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Techniques and Evaluation Tests for Colon Cancer Treatment Using Pellets: A Review

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ABSTRACT

This review outlines the manufacturing process for globular pellets. The production method includes the following steps: drug stacking, displacement-merumerization, cryopelletization, shrink, balling, hot-soften extrusion generation, freeze pelletization, spray-drying, and spray-congealing. The benefits and risks of several pelletization methods were discussed. The current study's objective is to examine the efficacy of anticancer drugs and metal chelators in treating colorectal cancer (CRC). Phytic acid, 5-fluorouracil (5-FU), microcrystalline cellulose (MCC) PH 100 and 1 compile in the pellets, hydroxypropyl methylcellulose (HPMC), and barium sulphate were processed utilizing the extrusion spheronization technology. To achieve colon-specific medication delivery, Eudragit S100 was layered over the ability pellets. Pellets have been praised for a variety of micromeritic and medicinal qualities. In the Ehrlich ascites carcinoma (EAC)-driven patient-derived zenograft (PDX) paradigm, the in vivo treatment potency separates the pharmacokinetic and pharmacodynamic bounds. By chelating manganese, phytic acid, and five-FU combinations, they appear to provide more cytotoxic interest through a better reactive oxygen species (ROS) stage. Later pharmacokinetic studies showed a maximum 50% drop in Cmax within the finished setup, indicating decreased inherent exposure to the drug component.

Key words: Pelletization, Merumerization, Drying, Cancer, Spheronization, colorectal cancer.

1. INTRODUCTION

Most pharmaceutical industries use extrusion-spheronization technology to create pellets. Factors that primarily affect pellet production have been studied and found to be pre-formulation parameters that, regardless of the stable dosage shape, have an impact on both the operation and the standard of the finished product.[1] Pellets are round or free-flowing fragments within a limited length dispersed, frequently falling between 500 and 1500 m, and are used for pharmaceutical packaging. They are often produced via the pelletization method, which entails agglomerating an API and excipient waste powder mixture into sphere-shaped granules.[2]

A geometrically defined agglomeration that has been consistently created from a variety of starting materials under certain processing conditions has been referred to as a pellet. They are primarily employed for oral management and are made up of a variety of robust, free-flowing, spherical, or semi-spherical items that can be between 0.5 mm and 1.5 mm in size.[3,4]

A homogeneous film coating resulted from the pellets' spherical form and low surface area-to-extent ratio.[11] Chemically compatible or incompatible drugs may be produced in a single dosage form at similar plots or at distinct plots inside the gastrointestinal system. Additionally, dissimilar drug dissolution rates might be offered.[12] Documents for multiple unit dosages demonstrate several advantages over such as pills, suspensions, or medications that dissolve in the mouth.[13]

When using pellets, the aforementioned desires may be satisfied by using coating materials (mostly exclusive polymers), which present the preferred function, or matrix pellets, which provide the preferred effect.[14] Incidences of colorectal cancer (CRC) in young patients have rapidly increased. Alcohol consumption also raises the risk of CRC development. Cancer causes 8.9 million deaths worldwide each year, making it the second-most common cause of death worldwide.[32] 5-fluorouracil (five-FU) was broadly utilised as oral chemotherapy for both promptly diagnosed and up-to-date CRC. Although 5-FU seems to be an effective treatment for CRC, its therapeutic potential is constrained by short half-lives of elimination that demand numerous managements.[33] Both early and advanced CRC patients have received oral chemotherapy with 5-fluorouracil (five-FU). Despite the fact that 5-FU appears to be a successful treatment for CRC, its therapeutic potential is limited by short elimination half-lives that necessitate multiple managements.[33] A continuous drug delivery system designed specifically for the colon increases the drug's effectiveness and safety. The danger of drug plasma volatility and decreased systemic adverse effects are both decreased by sustained-release technology. Specific Eudragit® acrylic polymers were advanced for oral dosage management due to the step-sensible launch of vital compounds in the GIT. The breakdown of Eudragit® coatings and the release of active ingredients take place near the colon in the pH range of 6.5–7.5 as a result of ambient pH.[34] A popular colon medication target is the pH-sensitive polymer Eudragit S 100. In order to establish a sustained drug delivery method that is colon-specific, we have developed Eudragit S100 overlayered pellets mitochondria. This process produces reactive oxygen species (ROS), mainly superoxide radicals (O2).

