

MUCOADHESIVE PELLETS AS A DRUG DELIVERY SYSTEM**Patel Utkarsh Mukesh, Satyajit Sahoo*****Department of Pharmaceutics, Pioneer Pharmacy College, Vadodara, Gujarat, India – 390019***Corresponding Author's E mail: satyajitppdc@gmail.com

Received 17 March 2025; Revised 21 March. 2025; Accepted 28 March. 2025, Available online 15 April. 2025



Cite this article as: Sahoo S and Patel UM. Mucoadhesive Pellets as a Drug Delivery System. Asian Journal of Pharmaceutical Education and Research. 2026; 15(2):18- 35.

<https://dx.doi.org/10.38164/AJPER/15.2.2026.18-35>**ABSTRACT**

Pellets are spherical shaped multiparticulate drug delivery systems with size ranging between 0.5-2.0 mm. Free flow, good mechanical properties, improved physical and chemical properties of powder, and stability are some advantages of pellets. Mucoadhesive pellets could be developed by using appropriate concentration and type of mucoadhesive polymer. Mucoadhesive pellets can be used for delivery of drugs to gastric, colonic, and vaginal regions. Immediate release, sustained/controlled release and implantable delivery could be incorporated using mucoadhesive pellets. Reproducibility, ease of scalability, quality control checks and significant mechanical strength are some advantages making pellets widely acceptable by pharmaceutical industry. In the present review, mucoadhesion process and theories, mucoadhesive polymers, pelletization process, evaluation of pellets and reported research/patents on mucoadhesive pellets for delivery of different categories of drugs have been presented.

Keywords: Mucoadhesion, pellets, multiparticulate, drug delivery system, mucoadhesive pellets.**INTRODUCTION**

Bioadhesion refers to the phenomenon of adhesion of natural or synthetic materials to biological substrates for a prolonged period. An understanding of the fundamental mechanisms of bioadhesion is of great interest for researchers aiming to develop new biomaterials, therapies and technologies.¹ Mucosal membrane are the moist surfaces lining the walls of respiratory, gastrointestinal and reproductive tracts as well as the nostrils, the eyes and the mouth. Mucus plays an important role in protection, lubrication, wettability and regulation of moisture content of epithelial surfaces of the cells. In single-layered epithelia there are specialized goblet cells that secrete mucus directly onto the surface of the epithelium. However, multi-layered stratified epithelium contains specialized glands (e.g. salivary glands) for the secretion of mucus. The mucus gel is composed of water, glycoproteins, lipids and electrolytes; the water content is approximately 95%, the glycoproteins and lipids constitute between 0.5 to 5%, and about 0.5 to 1% is the content of mineral salts. Physicochemical characteristics like composition, pH, ionic strength and conformation are important to cater functions and rheological

properties of mucus. Toxic and potentially irritating substances can stimulate mucus secretion as a defense mechanism for the removal of irritants from the epithelium.² Mucoadhesion is defined as attractive interaction between a pharmaceutical dosage form and the mucosal membrane. Mucoadhesive drug delivery systems can be used for developing attractive and flexible dosage forms for administering therapeutic agents to ocular, nasal, buccal and gingival, gastrointestinal (oral), vaginal and rectal targets. The advantages associated with the use of mucoadhesives in drug delivery include increased dosage form residence time, improved drug bioavailability, reduced administration frequency, simplified administration of a dosage form, and possibility of targeting particular body sites and tissues.³ Mucoadhesive drug delivery systems may be formulated as tablets, films, gels, nanoparticles, microspheres, wafers, pessaries, viscous solutions, micro and nano-particulate suspensions, *in situ* gelling systems and sprays.^{4,5}

Mucoadhesion is a two-step process involving:

i. The contact Stage:

In the contact stage, there is development of intimate contact between the polymers of the drug delivery system and the mucosal membrane.

ii. Consolidation Stage:

The consolidation stage involves interpenetration and/or entanglement of the chains of the mucoadhesive polymer with those of the mucin. The mucoadhesive bond formation between the polymer and the mucosal surface occurs predominantly by weak van der Waals forces, hydrogen bonding, or by ionic interactions.⁶⁻⁸

