using Ethyl cellulose 7cps and Ethyl cellulose 50cps. Ethyl cellulose 50cps with 2%w/w was found to be robust	57
3	Ascorbic acid	Antioxidant	To formulate zinc sulfate, ferrous sulfate and ascorbic acid on the same pellet by combination pelletization technique and there and in vitro dissolution studies were performed by using United States Pharmacopoeia (USP) apparatus type II	Wruster process	HPMC 5cps, HPMC 15cps, Methocel K15M	Hydrophobic matrix pellets prepared using lower concentrations of Methocel K15M(<10%) CR were found to be best suited for modulating the delivery of the Ascorbic acid from the combination	58
4	Ascorbic acid	Antioxidant	To prepare and evaluate the pellets, containing a highly soluble drug (ascorbic acid), by the extrusion-spheronization process and coated with a release	Extrusion-Spheronisation process	Kollicoat SR30D	Kollicoat SR 30 D can be used for preparation of pellets which has more effective control over the release of the drug than extrusion/spheronization technique	59

			controlling polymer. The coating was applied to three batches of the pellets with a dispersion of Kollicoat SR 30 D				
5	Aspirin	NSAID	To ensure the suitability of HMC as an enteric coating technique. Aspirin was used as model drug due to its stomach mucosal irritation and ulcerogenic property. Pellets of aspirin prepared by extrusion-spheronization technique were used as coating substrate	Hot Melt Coating	Stearic acid,Palmitic acid	The study indicates that both the hot-melt coating agents (PA and SA) were found to have excellent enteric coating ability. At 5% w/w wax coating level, negligible amounts of drug were released in the acidic environment after 2 hr. At and above a 7.5% w/w coating, practically zero drug release was observed in acidic pH.	60
6	Carteolol Hcl	Cardiac necrosis	To prepare carteolol hydrochloride matrix sustained-release pellets, and to compare its performance *in vivo* with carteololcommon tablets	Extrusion-Spheronisation process	MCC, Ethylcellulose,CMC-Na,Steric acid	The carteolol hydrochloride sustained-release pellets have reasonable formulation and simple preparation technology; the pellets acquired perfect sustained-release properties *in vitro*/in vivo.	61
7	Choloroquine Diphosphate	Anti-malarial	To formulate enteric coated Chloroquine diphosphate were designed with a view to enhance patient compliance by granulation and dip coating method	Dip coating method	Cellulose acetate phthalate	Chloroquine diphosphate without dibasic calcium phosphate cause float on the dissolution medium not goes to intestine but so better release profile	62
8	Diclofenac Sodium	NSAID	To formule and Evaluate of alcohol resistant dosage forms of Diclofenac sodium by various polymers.	Extrusion-Spheronisation process	Carbopol, Eudragit RSPO, Eudragit RLPO	The pellets prepared were found to alcohol resistant and dissolution profiles were comparable with the marketed formulation.	63
9	Diltiazem	Anti-hypertensive	To prepare hot melt matrix pellets of dilitiazem hydrochloride, using melt extrusion-spheronization methodology, which demonstrates extended drug release profile and complies with the dissolution pattern stated in USP.	Hot Melt Extrusion	Compitrol 888ATO, stearic acid	Diltiazem pellets can be prepared by Holt Melt Extrusion which has freedom from use of solvent during processing as well as short processing time, the products exhibited greater physicochemical stability.	64
10	Diltiazem	Anti-hypertensive	The effect of cellulose polymers Ethyl Cellulose &Hydroxy Propyl Methyl Cellulose, was evaluated on the release profile of drug from sustained release pellet.	Wruster process	HPMC 5cps,HPMC 15cps, Ethylcellulose 7cps	Polymer content with highest concentration of Ethyl cellulose on the pellets shows highest release retarding rate of the drug. The retarding capacity decreases with the decreased concentration of ethyl cellulose.	65
11	Dipyridamole,Aspirin	Anti-Platelet agent	To develop stable formulation of Aspirin /extended release Dipyridamole Capsules.	Wruster process	Eudragit S100,HPMC HP55,Triacetin	Pellets were prepared having aesthetic and pharmaceutically accepatance and a proposed shelf life.	66

