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# A REVIEW ON FORMULATION OF SUSTAINED RELEASE PELLETS BY DIFFERENT TECHNIQUES

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## ABSTRACT

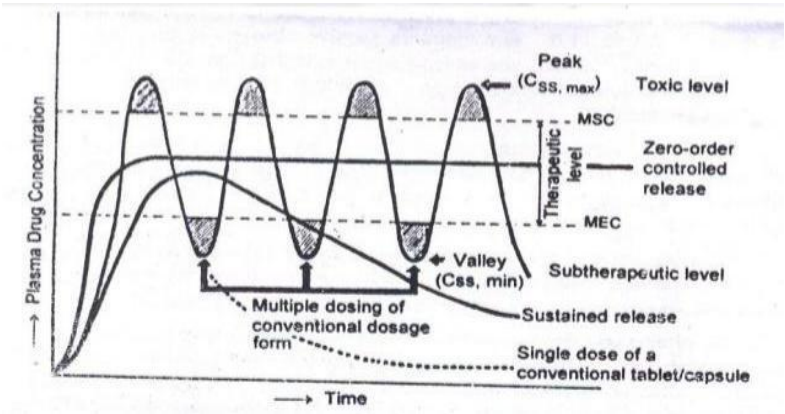
The best and fastest choice for administering different medications is oral drug delivery because it has the largest active surface area of any drug delivery system. Sustained release drug delivery has several benefits over traditional dosage forms such as increased patient compliance due to less frequent drug administration, maximum drug consumption, increased safety margin of potent drug, reduction of fluctuation in steady-state drug levels, reduction in healthcare costs due to better therapy, and shorter treatment period. The improvement of drug therapy is the primary objective of sustained release forms, which is determined by the connection between the benefits and drawbacks of sustained release system. By avoiding fluctuations in the therapeutic concentration of the drug in the body, sustained release is another hopeful method for reducing side effects. The therapeutic impact and safety of a drug will be optimised by the sustained release product, while patient convenience and compliance are also improved. According to recent trends, multiparticulate drug delivery systems are particularly well suited for producing extended release oral formulations with low dose dumping risk, flexibility in blending to achieve various release patterns, and repeatable and brief gastric residence times. The quantity of drug contained in pellets as well as the carrier used to create them are among the variables that affect how quickly the drug is released from them. Pellets thus greatly expand the potential for developing novel controlled and prolonged release oral formulations, thereby advancing pharmaceutical research. Micrometric characteristics, surface morphology, drug concentration, in-vitro drug release, and a dissolution kinetic model were all assessed for the pellets.

**KEYWORDS:** Pelletization, Extrusion Spheronization, Sustained Release Pellets, Powder Layering, Melt Extrusion.

## INTRODUCTION

Irrespective of the mode of delivery (immediate, sustained, or controlled release) and the design of dosage forms (either solid dispersion or liquid), all pharmaceutical products intended for systemic delivery via the oral route of administration must be developed within the inherent characteristics of GI physiology. To create an oral pharmaceutical dosage form successfully, a systemic approach involving pharmacokinetics, pharmacodynamics, and formulation design is required.[1-5]

To improve selectivity and extend the length of action, sustained release dosage forms are intended to supplement the drug's pharmaceutical activity.[6] Due to its maximum therapeutic efficacy and patient compliance oral sustained release systems are becoming more important in the industry. A reservoir, monolithic, matrix system is an oral sustained release device.[7] Several physiological factors frequently make oral delivery difficult. Pharmaceutical difficulties brought on by the drugs' intrinsic physicochemical properties and the wide range of GI conditions, including pH, food presence, transit times, and expression Of CYP3A and P-Glycoprotein (P-Gp), as well as enzymatic action in the gastrointestinal tract.[8,9] Any drug delivery system that accomplishes a slow release of the drug over an extended period of time is considered a sustained release system. A controlled-release device is one that successfully maintains constant drug levels in the blood or the intended tissue.[11]




### Multiparticulate drug delivery system

The oral formulation of the multiparticulate drug delivery system is appropriate for controlled or delayed release. It has benefits like dose dumping. Early in the 1950s, the idea of a

multiple unit dosage form was first presented. As its name suggests, this kind of dosage unit consists of multiple distinct units. These dosage forms can be characterised as oral dosage forms made up of numerous tiny discrete units, each of which possesses a desired property. Microgranules, pellets, and microcapsules are some of the numerous unit dosage forms.[10]