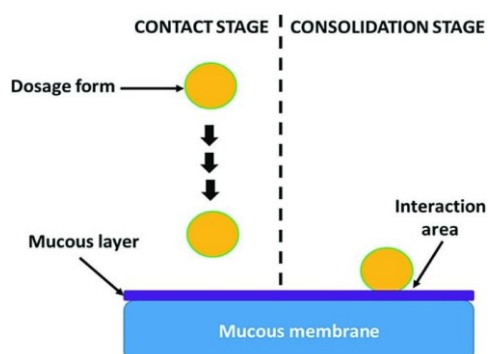


Figure 1: Mechanism of Mucoadhesion

THEORIES FOR PHENOMENA OF MUCOADHESION

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

Wetting theory: This theory takes into consideration the surface tension of mucus and the mucoadhesive polymer. It is broadly applicable to liquid mucoadhesive forms and involves the ability of a liquid to spread spontaneously onto mucosal surface for the development of adhesion.¹⁰

Diffusion theory: Inter-diffusion of the chain soft polymer and the mucin could be held responsible for the development of mucoadhesive bond. This process is driven by concentration gradients, molecular chain lengths, mobility, and hydrodynamic size.

Adsorption theory: This theory considers the involvement of hydrogen bonding and Vander Waals forces for mucoadhesive interactions. It also considers the possibility of chemisorption, when strong covalent bonds are formed between the mucoadhesive polymer and the mucin.

Electronic theory: This theory assumes that the electrostatic attraction between the mucin and the mucoadhesive polymer is responsible for the phenomenon of mucoadhesion. Transfer of electrons leading to the formation of electrical double layer occurs at the interface.

Mechanical theory: This theory considers the effect of surface roughness and mechanical interlocking for the development of mucoadhesion.

Fracture theory: It relates the difficulty of separation of two surfaces after adhesion and is considered to be appropriate for calculating the fracture strength of adhesive bonds.¹¹

The complex nature of a mucin molecule permits multiple interaction mechanisms between the polymer and mucin which involve various types of bonding, electrostatic, physical entanglement and hydrophobic interactions. Different factors affecting the mucoadhesive interactions are listed in Table 1:

Table1: Factors affecting the mucoadhesive interactions¹¹

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

Mucoadhesive polymers are polymers that exhibit sufficient mucoadhesive property involving strong intermolecular bonding with the mucosal layer. Mucoadhesive drug delivery systems have been explored for the localization of the active agents to a particular location/site. The polymers used in the drug delivery systems play an important role in designing such systems so as to increase the residence time of the active agent at the desired location. The polymer penetrates into the mucus network or tissue crevices. The easy wetting of mucosal layer and high molecular weight of the polymer chain facilitate mucoadhesion.¹¹ Classification, categories and examples of mucoadhesive polymers are given in Table 2.

Table 2: Classification, categories and examples of different mucoadhesive polymers

Sr.no.	Classification on the basis of	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	<i>Cellulose derivatives</i> Carboxymethyl cellulose, sodium carboxymethyl cellulose, thiolated carboxymethyl cellulose, hydroxyethyl cellulose, hydroxylpropyl cellulose, hydroxyl propyl methyl cellulose, methyl cellulose, methyl hydroxyl ethyl cellulose <i>Poly(acrylic acid)-based polymers</i> Carbopol, polycarbophil, polyacrylates, poly(methylvinylether-co-methacrylic acid), poly(2-hydroxyethyl methacrylate), poly(acrylic acid-coethylhexylacrylate), poly(methacrylate)
III	Charge	Cationic	Amino dextran, chitosan, trimethylated chitosan, dimethyl aminoethyl dextran
		Anionic	Carbopol, carboxymethyl cellulose, pectin, poly(acrylic acid), polycarbophil, sodium