12	Domperidone	Anti-emetic	To improve the dissolution behavior of Domperidone, a dopamine antagonist.	Extrusion-Spheronization	Sodium lauryl sulphate	Formulation prepared containing 0.06% sodium lauryl sulfate yielded desired drug release within 45 minutes. This definitely improves patient's compliances and reduces the gastric side effect	67
13	Duloxetine	SSRI	To develop a delayed release pellets dosage form of duloxetine hydrochloride with a suitable polymer by using suspension layered method	Suspension layering method	EudragitL30-D55,triethylcitrate,HPMC HP55	Formulation with Eudragit L 30 D55 showed enteric coated pellets with long term stability	68
14	Duloxetine	SSRI	To prepare robust and stable formulation and evaluation of duloxetine hydrochloride delayed release enteric coated pellets in capsules	Suspension layering method	HPMCP HP55,HPMCP HP-50	Formulation of Duloxetine Hydrochloride (MUPS) delayed release pellets in formulation [HPMCP (HP-50 and HP-55, 1:1)] was found to be optimized	69
15	Duloxetine	SSRI	Duloxetine hydrochloride is acid labile drug so Duloxetine hydrochloride enteric coated pellets were formulated using fluidized bed process and different enteric coating polymers.	Suspension layering method	HPMC 6cps,HPMC15cps,triethyl citrate	increase in the concentration of the barrier polymer increases the extent of obstruction of drug release, The concentration of the binding polymer did not affect acid resistance or the release in phosphate buffer	70
16	Erythromycin	Antibiotic	To prepare Erythromycin Base Pellets by using Extruder and Spheronizer and to coat the resulting spherules with enteric coating polymer.	Extrusion-Spheronization Process	Eudragit L-30-D-55,Triethyl citrate	Eythromycin pellets offer a advantage of having low gastric emptying rate and overall transit time than controlled release tablets	71
17	Esomeprazole	Proton pump Inhibitor	To conduct a preliminary investigation into preparing pellets containing esomeprazole magnesium by means of an extrusion spheronization process, using povidone and crospovidone.	Extrusion-Spheronization Process	Povidone,Cross Povidone	This study has demonstrated that the use of povidone (as a binder) and crospovidone (as a processing aid) are viable options for producing pellets using the extrusion spheronization process	72
18	Flubiprofen	NSAID	This study investigated sustained release pellets of flurbiprofen (FB) using RL30D as a coating material. The absorption properties was compared with those of common tablets.	Powder Layering Technique	HPMC, Eudragit RL 30D, Eudragit RS 30D	RL30D is used as coating material as the release patterns are influenced by the intrinsic physical property and was comparible with tablet formulation with no evidence of dose dumping.	73
19	Gliclazide	Anti Diabetic	the present study sustained release pellets of Gliclazide were prepared by drug loading on neutral pellets followed by spraying coating suspension on the drug loaded pellets to a thickness equivalent to theoretical polymer load of 6 % (*w/w*). The coating suspension were prepared by using combination of ethyl cellulose and hydroxy	Wruster Process	HPMC 5cps, HPMC 15cps, Ethylcellulose 7cps,	Gliclazide pellets were prepared using powder layering technique. Coating of the drug loaded pellets were done using different mixtures of Ethyl Cellulose 7 cps and Hydroxy Propyl Methyl Cellulose 5 cps as rate retarding polymers.	74

			propyl methyl cellulose				
20	Glimepiride	Anti Diabetic	To improve bioavailability and half-life we have designed sustained release pellets-filled-capsules of glimepiride.	Extrusion-Spheronization Process	Ethylcellulose(18-22cps), HPMC 5cps	Glimepiride pellets into an empty HPMC capsule shell which releases 97.29± 0.22 % of drug of the dose within for a period of 24 hrs, increases the half-life and bio-availability of glimepiride	75
21	Glipizide	Anti Diabetic	The present study, attempt was made to prepare alcohol resistant pellet formulations of glipizide.	Extrusion-Spheronization Process	Eudragit RSPO, EudragitRLPO, Cellulose Acetate Butyrate	Glipizide pellets prepared from extrusion spheronization showed resistance to alcohol dose dumping when coated with Egudragit polymers	76
22	Glipizide	Anti Diabetic	Pellet used in order to decrease the dosage regimen which is twice daily for conventional tablet formulation of Glipizide thus the pellet formulation are aimed to maintain the necessary blood Glipizide concentration for the treatment.	Pan Coating Method	Eudragit RL100 PM, Eudragit RS 100 PM, Polyethylene Glycol	The release time may be extended by changing the coating layer composition and coating layer. Further studies are needed for determining the in vivo performances of these formulations for the aim of extending the release of glipizide.	77
23	Ibuprofen	NSAID	To develop ibuprofen (IBU) - loaded pellets by melt solidification technique using Gelucire 50/13 (GL) as a lipid carrier in different concentrations	Melt Solidification method	Gelucrie 50/13.	Increasing GL amount also retarded the drug release. Gelucire 50/13 can be considered as an effective carrier for the preparation of sustained delivery of IBU.	78
24	Indomethacin	NSAID	To evaluate the effect of two factors (ratio of Eudragit S100 and Eudragit L100 and the coating level) on indomethacin release from pellets in order to optimize coating formulations for colonic delivery	Wruster Process	Eudragit S100, Eudragit L100	Formulation consisted of Eudragit S100:Eudragit L100 in ratio of 4:1 at 20% coating level has potential for colonic delivery of indomethacin pellets.	79
25	Indomethacin	NSAID	To develop an extended release pellet formulation of indomethacin by the centrifugation (rotary fluid bed granulation) or powder layering method.	Powder Layering method	Eudragit NE 30D, Opadry, Sodium dodecyl sulfate	Indomethacin pellets coated with Eudragit NE 30 D, SDS and Opadry achieved extended release profiles, 500g nonpareil, 400 g indomethacin, 400 ml HPC 8%, 61 g talc, 50 g Opadray® and coating of 37.5 g Eudragit NE 30 D, 1.8 g SDS, 7.5 g was optimised	80
26	Isoniazid	Anti TB	Formulation was designed to release the two drugs in a controlled manner with rifampicin being released in the stomach and isoniazid 3-4 h later in the intestine.	Extrusion-Spheronization Process	Cellulose Acetate Phthalate, Eudragit	Isoniazid pellets containing 30% enteric coating(Cellulose Acetate Phthalate, Eudragit RL100.) was found to be optimised.	81