1.1 Advantages of Many Devices for Healing Over Single Units

orally administered multiple unit dose type in the gastrointestinal route, spreading widely. Increase drug absorption as much as possible, reduce local mucosal inflammation by using aggravating tablets specifically designed for this purpose, keep peak plasma variations under control, and reduce possible side effects without significantly compromising drug bioavailability.[38]

1. Provide a reduced version of the stomach emptying charge and transit time that is less reliant on the nutritional country.
2. Reduces the risk of dosage dumping.
3. Lessens the localized effects of irritative medications.
4. Increases a drug's efficacy and protection.
5. Reduce heterogeneity between and within afflicted individuals.
6. More appropriate for producing formulations with acid-sensitive capsules. Erythromycin, for instance) (Digeenis GA 1994).

1.1.1 Pellet Qualities that are Acceptable

- Uncoated pellets: premier size, between 600 and 1000mm; uniform round form; smooth floor.
- Moved ahead with features like flexibility.
- High physical stamina and moral character.
- Precise hardness and friability of coffee.
- High density in the bulk.
- Reproducible bed and column packing, ease of coating, and exceptional coating characteristics.

1.2 All of the fore Mentioned Dwellings are Preserved Using Lined Pellets (Coated Pellets).

- Include as much of the active component as you can while still maintaining the final dosage form's proportions within acceptable bounds.
- Possess desired drug launch properties.

1.2.1 Benefits of Pellets

- The homogeneous coating is made possible by the smooth surface and regular length of the pellets, both within and between batches. To permit a controlled release rate, pellet coating might be completed with certain capsules.
- Large pellet floor areas allow for better dispersion of newly released products.
- Pellets made of goods that are incompatible with one another chemically can be administered in a single dose.
- To get the desired effect, different coating thickness bead or granule mixtures are blended in the optimal ratios.
- The broadness of the layer at the pellets determines how quickly medication or other substances are obtained from the coated fragments.
- By utilizing the right technique, recycling conditions, and recycling equipment, it may produce pellets with clean surfaces and consistent sizes.
- The middle of the product has an advanced, attractive pharmaceutical appearance.
- They provide an excessive amount of design and development flexibility for oral dose forms like deferment, pill, and tablet.
- Recently, compressed, overlayered pellets are used to quickly dissolve medications. Due to this, tiny pellets with mean diameters of no more than 0.5 mm are ideal. Direct palletization techniques can be used to create these pellets.

1.2.2 Dangers of Pellets

- The preparation of paperwork for multiple unit doses is extra challenging and costly.
- Completing the padding of gelatin capsules can be tough, typically when numerous divided units are implemented.

2. PROBLEMS WITH THE PELLETIZATION METHOD

2.1 Humidity-Containing Materials

Particular crucial elements for the pelletization process. In order for the moist mass to be removed and spheronized to create a spherical shape, moisture within the wet mass provides cohesiveness to the powder. Spheronization is one of the methods for pelletizing materials, and excessive moisture content causes the pellets to clump together. Conversely, low-moisture-content materials result in the production of fines with a wide range in length distribution.[11]

2.2 Rheological Traits

The float capability of an extruder is determined by the rheological state of the wet mass. In order to extrude the wet mass version, rheological conditions must be met. This causes an inappropriate and uneven extrusion.[15]

2.3 Excipient and Drug Solubility in Granulating Fluid

A granulating liquid dissolves a medication that is soluble in it. As a result, increasing the liquid segment's volume leads to excessive wetting of the device and the formation of pellet sand agglomerations. Wetting liquid will also increase plasticity while producing sticky mass.[12]

2.4 Fluid Granulating Composition

In addition to water, alcohol, and water/alcohol aggregate, other liquids employed as granulating agents include ethyl ether, diluted acetic acid, and isopropyl alcohol. Researchers like Millili and Schwartz claim that in order to sequence manufactured pellets containing Theophylline and Avicel pH (101), the granulation liquid must contain at least 5% water.[16] Using water and diluted acetic acid in a certain powder-to-liquid ratio, several researchers came to the conclusion that using demineralized water and diluted acetic acid for the granulation step would increase the mass fraction by up to 100%.[29] In the process, an aqueous polymer dispersion containing gelatine, hydroxypropyl methylcellulose (HPMC), and polyvinyl pyrrolidine (PVP) is employed.