**Pellets**

Pellets are small, spherical, free-flowing granules with a narrow size distribution that usually have a diameter between 500 and 1500 um and contain the active pharmaceutical ingredient (API) as a number of tiny independent molecules subunits. These subunits are packed into a sachet and enclosed or compressed into a tablet to give the suggested total dose. Pellets that easily disperse in the G.I.T. maximise drug absorption and reduce mucosal irritation caused by some irritant drugs locally. Reduced variations in gastric emptying rates, flexibility for dosage forms, and simplicity of coating are some benefits of pellet over tablet.[12] They can be designed with an immediate release dosage form, a sustained release dosage form that releases the drug over an extended period of time, or they can be coated to transport the drug to a specific site in the digestive system. [13]

Without changing the formulation or process, they can be divided into desired dose strengths and blended to deliver incompatible bioactive agents concurrently or particles with different release profiles at the same site or at different sites within the digestive system.[14] Due to their free-flowing nature, pellets offer a high degree of freedom. Therefore, without any problems, they can be packed. Pellets had a uniform film covering due to their spherical shape and low surface area to volume ratio.[15] Pellets avoid the dosage dumping effect, resulting in a smoother plasma concentration profile and more gradual drug absorption than tablets, which further reduces the negative effects of medications.[16]

**Advantages of pellets**

- They can be divided into the required dosage strength without modifying the manufacturing procedure or formulation.
- Enhance the product's appearance.
- Compared to powder, pellets are smaller and have better flow properties.
- Ease of use, such as while filling pills.
- Mixing unrelated components into a single dosage form.
- Varying release rates at various gastro-intestinal tract locations.

- The use of film coating to protect active substances from oxidation or moisture-related degradation.
- Greater patient approval when administered in capsules than in tablets due to the former's elegance.
- Because of the low surface-to-volume ratio, this form is ideal for applying film coatings.
- High drug loading capability without the production of big particles.
- Pellets reduce adverse effects and are less susceptible to the dose dumping effect.

**Disadvantages of pellets**

- The process of filling pellets involves filling capsules, which can raise costs.
- When pellets are tableted, the pellets' film covering is destroyed.
- The pellets' size may differ from formulation to formulation, but it typically falls within the range of 2mm and 0.05 mm.
- Low drug loading.
- Relatively greater demand for excipients.
- A lack of manufacturing effectiveness and reproducibility.

**Objectives of sustained release dosage form**

1. To keep the drug concentration consistent for the desired period of time.
2. To administer doses less frequently compared to a conservative dosage type.
3. It should minimise or completely eliminate side effects by delivering active entity to the site of action.[17]
4. This may necessary for localization to cells or delivery to certain bodily regions or receptors.
5. It is possible to increase the safety margin for potent drug.
6. Patients who are susceptible may experience fewer adverse side effects, both local and systemic. [18]

**Advantage of sustained release drug delivery**

1. A reduction in consumption frequency.
2. Reduce adverse consequences.
3. Consistent drug delivery over time.
4. Increased patient adherence.[19]

**Disadvantages of sustained release drug delivery**

1. Cost increases.
2. Toxic effects of dose dumping.
3. Uncertain and frequently poor in vitro-in vivo correlation.
4. Risk of adverse reactions or toxicity following the rapid release of the medication from its container (mechanical failure, chewing or masticating, alcohol consumption).
5. Greater chance of first-pass clearance.
6. The demand for more patient counselling and education.[20]

**Various techniques of pellitization**

**A. Powder layering techniques**

**B. Solution / Suspension layering technique**

**C. Extrusion- Spheronization technique**

**D. Melt extrusion technology**

**A. Powder layering technique**

The following are some of the stages this technique involves:

1. Sifting/milling
2. Loading of non pareil seeds
3. Drug coating
4. Drying
5. Sizing
6. Encapsulation

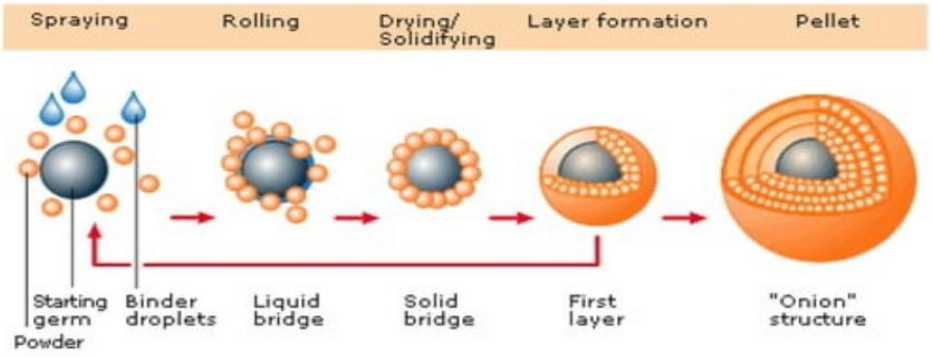
A number of methods can be used to turn granules into pellets. A seed material can be coated with a drug suspension or solution to create pellets with a uniform size distribution and usually very good surface morphology. These characteristics are particularly desired when the pellets will be coated for a controlled release over a period of 24 hours. The starting seeds, which could be inert materials or drug granules, are placed on top of successive layers of solutions and/or suspensions of drug substances and binder. In theory, the same variables that affect coating processes also affect solution or suspension layering, requiring essentially the same manufacturing machinery. Initially, liquid bridges derived from the sprayed liquid are used to .bind the drug particles to the starting seeds and later to the forming pellets. These liquid bridges are ultimately replaced by solid bridges made of a substance that is soluble in the liquid, such as a binder present in the application medium, or from any other substance,

including the drug substances. The medication and binder solution are successively layered until the desired pellet size is obtained. It is crucial to precisely deliver the powder at a predetermined rate throughout the procedure and to do so in a way that maintains equilibrium between the application rate of the binder liquid and the delivery rate of the powder. If the powder delivery rate is not kept at pre equilibrium levels, over-wetting or dust generation may happen, making it impossible to maximise both the quality and yield of the final product. Due to possible inter-particle and wall-to-particle friction that could occur towards the end of the layering process, it is likely that fines will be produced and show in the finished product, lowering the yield. If the powder delivery rate is not kept at pre equilibrium levels, over-wetting or dust generation may happen, making it impossible to maximise both the quality and yield of the final product. Due to possible inter-particle and wall-to-particle friction that could occur towards the end of the layering process, it is likely that fines will be produced and show in the finished product, lowering the yield. The issue can be solved by applying the application medium to the cascading pellets at the conclusion of the layering process, which will raise the moisture content at the surface of the pellets and facilitate the arranging of the fines onto the pellets. For this, equipment like rotating granulators, centrifugal fluid bed granulators, and tangential spray equipment are used.[21]

**B. Solution / Suspension layering technique**

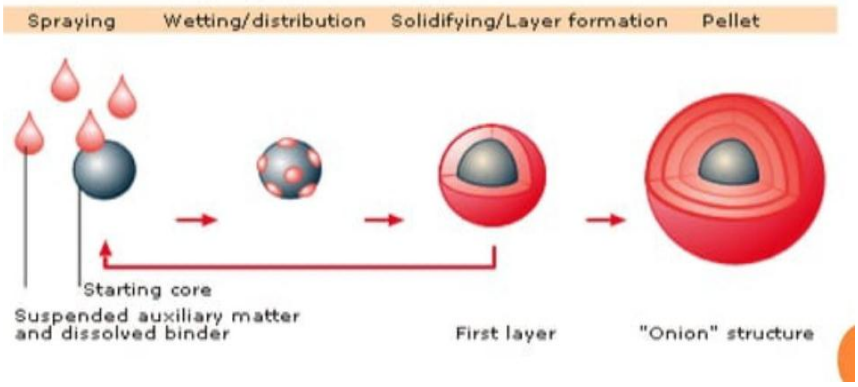
Various steps involved in this technique are as follows:

1. Mixing/Milling
2. Loading of non pareil seeds
3. Drug coating
4. Drying
5. Sizing
6. Functional coating
7. Encapsulation




**Principle of Powder layering process**

In this technique, starter seeds—which could be inert materials or crystals or granules of the same drug—are covered with consecutive layers of solution and/or suspensions of drug substances and binders. Solution or suspension layering requires the same processing equipment as coating procedures and is affected by the same variables.[22] As a result, the production of pellets has been accomplished effectively using conventional coating pans, fluid bed granulators, and Wruster coaters.