					RL100.		
27	Itraconazole	Antifungal	To prepare and evaluate immediate release itraconazole pellets and comprehensive studies of the same.	Wruster Process	HPMC-5cps,PEG20000	These results indicate that pellets containing 10 % HPMC of total weight of pellets give better quality of itraconazole pellets for immediate release	82
28	Ketoprofen	NSAID	To study the effect of HPMC on in-vitro dissolution of Ketoprofen from micro pellets.	Direct Pelletization	HPMC	Sustained release micro pellets containing water insoluble drug were successfully prepared employing ionotropic gelation technique, entirely avoiding the use of organic solvents.	83
29	Lansoperazole	Antiulcer	To develop a stable, pharmaceutically equivalent, robust and delayed release micro pellet formulation of Lansoprazole.	Suspension Layering Technique	HPMC K5, Eudragit L 30, Eudragit D55.1	Lansoprazole Enteric Coated Pellets drug delivery system by using Eudragit L-30D-55, HPMC K5 as retarding agents. Was formulated and was compared with the innovator formulation	84
30	Lansoperazole	Antiulcer	To make a comparative evaluation among these polymers and excipients and to assess the effect of physicochemical nature of the Lansoperazole on the drug release profile	Wruster Process	HPMC E5,Acrycoat L30D	Formulation done by FBC process was compared with marketed product by an *invitro* study, which definitely improves patient's compliances and reduces the gastric side effect..	85
31	Mebeverine	Anti Spasmotic	To formulate and evaluate modified release mebeverine Hydrochloride capsules containing coated mebeverine hydrochloride pellets by eudragit L-100 & ethylcellulose N-50.	Drug Layering method	Eudragit L100,Ethylcellulose N50,PEG6000	Pellets no need of disintegration time. As pellets are small in size they enter into the systemic circulation very fast, there was no accumulation of drug in the body. Drug release rate was more when compared with the innovator (Colofac MR)	86
32	Meloxicam	NSAID	the ability of κ-carrageenan as a pelletizing agent to improve the disintegrating properties of various disintegrants like sodium starch glycollate, β-cyclodextrin, crossprovidone and kollidon as a means of increasing dissolution rate of poorly soluble drug was evaluated	Extrusion-Spheronization Process	Modified starch,k-carrageenan,Microcrystalline cellulose	κ-carrageenan pellets prepared by extrusion–spheronization lead to their disintegration in drug dissolution medium which eventually results in to significantly improved dissolution rates of the poorly soluble drug.	87
33	Nifedipine	Anti angina	To formulate and enhance the bioavailabilty of nifedipine which is a poorly soluble drug	Wruster Process	Ethyl cellulose N20, HPMC E5	Nifidepine pellets prepared with ethlycellulose N20 of 0.5% and HPMC E5 with 20% concentrations was found to be optimised	88