2.5 Physical Structures Made with Early Cloth

The formula variable, the sort and content of the beginning material, the kind of filler, and the size of the component particles all have an impact on the pelletization process. Pellet quality is dependent not only on the product's ideal composition but also on its superior grades.[30] The rate at which the medication will escape from the pellets depends on the swelling resources of the components employed in the pelletization process.

2.6Spheronizer's Pace

The tempo of the spheronizer influences the pellets size, toughness, wholeness, and thickness; excessive tempo produces excessive wholeness, decreased brittleness, a clean plane, and greater breaking potency.[31]

2.7 Temperature and Drying Method.

The size, shape, and flow of the pellets must be proper, and they must be repeatable and constant throughout all groups. Changes in the final dosage form's physicochemical characteristics, such as weight fluctuation, improper filling, and many others, will result from changes in the pellet's size, shape, and float. These variations will also have an effect on the therapeutic effectiveness of the transport device. A variation in the drug shipping dose may also be caused by a wider particle length distribution. Variance in float and compressibility may also result from shape variance.

2.8Extrusion-Based Display Screen

The parameters of the screen's orifice significantly influence how well the extrudate or pellets perform. Increasing orifice size led to longer, suggestible pellets. Water on the extruded surface caused the boom in orifice depth to decrease, increasing the extrusion pressure, which consequently had an adverse effect on granulometric distribution and shape.[20]

3. APPROACHES FOR PELLETIZING

Pelletization is a cluster approach that produces acceptable pellets from powders or granules of bulk drugs and excipients. Pellets are small, free-flowing, spherical, or semi-spherical devices. The type of layering approach has a significant impact on the movie microstructure, which in turn has an impact on the charge and discharge mechanisms of pellets covered in polymer blends. Many different production strategies exist.

3.1 Agitation

3.2 Balling

When the proper amounts of liquid are added, finely separated particles are transformed into circular waste with the help of a continuous rolling or tossing motion. The balling can be used to distribute pellets into mixers, pans, drums, or discs.

3.3 Compression

The manufacturing of compacting mixes and bulking agents results in pellets with a specified shape and length.

3.4 Spheronization and Extrusion

Nakahara developed a multi-step method for doing it in 1964. The primary steps in extrusion spheronization are five. Extrusion, spheronization, coating, and drying can all be used to characterise this.

- Ingredients are dry-blended to create a homogeneous powder talc dispersion.
- Moisture accumulates to provide enough adaptable mass.
- Discharge, which produces debris whose diameter is constant.
- Spheronization, which creates spherical particles with a narrow length distribution from the rod-shaped debris,
- Drying to get the final moisture content you want; screening to get the sphere or pellet size you want.

The active component and excipients are dry mixed; the wet mass is granulated, extruded, transferred to a spheronizer to make round forms, dried in a dryer, and then screened to get the desired particle size.

3.5 Layering

This technique produces heterogeneous pellets with an interior core location and an external shell location of a distinct composition by coating the medication onto the seed material (typically a nonpareil or rough substance) in the form of a powder, solution, or suspension. Direct pelletization, response or suspension layering, and powder layering are the three categories into which this technique is classified.

3.5.1 Aglomereting

It is possible to identify a system that produces homogenous pellets with no middle and a microscopically consistent shape. Direct pelletization is especially carried out in fluidized bed devices and high-shear mixers.[22]

3.5.2Powder Sprinkling

Powder layering involves placing consecutive coatings of dry pharmaceutical fragments, excipients, or both on ready nuclei or cores while using a binding solvent. A tangential spray, centrifugal, or rotary fluidized mattress granulator is the tool used.[14] Among the risks are:

- Low drug loading amounts that are inappropriate for tablets with high doses.
- If a decrease in spray rate is seen, then the final composition of the pellets may change.