The Wruster coating process, which was invented about thirty years, has undergone extensive design modifications and refinement to become the perfect tool for the solution/suspension layering process used to make pellets. Fluid bed equipment has a high intrinsic drying efficiency, and this combined with the creative and effective design elements of the Wruster process has enabled the machines to take the lead in pharmaceutical processing technology. The Wruster method's drawback is the nozzle's difficulty of access. When layering, if the nozzles become clogged at any point, the procedure must be stopped, and the spray guns must be taken apart for cleaning. The mixture can be screened to reduce the issue, or a sprayer with a larger nozzle can be used. The potential overlap of adjacent

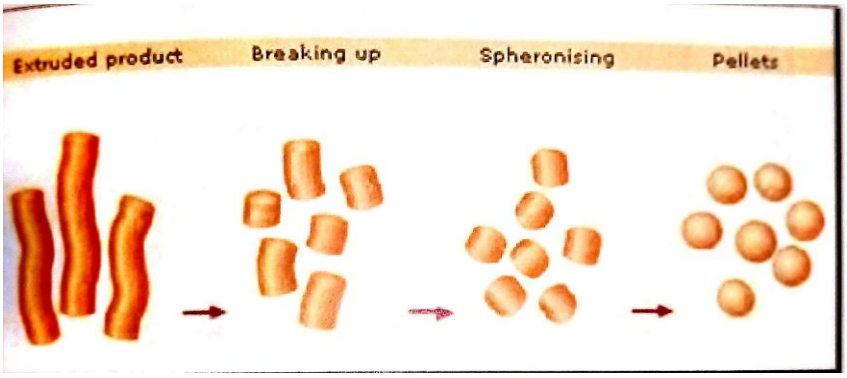
spray zones is another factor that makes the procedure difficult when multiple nozzles are employed. The spray zone overlap can be reduced by using the air cap on the spray gun's end, even though the nozzle's location is fixed.

A formulation with the desired viscosity is created during processing by first dissolving or suspending all of the formulation's components in a suitable amount of application medium. This formulation is then sprayed onto the product bed. As long as the drying conditions and fluid dynamics are favourable, the sprayed droplets immediately contact the started seeds and distribute evenly on the surface. Then comes a drying phase, which causes the dissolved substances to precipitate and create solid bridges, holding the formulation's components more firmly as additional coatings are applied to the started seeds. The procedure is repeated until the pellets reach the targeted level of potency and the desired amount of drug material is obtained. As much as possible, no new nuclei should develop, and the number of particles must remain constant. The size of the pellets does, however, grow over time, and as a consequence, the system's overall mass grows. For the effective development of a palletized product, process variable optimisation is challenging. Although it is possible to create pellets from a formulation without binders, the layers of drug applied almost always have a tendency to separate from the cores in the later stages of the layering process or in the following drying phase. In order to give the pellets strength during this procedure, binders are frequently used. Typically, they are low-molecular-weight polymers that can be used with the drug ingredient.[22]

### C. Extrusion and Spheronization

Various steps involved in this technique are

i. Encapsulation
ii. Sifting/milling
iii. Mixing/binding
iv. Extrusion
v. Spheronization
vi. Drying
vii. Sizing
viii. Coating
ix. Encapsulation




The idea of multi-particulate dosage forms was first proposed in the 1950s, but as the use of multi-particulate extended release (CR) oral dosage forms has grown, there has been an increase in interest in the processes used to make these dosage forms.[23] For the preparation of multi-particulate CR dosage forms, it has been widely used as a potential technique and as a future method of preference.[24]

**Figure.5. Process of spheronization**

Dry mixing, wet granulation, extrusion, spheronization, drying, and screening are all steps in this multi-step procedure. In the first stage, the drug and excipients are dry-mixed in appropriate mixers. Next comes wet granulation, in which the powder is transformed into a plastic mass that is simple to extrude. The extruded strands are then introduced into a spheronizer, where they are instantly split into short cylindrical rods upon contact with the revolving friction plate and propelled outward and upward by centrifugal force against the stationary wall of the processing chamber. Once the required sphericity is attained, the particles finally return to the friction plate due to gravity, and the cycle is repeated. The technology is distinctive in that it can produce extended-release pellets in specific circumstances in a single process, eliminating the need for additional film coating. It is also

