# A REVIEW ON MUCOADHESIVE PELLETS AS A DRUG DELIVERY SYSTEM

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## ABSTRACT
Mucoadhesive pellets have emerged as an advanced multiparticulate drug delivery system designed to improve therapeutic efficacy and patient compliance. It utilizes specific polymers that adhere to mucosal surfaces and prolong the residence time of drugs at the site of absorption. Thus, it may enhance bioavailability. Mucoadhesive pellets have a number of benefits, including as consistent medication distribution, less dose variability, less chance of dose dumping, and regulated or site-specific drug release. They are especially helpful for directing medications to certain mucosal areas like the buccal, vaginal, or gastrointestinal tract. Advances in polymer science, manufacturing technologies, and evaluation methods have further improved the performance and industrial feasibility of mucoadhesive pellets. Overall, mucoadhesive pellet-based systems represent a promising and versatile platform for the development of effective, safe, and patient-friendly drug delivery systems.

**Keywords:** Mucoadhesive pellets, Drug delivery system, Multiparticulate dosage forms, Controlled drug release, Site-specific drug delivery, Bioavailability

## INTRODUCTION
The phenomena of natural or artificial materials adhering to biological substrates for an extended amount of time is known as bioadhesion. Researchers looking to create novel biomaterials, treatments, and technology would greatly benefit from an understanding of the basic principles of bioadhesion.[1] The moist surfaces that line the walls of the mouth, nose, eyes, and reproductive, gastrointestinal, and respiratory systems are called mucosal membranes. Mucus is crucial for the wettability, lubrication, protection, and control of the moisture content of the cell's epithelial surfaces. Specialized goblet cells in single-layered epithelia produce mucus directly onto the epithelium's surface.However, specific glands (such as salivary glands) for mucus secretion are present in multi-layered stratified epithelium. Water, glycoproteins, lipids, and electrolytes make up the mucus gel; the water content is roughly 95%, the glycoprotein and lipid content is between 0.5 and 5%, and the mineral salt level is between 0.5 and 1%.
Mucus's physicochemical features, such as composition, pH, ionic strength, and conformation, are crucial for its functions and rheological characteristics. Mucus secretion can be triggered by toxic and perhaps irritating substances as a defense mechanism to remove irritants from the epithelium.[2] A pharmacological dosage form's appealing interaction with the mucosal membrane is known as mucoadhesion. Mucoadhesive drug delivery systems can be utilized to provide aesthetically pleasing and adaptable dosage forms for delivering therapeutic agents to gastrointestinal (oral), ophthalmic, nasal, buccal, gingival, vaginal, and rectal targets. Increased dosage form residence time, enhanced drug bioavailability, decreased frequency of administration, convenience of dosage form administration, and the potential to target specific body sites and tissues are all benefits of using mucoadhesives in drug delivery.[3] Tablets, films, gels, nanoparticles, microspheres, wafers, pessaries, viscous solutions, micro and nano-particulate suspensions, in situ gelling systems, and sprays are examples of mucoadhesive drug delivery systems.[4,5]

The process of mucoadhesion involves two steps:
i.The contact stage: The drug delivery system's polymers and the mucosal membrane come into close contact during the contact stage.
ii. Consolidation stage: The mucoadhesive polymer's and the mucin's chains interpenetrate and/or entangle at this stage.
The polymer and the mucosal surface produce a mucoadhesive binding primarily by ionic interactions, hydrogen bonding, or weak van der Waals forces.[6–8]

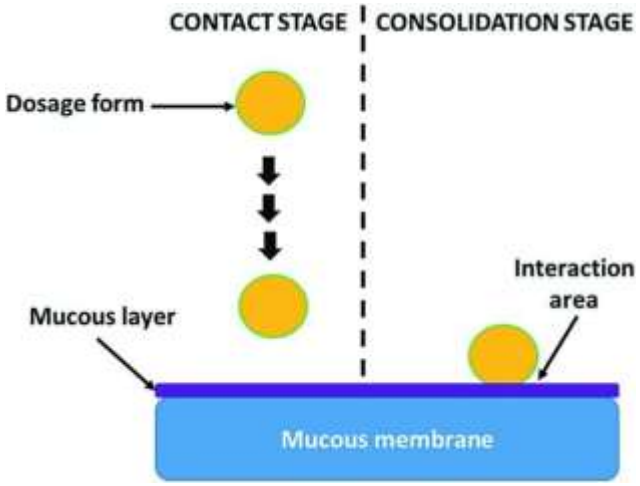


**Figure 1: Mechanism of Mucoadhesion**

## THEORIES FOR PHENOMENA OF MUCOADHESION

Six general theories have been adapted for explaining the phenomenon of mucoadhesion:[9]