3.5.3 Solution/Suspension Layering

- The creation of pellets in the case of solution or suspension layering entails the downfall of consecutive coverings of solution and bands on the existing nuclei. Whether the binder is present or not, the drug residue disintegrates in the binding liquid. The surface of the nuclei was covered in drops of the binding liquid. Drying involves the evaporation of liquid, the crystallization of dissolved chemicals, and the formation of capillary forces that attract the debris towards one another and towards the inert seed, creating stable bridges.
- Strong bridges made from the hardening binder are used to bind detritus in suspension layers because it has limited solubility; thus, a greater awareness of the binder is needed.
- The type of system being employed has a significant impact on both the procedure's effectiveness and the quality of the pellets generated.
- In place of the old sugar spheres, sugar-starch aggregate, and pure drug crystals, raw unmixed drug crystals and microcrystalline cellulose pellets are now used as beginning seeds.
- The Wurster bottom spray coater is the most widely used configuration. Due to the improvement of the polymer movie development at the pellet's surface Using this technique, enteric-coated Esomeprazole pellets are provided, enhancing the medication's stability in acidic environments.
- However, enteric coating ensures that the action will be released in a specific area of alkali media at the action site.

3.6 Globulation

Spray drying and congealing both occur during globulation or droplet formation.

3.7 Sprayed Drying

The solution, which contains drugs with or without bulking agents, is sprayed into a heated air circulation to produce dry, basically circular fragments. It is widely employed to boost the bioavailability of less soluble capsules and, consequently, their rates of dissolution.

3.8 Congealing Spraying

A technique that, under the right processing conditions, produces round congealed pellets by allowing a drug to soften, an air chamber in which the temperature is held below the melting point of the manufactured product gets sprinkled with drug.

4. PELLETIZATION PROCEDURES

1. Spheronization after extrusion
2. Layering strategy
3. Cryopelletization
4. Extrusion with hot softening
5. Pellet freezing

5. ASSESSMENT OF PELLETS

5.1 Dimensional Diversity

The size of the pellets is crucial since it significantly affects the release kinetics. The geometric mean diameter, way average diameter, way particle width, and way particle duration are some of the variables that can be utilized to calculate the length of pellets. The majority of the time, vernier calipers are used to measure the dimensions of the pellets before doing a basic sieve analysis to ascertain the particle size.[24]

The most important characteristic of the pellets is their sphericity, which was determined using a variety of techniques. Based on the projected location of the pellets and their diameter, the form factor determines a circle's circumference and evaluates how far the projected image of the particles deviates from it.[25]

The roundness index or form element of pellets must fall between 1 and 2 in order to be considered excellent. The shape aspect must be 1 for a perfectly spherically distributed particle to be described by a particle with a cost of 0.6. An alternate method to determine the shape of pellets is to visually analyze them with a stereomicroscope or microscope.[26]

The single-plane crucial stability, or the gradient at which a plane must be bent prior to fragments starting to roll, is a particular type of the primary techniques for figuring out design. The attitude of repose, which is a proximate predictor of the sphericality of pellets, is measured as the ratio of twice the pile peak to twice the pile radius. This proportion is measured after a predetermined number of pellets have been permitted to descend from a particular peak via a predetermined orifice.[5]

5.2 Surface Morphology

The floor morphology and motion phase of pellets are examined using scanning electron microscopy. Sood and others. It was initially described in 2004 as employing optical microscopy to investigate the surface microstructure of pellets.[27] A non-contracting laser profile meter was employed in a few studies to gauge the roughness of pellet floors.[28]

5.3 Special Surface Area

The size and shape of the pellets are strongly related to their surface area. It is best to be aware of the surface area, especially when film coating is taken into account. Even in the case of uncoated pellets, knowledge of the floor region is crucial since the surface region affects drug release. Fuel adsorption technology selects a specific surface area for pellets.[28]

5.4 Friability

For processing, pellets' mechanical houses are essential. Dust is produced as a result of pellets flaking off when handled and coated. It is ideal to use pellets with low friability for the next coating. When determining the friability of pellets, glass beads with a positive diameter are used to create abrasion together with an Erkewa-type pill friabiliator or turbula mixer for a predetermined period of time. The use of a fluidized bed with a Wurster insert can be used to determine friability as well.[17]