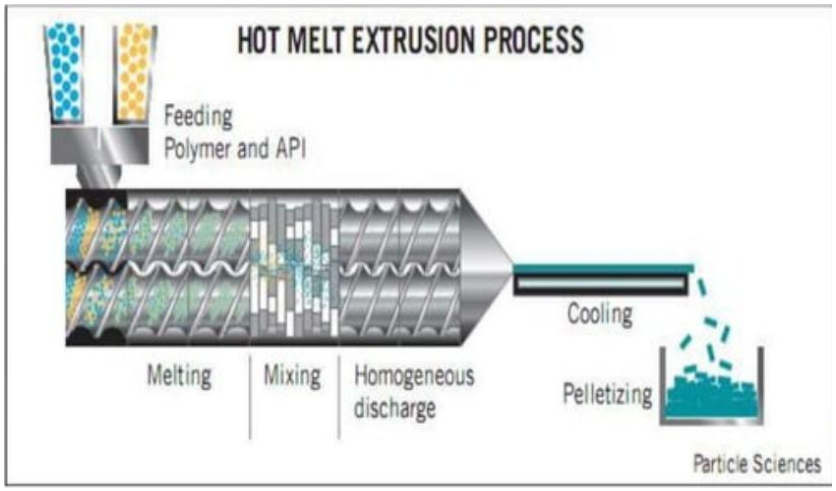
suitable for the manufacture of pellets with high drug loading. Extrusion-spheronization is a multi-step procedure requiring a variety of equipment and unit activities. The extruders and spheronizer, however, are the most important processing tools that, in essence, determine how the process will turn out altogether.[25]

Currently available extruders fall into three categories: screw-fed extruders, gravity-fed extruders, and Ram Extruders. These extruders vary in design elements and operational principles. Screw-fed extruders move the material horizontally by having screws that revolve around the horizontal plane. Both longitudinal and radial screw extruders are possible. A loading zone, a compression zone, and an extrusion zone make up an axial extruder, which has a die plate positioned axially. Jacketed cylinders regulate the product temperature while it is being extruded .In radial extruders, the material is extruded radically through screens positioned around the horizontal plane of the screws, with a short transport zone.

The rotary cylinder and rotary gear extruders, which are both gravity-fed extruders, differ mainly in the layout of their two counter-rotating cylinders. One of the two counter-rotating cylinders in the rotary-cylinder extruder is empty and perforated, while the other cylinder is solid and serves as a pressure roller. Two hollow, counter-rotating gear cylinders with counter-bored apertures compose the so-called Rotary-gear extruder. In ram extruders, a piston moves the substance and pushes it through a die at the very end. Ram extruders are favoured when developing formulations because they make it possible to measure the rheological characteristics of the formulation. Filler, lubricants, and pH modifiers are formulation elements that are essential for creating pellets with the desired properties during an extrusion-spheronization process. For extrusion, the granulated mass needs to be plastic, adequately cohesive, and self-lubricating. The extrudates must break at the proper length and have enough surface moisture to facilitate the formation of uniform, spherical pellets during the spheronization phase.[26]

### C. Melt-Extrusion technology

The most popular method currently used, aside from the extrusion spheronization technique for producing spherical pellets, is wet mass extrusion. However, since the granulating fluid used in this process is typically water, many drugs show stability issues. Furthermore, if controlled release properties are to be kept, pellets need a film coating because they release drugs quickly.[27,28]




It has recently been reported that spherical pellets can be produced without the use of water or other solvents using a novel hot-melt extrusion and spheronization method. This technique has the benefit of eliminating water-related processing instability issues. It has also been beneficial because the melt-extruded pellets don't need additional film coating because the drug release is diffusion-controlled. Initially used in the plastics industry, hot melt-extrusion is slowing gaining acceptance in the pharmaceutical sector for the manufacture of pellets, immediate-release and sustained-release tablets, and transdermal drug delivery systems.[29,30,31] Three fundamental stages make up the melt extrusion process: melting or plasticizing a solid material, shaping the molten material, and solidifying the material into the desired shape. An extruder inside a heated barrel that has three distinct sections, a spheronizer, and a material feed hopper make up a hot melt extrusion machine. The material is constantly fed from the feed hopper into the extruder, which has a heated barrel with a rotating screw inside of it. After being evenly divided into cylindrical pieces, the extrudate is spheronized to create pellets of a consistent size. The extrudate should be partially softened, allowing for easier deformation and ultimate spheroid formation, and the temperature maintained in the spheronizer should be high enough to accomplish these goals.