1. *Wetting theory:* This theory considers the mucoadhesive polymer and mucus surface tension. It involves a liquid's capacity to spontaneously spread over a mucosal surface for the creation of adhesion and is often applicable to liquid mucoadhesive forms.[10]

*2. Diffusion theory:* The formation of the mucoadhesive bond may be attributed to the inter-diffusion of the polymer and mucin chains. Concentration gradients, molecular chain lengths, motility, and hydrodynamic size all influence this process.

*3. Adsorption theory*: This hypothesis takes into account the role of van der Waals forces and hydrogen bonds in mucoadhesive interactions. Additionally, it takes into account the potential for chemisorption, which occurs when the mucoadhesive polymer and the mucin form strong covalent connections.

*4. Electronic theory:* According to this idea, mucoadhesion is caused by the electrostatic attraction between mucin and the mucoadhesive polymer. At the interface, electron transfer results in the creation of an electrical double layer.

*5.Mechanical theory*: This theory takes into account how mechanical interlocking and surface roughness affect the formation of mucoadhesion.

*6. Fracture theory*: It is thought to be suitable for determining the fracture strength of adhesive connections and connects the difficulty of separating two surfaces after adhesion.[11] Because mucin molecules are complex, they can interact with polymers through a variety of processes, including bonding, electrostatic, physical entanglement, and hydrophobic interactions.

**Table 1: Factors affecting the mucoadhesive interactions**[11]

| Sr. no. | Factors affecting mucoadhesive interactions | Description |
|---|---|---|
| 1 | Biological factors pH of the biological membrane, mucin | Biological factors pH of the biological membrane, mucin |
| 2 | Characteristics of the mucoadhesive polymer | Molecular weight, flexibility of polymer chains, spatial conformation, charge, Hydrogen bonding capability, hydration (swelling), concentration and pH of polymer |
| 3 | Characteristics of the drug delivery system | pH, presence of water phase, rheological behaviour and spreadability |
| 4 | Method of application | Initial pressure applied at contact formation, contact time |

| | | |
|---|---|---|
| 5 | Environment-related factors | Presence of water, contaminants |

**MUCOADHESIVE POLYMERS**

Polymers that have strong intermolecular bonds with the mucosal layer and sufficient mucoadhesive properties are known as mucoadhesive polymers. Mucoadhesive drug delivery methods have been investigated with the purpose of localizing the active agents to a specific spot. In order to extend the active agent's residence time at the intended site, the polymers utilized in drug delivery systems are crucial to their design. The polymer enters tissue fissures or the network of mucus. Mucoadhesion is facilitated by the polymer chain's high molecular weight and the mucosal layer's ease of wetting.[11]

**Table 2: Classification, categories and examples of different mucoadhesive polymers** [11]

| Sr. no. | Classification basis | Category | Examples |
|---|---|---|---|
| I | Generation | First generation | Cationic, anionic, non-ionic |
| | | Second generation | Lectins, thiomers, amino acid sequences |
| II | Source | Natural | Agarose, chitosan, gelatin, pectin, sodium alginate, various gums (guar, xanthan, gellan, carrageenan) |
| | | Synthetic | cellulose, hydroxylethyl cellulose, hydroxylpropyl cellulose, hydroxylpropyl methyl cellulose, methyl cellulose, methylhydroxyethyl cellulose *Poly(acrylic acid)- based polymers* Carbopol, polycarbophil, polyacrylates, poly(methylvinylether- co-methacryliacid), poly(2-hydroxyethyl methacrylate), poly(acrylic acid- coethylhexylacrylate), poly(methacrylate) |
| III | Charge | Cationic | Aminodextran, chitosan, trimethylated chitosan, dimethylaminoethyl dextran |
| | | Anionic | Carbopol, carboxymethyl cellulose, pectin, poly(acrylic acid), polycarbophil, sodium alginate,sodium carboxymethyl cellulose, xanthan gum |
| | | Non ionic | Hydroxyethyl starch, hydroxypropyl cellulose, poly (vinyl alcohol), polyvinylpyrrolidone, scleroglucan |
| IV | Solubility | Water soluble | Carbopol, hydroxylethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, poly(acrylic acid), sodium alginate |
| | | Water insoluble | Chitosan, ethyl cellulose, polycarbophil |
| V | Mucoadhesive interaction | Electrostatic interaction | Chitosan |
| | | Covalent bonding | Cyanoacrylate |
| | | Hydrogen bonding | Poly(methacrylic acid), carbopol, polycarbophil, poly(vinyl alcohol) |