6.COLON CANCER'S ONSET AND TREATMENT METHODS

Wistar rats weighing 200–250 g was used to create the colon cancer, and 107 EAC cells from NCCS Pune were injected intrarectally as the treatment. Within 14 days of the disorder's onset, an X-ray of a Wistar rat indicated that the animal had colon cancer. The animals were obtained from ISF College of Pharmacy, Moga, with the aim of measuring behavioral parameters as well as biochemical perception both before and after the administration of the drug. Rats were housed in CPCSEA guidelines-followed conditions (i.e., room temperature of 25 °C; relative humidity of 55%; 12/12 h light/dark cycles) with free entrance to a profit-oriented rodent meal plan and water. For the pharmacokinetic investigation, animals were starved all night and for eight hours after the dosage. The study agreement was authorized by the Institutional Animal Ethical Committee (IAEC) at the ISF College of Pharmacy in Moga, India. When conducting the experiment, the CPCSEA (Committee for Prevention, Control, and Supervision of Experimental Animals, ISFCP/IAEC/CPCSEA/Assembly No. 22/2018/Protocol No. 367) process has been adhered to. After oral administration of the components under study (phytic acid, simple drug, phytic acid-Eudragit S 100 system, 5-FU-Eudragit S100 components, and final formulations), various pharmacokinetic needs were achieved on the 14th day. With the single oral dosage form employed in the experiment above, blood samples are taken at 0 hours, 2 hours, 4 hours, 12 hours, and 24 hours in order to achieve the desired results.[38,39]

6.1 X-ray Transmission Radiography is Used to Assess the Compound's Capacity

The use of radiographic imaging was determined by the behavior of the enhanced pellet formula in the rat. In order to do this, X-ray examination animals were preferably held apart from food and drink for a single day, with free access to water. To locate the pellets, it was concerned about incorporating the radio-opaque indicator barium sulphate into the mix. The barium sulphate dosage was modified to be optimized without affecting the optimized pellet system's physical properties. At several time points, particularly two and four hours after delivery, an X-ray portrait of the drug-administered rats' colons was grasped in order to monitor the mobility and behavior of the pellets in the GIT in vivo. A L&T Vision 100 (C-arm) X-ray machine operating at 64 mAs and 63 kV PS was used to obtain an X-ray portrait of the rats in an exposed location.[40,41]

6.2 Cancer Regression Analysis

On the twenty-first day after the start of treatment, a tumor discount evaluation was carried out. On the twenty-first day of the examination, the tumor regression was tracked using a Vernier-Calipertumor extent computation. The two biggest perpendiculars in the X and Y planes that were surgically removed were measured by four impartial observers using a Vernier caliper.[42,43] The shortest Y-defined perpendicular axis was thought to be equivalent to the intensity. The extent was calculated using the following equation:

$$\text{Quantity}=XY2/2$$

6.3 Study of Histopathology

On the twenty-first day of treatment, it was carried out. The Wistar rats' surrounding tissue and tumor were successfully removed for use in a histopathological examination. After being removed, the tissue was first fixed in 10% formalin, then dried and embedded in paraffin. The size of the pass-sections was four to five millimeters, and they were stained with hematoxylin and eosin. To examine the trade that developed as a result of the activity of the organized formulations, the colonic segment that had been removed was examined under a microscope.[45-47] The most crucial antioxidant defense mechanisms against oxygen are SODs. For their activation, all isoforms require a catalytic metal (Cu or Mn). Antioxidant enzymes are frequently overexpressed in cancer cells in order to shield them from ROS. According to reports, MnSOD levels in colon cancer are higher. Chelating retailers have the ability to bind to free steel ions, rendering them inaccessible to enzyme activity. It has an excessive propensity to react with the divalent steel ions present in food, resulting in the formation of phytates, which are insoluble complexes. It was discovered that, at pH 7, the relative order of metallic chelation was Cu2+>Zn2+>Co2+>Mn2+>Fe2+>Ca2+. Steel chelates have the potential to boost the anticancer potency of chemotherapeutic drugs when used alone or in combination. because phytic acid enhancement is known to highlight anti-cancer, anti-inflammatory, and antioxidant potential. The goal of the current investigation was to investigate the efficacy of combination approaches (5-FU and phytic acid) for the treatment of cancer in xenograft animal models.[37] Mobile oxidative stress, which is brought on by the buildup of ROS, can damage essential organic molecules such as proteins, DNA (deoxyribonucleic acid), and membrane lipids. High amounts of free radicals that accumulate over time in cells can ultimately cause irreversible damage that results in cellular death. Because SOD is the main enzyme associated with regulating free radicals, its silence results in increased O_2 buildup, which finally causes cell death. Since SOD in mammals comprises three isoforms—mitochondrial MnSOD (SOD2), extracellular Cu/ZnSOD (SOD3), and cytoplasmic Cu/ZnSOD (SOD1)—inhibiting SOD may provide a potential alternative to eliminating the majority of cancer cells.[35]