34	Rabeprazole Sodium	Proton pump Inhibitor	To prepare delayed release pellets of rabeprazole using HPMC based sub coating and methacrylic acid copolymer based enteric coating	Suspension method	Polyplasdone INF10, Polyplasdone XL 10	Pellets can be prepared but the safer side with acid resistance was at 30% enteric coating and 8% sub-coating was optimised.	89
35	Ramipril	Anti Hypertensive	To produce Multiple Unit Particle System (MUPS) of stabilized Ramipril pellets, Hydrochlorothiazide for better bioavailability with improving stability and bioavailability of Ramipril	Wruster Process	HPMC, Crosscaramellose sodium	Ramipril pellets with polymer coating and Hydrochlorothiazide and other excipients shown better stability of Ramipril along degradation and synergistic effect amongst hypertension in immediate delivery	90
36	Salbutamol	Anti Asthma	To prepare sustained-release pellets of salbutamol sulphate using extrusionspheronization technique followed by coating with the aqueous dispersion of methacrylic acid esters (Eudragit RS® 30 D) and commercial aqueous polyvinyl acetate dispersion (30% dispersion) (Kollicoat SR® 30 D).	Extrusion-Spheronization Process	Eudragit RS30D, Kollicoat SR 30D	salbutamol sulphate prepared by extrusion-spheronization technique was successfully coated in Wurster column with Eudragit® RS 30 D and Kollicoat® SR 30 D using a fixed amount of plasticizer, triethyl citrate (TEC).	91
37	Simvastatin	Anti Hyperlipidemic	To design oral controlled release matrix pellets of water insoluble drug Simvastatin, using blend of Sodium Alginate (SA), Eudragit RSPO and Eudragit RSPO as rate controlling polymers, micro crystalline cellulose (MCC) as spheronization aid and calcium carbonate to enhance sodium alginate matrix strength.	Extrusion-Spheronization Process	Eudragit RSPO, EudragitRLPO	Pellets prepared with Eudragit RSPO and Eudragit RPLO had high friability that was because of poor matrix formulation ability of Eudragit polymers.In combination with sodium alginate Eudragit RSPO and Eudragit RLPO produced pellets with acceptable physical and flow properties.	92
38	Tamsulosin	UIT	To develop and optimize oral extended release formulation for tamsulosin hydrochloride using a combination of ethyl cellulose N-50 and Eudragit L-100 as a coating material.	Drug Layering process	Eudragit L-100, Ethlylcellulose N-50	The optimal coating formulation was achieved with Eudragit L-100 9% of the weight of the drug loaded pellets and ethyl cellulose N-50 with 25% of the Eudragit L-100 content	93
39	Terbutaline	Anti Asthma	To improve bioavailability, half-life and efficacy the sustained release film-coated pellets of terbutaline sulphate were designed	Extrusion-Spheronization Process	HPMC, Ethlylcellulose	Pellets developed by filling film coated Terbutaline sulphate pellets into an empty HPMC capsule shell which releases 96.83±1.64 % of drug of the dose within for a period of 24 hrs.	94
40	Venelafaxine	Anti-Depressant	To avoiding first pass metabolism and controlling the release of drug for prolog period of time. Extended released pellets containing venlafaxine hcl was prepared	Wruster Process	Hypermellose 15cps, EudragitNE 30D	The formulation with 0.45% HPMC, 65.94% MCC and 13% Eudragit NE 30D coating was consider as a best product with respect to perfect size and shaped pellets and In-vitro drug	95

			using an extrusion spheronization technique.			release study.	
41	Venelafaxine	Anti-Depressant	Extended release pellets of Venlafaxine was prepared by extrusion spheronization method using combination of hydrophobic low melting wax and hydrophilic polymers as release retarding agent.	Extrusion-Spheronization Process		Venlafaxine hydrochloride extended release matrix pellets was successfully formulated with Sterotex® K, HPMC K 4M and Polyox WSR ®303 as matrix former polymer.	96
42	Venelafaxine	Anti-Depressant	To prepare venlafaxine extended release pellets by extrusion spheronization technology, coating them with mixture of rate controlling polymers Ethyl cellulose and different grades of (Hydroxy propyl methyl cellulose (HPMC)	Wruster Process	Ethlylcellulose, HPMC	Pellets prepared were compared with the innovator sample (VENLAR) and it has a better bioavailablity.	97
43	Verapamil	Anti Hypertensive	To prepare a floating drug formulation in a gelatin capsule filled with verapamil hydrochloride pellets for better solubility in an acidic environment of the stomach may result in greater amount of the drug absorbption.	Spheronization Process	AvicelPH 101, Avicel PH102, Arbocel P290, Eudragit NE 30 D55, Eudragit L 30D 55, Eudragit Rl30 D	Floating pellets were prepared with verapamil which offered a longer stay in the maximum solubility conditions unlike the conventional tabelets.	98
44	Verapamil	Anti Hypertensive	The present study was to develop a multiple-unit, extended release drug delivery system for verapamil hydrochloride and to evaluate the influence of organic acids on drug release from pellets.	Extrusion-Spheronization Process	Fumaric acid, Mallic acid	The dissolution rate of the drug from pellets containing fumaric acid was high even in the elevated pH corresponding to intestine.	99
45	Verapamil	Anti Hypertensive	To develop a multiple-unit, extended drug delivery system for prolong drug release throughout the day, having pH dependent solubility and is being used successfully for the treatment of hypertension	Extrusion-Spheronization Process	HPMC E5, Ethlylcellulose 5cps, Eudragit	PH-independent drug release was achieved from pellets consisting of organic acid in their core when coated with selected pH-independent coating polymers like ethyl-cellucose, hydroxypropylmethyl cellulose and Eudragit polymers	100

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