## PELLETS

The process of agglomerating and enlarging powdered pharmaceutically active substances and excipients into small, spherical, free-flowing units known as pellets is known as pelletization. Pellets are mostly meant to be used orally and range in size from 0.5 to 2.0 mm. Nevertheless, intramuscular and subcutaneous medication administration has also been accomplished with pellet-based implants. The pharmaceutical sector has embraced pellets because of their advantages, which include specified shape, consistency of contents, free flowing property, mechanical strength, and ease of polymer coating.[12]

## ADVANTAGES:

Pellets offer several advantages as a pharmaceutical dosage form, making them widely used in modern drug delivery systems. Being multiparticulate in nature, pellets provide uniform drug distribution and reduce the risk of dose dumping compared to single-unit systems. They exhibit excellent flow properties, low friability, and good mechanical strength, which facilitate capsule filling and tablet compression. Pellets allow flexibility in designing immediate, delayed, or controlled drug release profiles by applying suitable coatings. They also minimize local irritation in the gastrointestinal tract by spreading uniformly, improve drug bioavailability, and enhance patient compliance. Additionally, pellets enable combination therapy by incorporating different drugs or release patterns within a single dosage form, making them a versatile and efficient drug delivery approach.

**DISAVANTAGES:Despite their numerous advantages, pellets also have certain limitations. The manufacturing process of pellets is relatively complex and time-consuming, requiring specialized equipment and skilled personnel, which can increase production costs. Process optimization and scale-up may be challenging due to sensitivity to formulation and processing parameters. Uniform coating of pellets is critical but difficult to achieve, and variations can affect drug release profiles. Pellets may also show segregation during handling or capsule filling if size distribution is not well controlled. Additionally, the use of multiple excipients and polymers may raise concerns related to stability, compatibility, and regulatory approval. These factors can limit the widespread adoption of pellets, particularly in cost-sensitive pharmaceutical applications.[12]**

## PREPARATION OF PELLETS

Pellets for pharmaceutical applications can be produced by several methods with different principles as shown in Figure 1.

Extrusion-spheronization and layering techniques are the most commonly used methods for the production of pellets.

i. Extrusion-spheronization is a multi-step method which involves mixing, wet granulation, extrusion, spheronization and drying processes leading to the formation of spherical pellets.

- During spheronization, the rod-shaped extrudates are broken and shaped into almost spherical particles of uniform size.
- Extrusion spheronization method is simple, easily scalable, flexible in operation, lower production cost and easier to automate.[13]

ii. Layering is another commonly employed technique for the production of pellets.

This technique is of two types:

a) solution/suspension layering and
b) powder layering.

In solution or suspension layering, powder feed material and other components are dissolved or suspended in suitable solvent. The solution or suspension is sprayed on the surface of the **core** followed by drying which allows dissolved material to get crystallized leading to layering of the **core.**[14]