**Evaluation of pellets**

**1) Flow property[33-40]**

Flowability could be predicted by angle of repose, bulk density, tapped density, carr's index, and hausner ratio.

The angle of repose of the pellets is the maximum angle that can be formed between the pile's surface and the horizontal plane using the fixed funnel technique and using the following formula:-

$$\theta = \tan^{-1} h/r$$

Bulk Density is an exact quantity "M" of pellets was taken and placed into measuring cylinder and Volume "V" occupied by the pellets was noted without disturbing the cylinder and bulk density was calculated :-

$$\text{Bulk density} = \frac{\text{Mass of the powder}}{\text{Bulk volume of the powder}}$$

Tapped density is obtained by mechanically tapping measuring cylinder containing pellets

$$\text{True/Tapped density}\,(\rho_t) = \frac{\text{Weight of microcapsules(g)(M)}}{\text{Tapped volume(ml)}\,(V_t)} \quad (3)$$

Hausner Ratio and Carrs Index were calculated as follows:

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Poured or bulk density}}$$

$$\text{Carr's index (\%)} = \frac{\text{Bulk density} - \text{Tapped density}}{\text{Tapped density}} \times 100$$

**2) Friability**

From each batch of pellets, 2gm precisely weighed pellets were removed and tumbled for 100 rotations at 25 rpm in a friabilator. The attrition agent consisted of twelve steel balls, each weight 0.445g. The granules were sieved through sieve no. 22 after being subjected to a friability test.[41] The weight loss after friability testing was calculated as follows

Where, W1- Initial weight of pellets and W2-final weight of pellets

$$\text{Friability (\%)} = \frac{\text{Initial Weight (W1)} - \text{Final Weight (W2)}}{\text{Initial Weight (W1)}} \times 100$$

Upper acceptability limit of friability was 0.8-1%

**3) Drug content**

In a dried mortar and pestle, 450 mg of pellets that were precisely measured (equivalent to 90 mg of drug) were pulverised. In 100 ml of distilled water, pellet powder was dissolved. After 15 minutes of stirring, the sample was filtered. The sample was made as a standard dilution and put through a UV spectrophotometer analysis.

**4) In-vitro drug release study**

Dissolution studies were carried out in a USP Type-l dissolution apparatus with 900 ml of distilled water as the dissolution medium. The temperature was kept at 37±40.5°C while the basket rotated at a speed of 100 rpm. This procedure was carried out for 12 hours. To keep the volume consistent, 5 ml samples were taken out of the dissolution medium every hour and replaced with new dissolution medium. The sample fluid was filtered and properly diluted before being subjected to UV spectrophotometer analysis. Using a straight-line equation derived from the calibration curves for the individual drugs, the amounts of drug found in the samples were calculated.[42, 43]

**5) Particle size analysis**

Using a mechanical sieve shaker, the size range of the pellets was identified. The number 10, 12, 16, 22, 36, and 44 BSS standard stainless steel sieves were arranged in decreasing sequence of aperture size. Each batch's drug-loaded pellets (10 gm) were weighed precisely before being put on the uppermost sieve. The sieves were shaken for ten minutes, and the material's arithmetic mean size versus the percentage of weight kept was plotted to determine the size of the pellets.[44]

**6) Hardness**

Using a digital hardness detector, the hardness of the pellets was determined. 12 randomly selected pellets were collected, and their hardness was assessed. It computed the average value.[45]

## CONCLUSION

Based on above discussion, it is clear that sustained-release formulations are both helpful in enhancing dose effectiveness and also useful in making the condition more compatible.

In contrast, sustained release refers to the substance being released gradually over time. Controlled release composition may or may not be sustain released. From the talk above, it is clear that a number of variables, including biopharmaceutics, influence the development of SRDDS characteristics of the drug's pharmacokinetic and pharmacodynamic actions. The market entry of sustained release drug delivery systems as an alternative to oral predictable drug delivery systems has not proven to be challenging. By reducing the dosing interval and minimising adverse effects, release formulations are a promising method to increase patient compliance.

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