V	Solubility	Non ionic	alginate, sodium carboxymethyl cellulose, xanthan gum Hydroxyethyl starch, hydroxypropyl cellulose, poly (vinyl alcohol), polyvinylpyrrolidone, scleroglucan
		Water soluble	Carbopol, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, poly(acrylic acid), sodium alginate
V	Mucoadhesive interaction	Water insoluble	Chitosan, ethyl cellulose, polycarbophil
		Electrostatic interaction	Chitosan
		Covalent bonding	Cyanoacrylate
		Hydrogenbonding	Poly (methacrylic acid), carbopol, polycarbophil, poly (vinylalcohol)

PELLETS

Pelletization can be defined as an agglomeration/size-enlargement process of conversion of powdered pharmaceutically active ingredients and excipients into small, spherical, free-flowing units, called pellets. The size of pellets ranges between 0.5 and 2.0mm and are intended mainly for oral administration. However, pellet-based implants have also been used for drug administration via intramuscular and subcutaneous routes. Pellets have been widely accepted by the pharmaceutical industry due to advantages like defined shape, uniformity of contents, free flowing property, mechanical strength, and ease of polymer coating.¹²

ADVANTAGES:

Pharmaceutical pellets have several therapeutic advantages over conventional oral dosage forms (tablets or capsules), such as:

- Pellets can disperse freely throughout the gastrointestinal tract leading to even drug absorption profiles;
- Peak plasma level of drugs can be customized by the use of polymer coated pellets with different drug release rates;
- Potential side effects are minimized without altering bioavailability of the drug;
- The wide distribution of spherical pellets limits the dose dumping of drugs in the gastrointestinal tract and is also effective in reducing potential irritation effect of some drugs on the gastric mucosa.

DISADVANTAGES:

Potential disadvantages associated with pellets as drug delivery systems include:

- difficulty to compress pellets into tablets, production of pellets requires specialized equipment making the process relatively expensive,
- control of the production process is difficult as it involves a number of process variables.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. 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

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

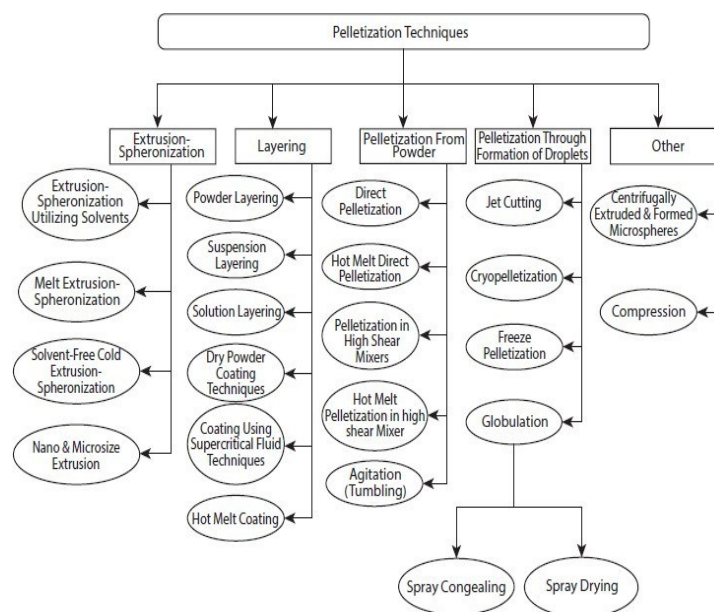


Figure 2: Different pelletization techniques

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
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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	<i>In vitro</i> disintegration, dissolution, swelling, drug content
v.	Mucoadhesive property	<i>Ex vivo</i> mucoadhesion

I. Flow properties

a) 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 away that the tip of the funnel remains 2cm above the base. The pellets were allowed to flow through the funnel freely onto the surface. The diameter of the pellet cone was measured and angle of repose was calculated using the following equation:

where h = Height(cm)

r = Radius(cm)

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

b) 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:

$$\rho_b = \frac{M}{V_b}$$

where, ρ_b = Bulk density (gm/cm³), M = Weight of pellets (gm), V_b = Bulk volume (ml)

c) 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:

$$\rho_t = \frac{M}{V_t}$$

where, ρ_t = Tapped density (gm./cm³), M = Weight of pellets (gm), V_t = Tapped volume (ml)

d) Hausner's ratio (H_p)

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:

$$H_p = \rho_t / \rho_b$$

e) Mechanical properties

i. 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 25rpm for 4min. 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.