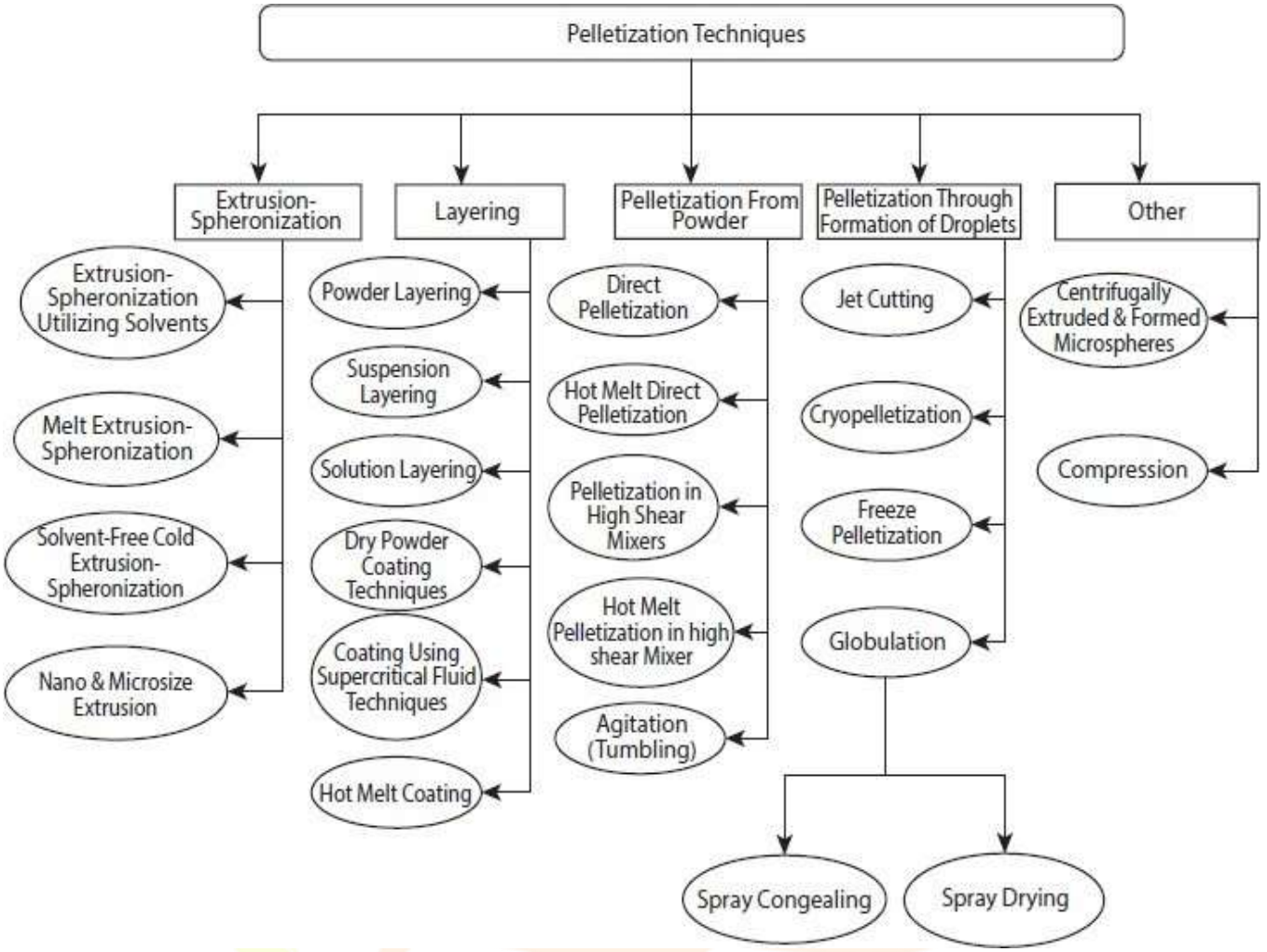


**Figure 2: Different pelletization techniques**

## EVALUATION OF PELLETS

Pellets can be evaluated for various parameters representing specific properties as depicted in Table 3.

- Flow properties of pellets can be evaluated by determining porosity, angle of repose, flow rate, Carr's index and Hausner's ratio.
- Pellet size, shape, roundness and circularity can be correlated with their morphological properties.
- Strength and friability represent mechanical properties of the pellets.
- *In vitro* disintegration, *in vitro* dissolution, swelling and drug content are the evaluation tests representing drug entrapment and drug release characteristics of the pellets.
- *Ex vivo* mucoadhesion may be determined by the wash-off test and mucoadhesive strength determination by a texture analyser.[15]

**Table 3: Evaluation of various properties of pellets**

| Sr. no. | Evaluation property | Test |
|---|---|---|
| i. | Flow properties | Porosity, angle of repose, flow rate, Carr's index, Hausner's ratio |
| ii. | Morphological properties | Size, shape, surface area, roundness, circularity |
| iii. | Mechanical properties | Tensile strength, crushing strength, friability |
| iv. | Drug entrapment and drug release | *In vitro* disintegration, dissolution, swelling, drug content |
| v. | Mucoadhesive property | *Ex vivo* mucoadhesion |