7. STATISTIC EVALUATION

The use of ANOVA and Tukey's multiple composition analysis allowed for the statistical evaluation of the assertion. The findings were shown as implied SD to highlight the variety of repeats. Statistically significant expenses were defined as those with P-values less than 0.05.[49,50]

7.1 Drug launch *in vitro*

The eight-hour disintegration of an antitumor medicine from an enteric-covering manufactured product is shown by the growing percentage of drug disintegration against time plot evaluating coated and uncoated pellets. Due to its polyanionic composition, eudragit prevents five-FU from bursting at the stomach site. This was noticed by the constructed device's approximation of zero-order release, which denotes a consistent drug release based on Eudragit S 100's pH-established drug release behavior. The Inflammation of Eudragit S100 in an alkaline pH 7.4 is required for drug release since the polymer employed to cover the system is pH-sensitive. Due to the Eudragit S 100's propensity to swell at an alkaline pH, the coating layer's pores begin to deteriorate. Since then, changes in pore size and pore density over time have encouraged the discharge charge. The drug launch sample for the 5-FU-loaded anti-most tumor pellets that are lined and uncoated is highly different.[50,51]

7.2 Test for cytotoxicity (MTT assay)

Regularly cultivated in RPMI 1640 growth medium with 10% FBS (fatal bovine serum), 1% antibiotic antimycotic solution, and 1% L-glutamine as supplements were the human epithelial colorectal adenocarcinoma cell line EAC. In order to preserve the cellular traces, they were kept in an incubator that was humidified and contained 5% CO_2. The temperature was maintained at 37 °C until excellent cell joining was found. After incubating the EAC cells for twenty-four hours, the Toxicity potential of the apparent dose, drug-loaded uncoated processed product, and drug-loaded covering formulation was assessed using the MTT test. The toxicity of drug-filled lined and drug-filled uncoated pellets was tested with various quantities of an anti-cancer medication in order to explain the antitumor activity of manufactured components with reference to dose and duration.[51,52] A trustworthy connection was discovered. The cytotoxic effect also grows as anticancer drug concentration and contact time with the component lengthen. The drug-loaded coated formulation, however, showed a noticeably higher level of cytotoxicity as compared to the full formulations under the same circumstances. The straightforward anticancer drug confirmed 42.9 percent mobile vitality after 24 hours at the maximum range of the tested dose of 800 g/ml. The final components had a percentage cellular viability of 14.8% and improved cytotoxicity at the right concentration of 5-FU after twenty-four hours of incubation.[54,55]

7.3 The Histopathological Analysis

If the organized formulation had a synergistic effect when compared to a standard anticancer treatment, the tumor was frozen at -20 °C and viewed under a bright-field microscope at a magnification level of 100 X. To obtain more precise results, the test was conducted three times on test samples. The anticancer medicine's targeted release suggests a stronger repair of the basement membrane and lamina propria as compared to the drug's obvious anticancer effects.[58] The lamina propria restored its original finger-like shape in the sample treated with the final ingredients, illuminating the synergistic effects of the mixture. Similar findings were reported by Foroushani and colleagues, who found that graphene oxide-coupled polydopamine supports improved payload localization without any sign of tissue abnormality.

8. CONCLUSION

In comparison to the granulation process, the pelletization strategy yields more rounded pellets and offers additional benefits. Additionally, the hot-soften extrusion method has given producers of spherical medicine pellets that are unstable or have problems fitting in the presence of solvents a new, larger platform.

It has been established that metal chelators are a desirable way to increase the cytotoxic activity of chemotherapy drugs. The study also emphasizes the potential effectiveness of blocking redox enzymes to compromise cancer cells' defense mechanisms, thereby enhancing treatment activity. The distribution of anticancer tablets utilizing pH-delegated polymers assures drug concentration at a local high level to produce a particular toxic action and also minimizes systemic release of the drug, potentially lowering the danger of drug-based systemic toxicity. The eW research paves the road for colon cancer treatments that work. However, it's equally important to look into the potential medical benefits of organ-specific toxicity.

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