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

where, W₁ is the initial weight,

W₂ is the final weight of the formulation

ii. *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.

iii. Mucoadhesive property

Ex vivo studies

Male Albino Wister rats were used for the pharmacokinetic study. 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

Multi-unit pellet systems (MUPS) are the dosage forms in which coated or uncoated pellets are either compressed into tablets (MUPS tablets) or filled into hard gelatin Capsules (MUPS capsules). MUPS are popular

multi-unit dosage forms because of their unique physical properties (e.g. spherical shape) and mechanical properties (e.g. tensile strength, elastic and plastic deformation ability). MUPS tablets and MUPS capsules have several pharmacokinetic and pharmacodynamics advantages over conventional single unit dosage forms. For controlled drug release applications, MUPS provide more uniform drug release profiles, reduced risk of dose dumping, and lesser inter-subject variations. Mucoadhesive and colon targeted drug delivery systems could be effectively designed using MUPS. Fast disintegrating MUPS, modified release MUPS, matrix type MUPS, targeted drug delivery MUPS (gastro-retentive MUPS, colon targeted MUPS) are some of the commonly available MUPS formulations.^{16,17}

Mucoadhesive Pellets For Drug Delivery Applications

Pharmaceutical pellets being spherical in shape can be used as carriers for loading or layering the drug and could be coated easily with a mucoadhesive polymer for developing mucoadhesive pellets for specific drug targeting to gastric or colonic regions. Mucoadhesive performance of the pellets could be evaluated by mucoadhesion wash-off test or with the help of a texture analyzer. Biopolymers, synthetic polymers and composite polymers can be evaluated for comparative mucoadhesive performance using pharmaceutical pellets. Easy development, easy evaluation and industrial scalability are some advantages of mucoadhesive pellets which are attractive to pharmaceutical researchers and industry for commercial exploitation. The literature reports for development of mucoadhesive pellets of different drugs, their polymeric components, preparation techniques and specific research outcomes are listed below:

- Cao *et al.* used hydroxypropyl methyl cellulose (HPMC) and carbomer in different ratios for preparing mucoadhesive pellets of valsartan by extrusion spheronization technique. The mucoadhesion and bioavailability of polymer coated pellets were reported to be significantly higher when compared with core pellets and suspension of the drug.¹⁸
- Piao *et al.* prepared polymer coated mucoadhesive pellets containing metformin hydrochloride by powder-layering technique using a centrifugal fluidizing granulator. Sodium carboxy methyl cellulose and sodium alginate were reported to be the promising mucoadhesive polymers by developing once-a-day sustained release mucoadhesive pellets of metformin hydrochloride.¹⁹
- Palem *et al.* developed buccal pellets of pioglitazone and felodipine by hot-melt extrusion as a combined dosage form for the management of diabetes and hypertension. Significant improvement in bioavailability was observed, 1.9-fold and 2.1-fold increases for pioglitazone and felodipine, respectively. The formulation was found to be stable in 6-month stability studies.²⁰
- Martin *et al.* performed thiolation of pectin by esterification with thioglycolic acid. Thiolated pectin was used for developing mucoadhesive pellets of ketoprofen by extrusion-spheronization technique. Thiolated pectin based mucoadhesive pellets were proposed to be a potential platform for the development of mucoadhesive drug delivery systems for the oral route.²¹