## I. Flow properties

i. Angle of repose (θ)

It is used to estimate the flow property of pellets. The angle of repose of pellets was determined by the funnel method. The accurately weighed pellets were taken in the funnel. The height of the funnel was adjusted in such a way that the tip of the funnel remains 2 cm above the base. The pellets were allowed to flow through the funnel freely on to the surface. The diameter of the pellet cone was measured and angle of repose was calculated using the following equation:

$$\tan\theta = \frac{h}{r}$$

where h = Height (cm ,
r = Radius (cm) of the pellet cone

ii. Bulk density

Apparent bulk density was determined by pouring the pellets into a graduated cylinder. The bulk volume and weight of the pellets was determined. The bulk density was calculated using following equation:

$$\rho b = \frac{M}{Vb}$$

where, $\rho b$ = Bulk density (gm/cm$^3$),
M = Weight of pellets (gm),
$V_b$ = Bulk volume (ml)

iii. Tapped density

The measuring cylinder containing a known mass of pellets was tapped for 100 times. The minimum volume occupied in the cylinder and weight of the pellets was measured. The tapped density was calculated using following equation:

$$\rho t = \frac{M}{Vb}$$

where, $\rho t$ = Tapped density (gm. /cm$^3$),
M = Weight of pellets (gm),
$V_t$ = Tapped volume (ml)

iv. Hausner's ratio (Hp)

The Hausner's ratio is used for the estimation of the flow property of pellets. Hausner's ratio is the ratio of tapped density to bulk density of pellets. Its value less than 1.25 indicates excellent flow of particles and value more than 1.25 indicates poor flow property. The Hausner's ratio of the granules was determined by the equation:

$$Hp = \frac{\rho t}{\rho b}$$

## II. Mechanical properties

v. Friability

Friability of all pellets was determined by USP friability test. Friability of the pellet formulations was evaluated over 10 g of samples in Roche Friabilator at 25 rpm for 4 min. Prior to and following the test, the weights of the formulations were accurately recorded and the friability ratios were calculated. The results were expressed in terms of the percentage of weight lost during the process.

$$F = \frac{(W_1 - W_2)X\ 100}{W_1}$$

where, $W_1$ is the initial weight,
$W_2$ is the final weight of the formulation

**III. Drug entrapment and drug release**

*In vitro drug release studies*

The release of drug from the developed formulations in the environment of colon was determined using USP XXIII dissolution apparatus I. Pellets were placed in the basket, which was further immersed in beaker containing 900 mL of phosphate buffer pH 7.4 as dissolution media maintained at 37 ± 0.5 °C and 50 rpm. Aliquots of 5 ml were withdrawn every 15 min for first hr, 30 min for second hr and then every hour until 100% drug release was obtained, with the replacement of 5 ml of the fresh medium. Correction factors for each aliquot were considered in calculation of drug release profile. Absorbance of sample after proper dilution was measured at 303 nm using U.V. spectrophotometer against blank. Concentration of drug was determined from the standard plots of the drug in phosphate buffer pH 7.4 previously calculated and the% drug release was calculated at each sampling time. The study was performed in triplicates.

**IV. Mucoadhesive property**

*Ex vivo* studies

Male Albino Wister rats were used for the pharmacokinetic study (Protocol No. RPCP/IAEC/2013-2014/MPH-PT-42). The rat was kept in the fasted condition overnight. It was then sacrificed and the colon along with its contents was isolated. The lower end was closed by using thread or clip while from the upper end pellets equivalent to unit dose were placed and the upper end was also tied. The whole tissue was then placed in the assembly containing phosphate buffer pH 7.4 and continuous air supply was provided with the maintenance of temperature. Samples were withdrawn at every hour and analysis was performed by UV spectrophotometer at 303 nm.[15]

Coated or uncoated pellets are either compressed into tablets (MUPS tablets) or put into firm gelatin capsules (MUPS capsules) in multi-unit pellet systems (MUPS). Because of their distinctive mechanical and physical characteristics (such as tensile strength, elastic and plastic deformation ability, and spherical shape), MUPS are widely used multi-unit dosage forms. Compared to traditional single unit dosing forms, MUPS tablets and capsules offer a number of pharmacokinetic and pharmacodynamic advantages. MUPS offer less inter-subject variance, less chance of dose dumping, and more consistent drug release patterns for controlled drug release applications.MUPS could be used to efficiently design mucoadhesive and colon-targeted medication delivery systems. Among the widely accessible MUPS formulations are fast disintegrating MUPS, modified release MUPS, matrix type MUPS, and targeted drug delivery MUPS (gastro-retentive MUPS, colon targeted MUPS).[16, 17]