- Bautzova *et al.* fabricated mucoadhesive pellets for the colon-specific delivery of 5-aminosalicylic acid. Chitosan was used as mucoadhesive biopolymer and Eudragit FS was employed as pH-sensitive polymer for colon-specific delivery of the dosage form. Improved local drug concentrations were reported for an effective management of inflammatory bowel diseases.²²
- Kendre and Chaudhari prepared solid dispersion of eplerenone with the graft copolymer polyvinyl caprolactam–poly (vinyl acetate)–poly (ethylene glycol). These solid dispersions were used for developing mucoadhesive pellets using HPMCK4 and Carbopol 934 polymers. *In vivo* animal studies demonstrated significant mucoadhesion and improved bioavailability of eplerenone from the mucoadhesive pellets.²³
- Sonawane and Patil prepared extended-release pellets of zaltoprofen using starch- κ -carrageenan hydrogel composite as extended release polymer and binder. Significant mucoadhesion and sustained release of drug for prolonged period of time from the pellets were found.²⁴
- Sonawane and Patil formulated matrix pellets by extrusion-spheronization technique using gelatin– κ -carrageenan polyelectrolyte complex as a novel polymer. Significant mucoadhesion and extended drug release pattern were observed using this new polymeric material.²⁵
- Ige and Gattani developed matrix mucoadhesive pellets of hydroxypropyl methyl cellulose K200M and microcrystalline cellulose for controlled delivery of metformin. Various *in vitro*, *in vivo* and *ex vivo* tests were performed for evaluating the pellets. Mucoadhesive pellets were reported to be an effective and efficient gastroretentive drug delivery system.²⁶⁻²⁷
- Moschwitz and Muller prepared mucoadhesive pellets of hydrocortisone acetate nanocrystals by layering the freshly prepared nanosuspension of the drug onto sugar spheres using a fluidized bed coater. Improved drug solubility, better drug targeting and improved mucoadhesion were the outcomes of the research study.²⁸⁻²⁹
- Ige *et al.* formulated mucoadhesive pellets of nifedipine using HPMC K15M and κ -carrageenan by extrusion-spheronization technique. The pellets exhibited significant mucoadhesion and stability.³⁰
- Hiorthe *et al.* developed bioadhesive pellets of hexylamino levulinate for vaginal delivery. Pellets were formulated by extrusion-spheronization technique using Carbopol 934 as bioadhesive polymer. The developed bioadhesive pellets were reported to be promising carriers for vaginal delivery of hexyl amino levulinate pellets intended for photodynamic therapy in the treatment of cervical cancer.³¹
- Desai and Momin employed extrusion-spheronization method for preparing bioadhesive pellet cores of curcumin and cyclosporine using Carbopol 940 and hydroxypropyl cellulose and coating with a pH-sensitive polymer (Eudragit S100) for the delivery of the bioadhesive to the colonic region. Bioadhesive pellets of curcumin and cyclosporine were reported to be an effective drug

delivery system in the management of inflammatory bowel diseases.³²

- Mezreb *et al.* developed bioadhesive pellets by extrusion-spheronization method using Carbopol 974 and Carbopol 971P. Optimization of the various processing parameters such as extrusion speed, spheronizer speed, spheronization time, and amount of water was conducted to obtain the highest yield of spherical pellets ranging in size between 710–1000 μm diameter.³³⁻³⁷
- Weon *et al.* in their patented invention have prepared gastro-retentive pellets comprising an inner layer of drug and pharmaceutically acceptable carrier, and an outer layer comprising a polymer having the mucoadhesive and drug release controlling properties. The invention was reported to be effective for the management of 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. Specific advantages viz. physical, mechanical, pharmacokinetic and pharmacodynamics are responsible for wide acceptability of pellets as drug delivery carriers. Mucoadhesive polymers are used for developing mucoadhesive pellets. Research on mucoadhesive polymers is mainly focused on developing cost-effective polymers with higher mucoadhesive strength, modification of existing polymers, developing polymers with multifunctional properties, etc. Toxicity and stability of polymers are other important issues which need substantial focus for complying with the regulatory issues. 3D printing is an upcoming technology with vast applications. Reproducible, customized and stable pellets can be developed using novel 3D printers. With the advent of cost-effective 3D printing technology, the future of pharmaceutical pellets will witness novel applications as drug delivery systems^{56,57}. Computational modeling techniques can also be used for development and validation/optimization of manufacturing parameters for fabricating mucoadhesive pellets. Mucoadhesive pellets are industrially

viable formulations for specifically targeting gastric, colonic, vaginal regions for the management of different diseases/ disorders. The focus should be on development and validation of new techniques for manufacturing and evaluation of pellets with improved performances.

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