## MUCOADHESIVE PELLETS FOR DRUG DELIVERY APPLICATIONS

Pharmaceutical pellets can be used as carriers for loading or layering drugs because of their spherical shape,. They can also be easily coated with a mucoadhesive polymer to create mucoadhesive pellets that target certain areas of the stomach or colon. The pellets' mucoadhesive performance might be assessed using a texture analyzer or the mucoadhesion wash-off test. Pharmaceutical pellets can be used to compare the mucoadhesive properties of biopolymers, synthetic polymers, and composite polymers. Pharmaceutical researchers and industry find mucoadhesive pellets appealing for commercial exploitation due to their ease of invention, evaluation, and industrial scalability.

The literature reports for development of mucoadhesive pellets of different drugs, their polymeric components, preparation techniques and specific research outcomes are listed below:

**Table 4: Literature Reports**

| Researchers | Drug and polymers | Work Done |
|---|---|---|
| Cao *et al.* | Valsartan, hydroxypropylmethyl cellulose (HPMC) and carbomer | When compared to core pellets and medication suspension, polymer-coated pellets were found to have substantially higher mucoadhesion and bioavailability.[18] |
| Piao *et al.* | metformin hydrochloride, Sodium carboxymethyl cellulose and sodium alginate | They used a centrifugal fluidizing granulator to create polymer-coated mucoadhesive pellets with metformin hydrochloride utilizing a powder-layering approach.[19] |
| Palem *et al.* | Pioglitazone, felodipine | They created buccal pellets of felodipine and pioglitazone via hot-melt extrusion as a combination dose form for the treatment of hypertension and diabetes. Bioavailability significantly improved, with increases of 1.9 and 2.1 times for pioglitazone and felodipine, respectively.[20] |
| Martin *et al.* | Ketoprofen, pectin | They created thiolated pectin, which was utilized in the extrusion-spheronization process to create mucoadhesive ketoprofen pellets. Mucoadhesive pellets based on thiolated pectin were suggested as a possible foundation for the creation of mucoadhesive oral medication delivery systems.[21] |
| Bautzova *et al.* | 5-aminosalicylic acid, Chitosan, Eudragit FS | They created mucoadhesive pellets with Eudragit FS and chitosan to deliver 5-aminosalicylic acid specifically to the colon. There have been reports of improved local medication concentrations for the successful treatment of inflammatory bowel disorders.[22] |
| Kendre and Chaudhari | Eplerenone,HPMC K4M and Carbopol 934p | Eplerenone was produced as a solid dispersion using the graft copolymer polyvinyl caprolactam–poly (vinyl acetate)–poly (ethylene glycol). HPMC K4M and Carbopol 934p polymers were utilized in these solid dispersions to create mucoadhesive pellets. Significant mucoadhesion and increased eplerenone bioavailability from the muco adhesive pellets were shown in in vivo animal investigations.[23] |
| Sonawane and Patil | Zaltoprofen, starch-κ-carrageenan | Both made zaltoprofen extended release pellets employing a starch-κ-carrageenan hydrogel combination as a binder and extended release polymer. Significant mucoadhesion and long-term drug release from the pellets were discovered.[24] Additionally, a new polymer called the gelatin–κ-carrageenan polyelectrolyte complex was used to manufacture matrix pellets utilizing the extrusion-spheronization approach. This novel polymeric material demonstrated notable mucoadhesion and an extended drug release pattern.[25] |
| Ige and | hydroxypropyl methyl | They created hydroxypropyl methyl |

| | | |
|---|---|---|
| Gattani | cellulose K200M and microcrystalline cellulose | cellulose K200M and microcrystalline cellulose matrix mucoadhesive pellets to administer metformin under regulated conditions. The pellets were assessed using a variety of in vitro, in vivo, and ex vivo techniques. According to reports, mucoadhesive pellets are a successful and efficient gastroretentive drug administration method.[26-27] |
| Moschwitzer and Muller | hydrocortisone acetate | Both made mucoadhesive pellets of hydrocortisone acetate nanocrystals by employing a fluidized bed coater to layer the drug's freshly made nanosuspension onto sugar spheres. The study's findings included increased drug solubility, enhanced drug targeting, and improved mucoadhesiveness.[28-29] |
| Ige *et al*. | Nifedipine, HPMC K15M and κ-carrageenan | They formulated mucoadhesive pellets of nifedipine using HPMC K15M and κ-carrageenan by extrusion-spheronization technique. The pellets exhibited significant mucoadhesion and stability.[30] |
| Hiorth *et al.* | Hexylaminolevulinate, Carbopol 934 | They formulated bioadhesive pellets containing hexylaminolevulinate by extrusion-spheronization technique. According to reports, the bioadhesive pellets that were produced showed promise as vaginal delivery systems for hexylaminolevulinate pellets meant for photodynamic therapy in the treatment of cervical cancer.[31] |
| Desai and Momin | curcumin and cyclosporine Carbopol 940 , hydroxypropyl cellulose and Eudragit S100 | Both created bioadhesive pellet cores containing curcumin and cyclosporine using Carbopol 940 and hydroxypropyl cellulose, by extrusion-spheronization techniques. The bioadhesive was then coated with Eudragit S100, a pH-sensitive polymer, to deliver it to the colonic area. Cyclosporine and curcumin bioadhesive pellets have been shown to be an efficient medication delivery method for the treatment of inflammatory bowel disorders.[32] |
| Mezreb *et al.* | Carbopol 974, Carbopol 971P | They used Carbopol 974 and Carbopol 971P in the extrusion-spheronization process to create bioadhesive pellets. To achieve the maximum production of spherical pellets with a diameter of 710–1000 μm, the different processing parameters, including extrusion speed, spheronizer speed, spheronization time, and water amount, were optimized.[33 -37] |
| Weon *et al*. | | They created gastro-retentive pellets with an exterior layer made of a polymer with mucoadhesive and drug release-controlling qualities and an interior layer of medication and pharmaceutically acceptable carrier. |

| | | |
|---|---|---|
| | | According to reports, the idea works well for managing diabetes.[38-43] |

In another invention oral multiparticulate pharmaceutical pellets of size ranging between 50 to 2500 µm were developed. The formulation comprised of an inner matrix layer containing peptide/protein as an active pharmaceutical ingredient and an outer coating of an anionic polymer. The outer coating additionally acts to protect the active substance from proteolytic enzymes and to deliver the formulation in the intestine (duodenum, jejunum, ileum or colon)
where it starts to dissolve.[44-49]
Plant extract containing pellets have been developed by dispersing plant extract or extracts in a matrix of biopolymers such as collagen, gelatin, fractionated gelatin, a collagen hydrolysate, gelatin derivative plant proteins, or plant protein hydrolysates. The product is more stable and pharmacologically effective when compared with the native extracts.[49-53] Pharmaceutical pellets prepared by extrusion-spheronization method using modified starch were developed for vaginal drug delivery.[54]

## CONCLUSION

Pharmaceutical pellets are commonly used for developing immediate release and modified drug release dosage forms. Pellets are widely accepted as drug delivery vehicles because of certain benefits, including mechanical, pharmacokinetic, pharmacodynamic, and physical ones. Mucoadhesive pellets are created using mucoadhesive polymers. The primary goals of mucoadhesive polymer research are creating more affordable polymers with greater mucoadhesive strength, modifying already-existing polymers, creating polymers with many uses, etc. Other significant difficulties that require significant attention in order to comply with regulatory requirements include toxicity and stability of polymers. An emerging technology with a wide range of uses is 3D printing. Innovative 3D printers can be used to create sturdy, customizable, and repeatable pellets. Pharmaceutical pellets will have new uses as medication delivery methods in the future thanks to the development of affordable 3D printing technology [56,57]. The creation, validation, and optimization of manufacturing parameters for the production of mucoadhesive pellets can also be accomplished by computational modeling techniques. Mucoadhesive pellets are commercially viable formulations that target the gastric, colonic, and vaginal regions specifically to treat various illnesses. Developing and validating novel methods for producing and assessing pellets with enhanced performance should be the main priorities.

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