www.ThePharmaJournal.com

The Pharma Innovation

ISSN: 2277- 7695
TPI 2017; 6(2): 03-10

www.thepharmajournal.com
Received: 02-12-2016
Accepted: 03-01-2017

**Pratik Chaudhari**
Department of Pharmaceutics, R. C. Patel Institute of Pharmaceutical Education & Research, Shirpur, Dhule, Maharashtra, India

**Raju Sonawane**
Department of Pharmaceutics, R. C. Patel Institute of Pharmaceutical Education & Research, Shirpur, Dhule, Maharashtra, India

**Prashant Deore**
Department of Pharmaceutics, R. C. Patel Institute of Pharmaceutical Education & Research, Shirpur, Dhule, Maharashtra, India.

**Correspondence**
**Pratik Chaudhari**
Department of Pharmaceutics, R. C. Patel Institute of Pharmaceutical Education & Research, Shirpur, Dhule, Maharashtra, India

# Pelletization techniques: Novel approach for drug delivery

**Pratik Chaudhari, Raju Sonawane and Prashant Deore**

**Abstract**
Pellets are the agglomeration of small free flowing spherical particulates of fine powder or granules of bulk drug and excipients. Conventional immediate drug delivery is based on single/multiple unit reservoir or matrix system. The different polymers used with the superdisintegrants as pelletization aid in immediate release pellets like β–cyclodextrins, carrageenan, starches, chitosan, powdered cellulose, pectinic acids etc. Immediate drug delivery is suitable for drugs having poorly water soluble and belongs to BCS class–II. The different categories of drugs like $H_2$ – receptor antagonists, antacids, NSAID's, antilipidemic and diuretics etc. are studied with different variables by suitable techniques for better physical properties and it is characterized by different methods.

**Keywords:** MCC, κ – carrageenan, cyclodextrins, extrusion–spheronization, reservoir system, matrix system

## Introduction
Pellets are small free flowing spherical (0.5 - 2 mm) particulates agglomeration of fine powder or granules of bulk drugs and excipients. So, the agglomeration process of fine powder or granules is known as pelletization [13]. The term immediate release pharmaceutical formulation includes any formulation in which the rate of release of drug from formulation and absorption of drug is neither appreciably nor intentionally retarded by galenic manipulations [17]. Conventional immediate release drug delivery system are designed to give immediate release action in short period of time and it is based on single/multiple- unit reservoir or matrix system [12]. The maximum possible particle size range for pharmaceutical use should be considered as 600 – 1000 µm [6]. The basic approach regarding the immediate release pellets development is use of superdisintegrants like Ac-Di-Sol, primogel, explotab and polyplasdone [17]. The polymer used in the immediate release pellets are powder cellulose, starches, chitosan, pectinic acid, β – cyclodextrins, carrageenan, polyethylene oxide and sodium alginate; they used as an alternative to microcrystalline cellulose [1]. Microcrystalline cellulose is not a choice for extrusion -spheronization process because of various deficiencies like adsorption on it's surface, several drugs incompatibilities, prolong drug release was observed in poorly soluble drugs [1]. Appropriate selection and balance of excipients as well as process in solid dosage formulation are designed for improving micromeritic properties of materials during manufacture and providing a desired drug delivery system (Bianchini R. *et al.*) [12]. Various techniques used to developed immediate release pellets are extrusion - spheronization, drug layering, cryopelletization, freeze pelletization, globulation and balling [19]. Immediate drug delivery is suitable for drug substances with different categories having poor solubility. There were 40% or more of active substances are poorly soluble in water. This is the need of novel approaches to make such poorly soluble drug bioavailable [21].

## Advantages
The problem of lower bioavailability and acute local contact of aceclofenac cause irritation to gastric mucosa should overcome by enteric coated immediate release pellets [10]. The improving dissolution process of poorly soluble famotidine $H_2$ - receptor antagonist used for peptic ulcer by using highly hydrophilic pluronic F - 127 show higher HLB value [5]. The powder coated omeprazole immediate release pellets rapidly absorbed and have identical bioavailability than physical mixed powder [7]. The anti-lipidemic fenofibrate drug used in hypercholesterolemia have plasma half-life 22.1 hr. So, by using PVP K - 30 as binder and starch as disintegrant, drug diffusion and drug release kinetics was change [18]. Immediate release pellets are flexible to design the process and development of dosage form [13].

These are disperse freely with reducing plasma peak fluctuation to reach maximum drug absorption [13]. Immediate release pellets gastric emptying by minimizing variability of intra and inter subject plasma profile [13]. They dispersed freely because of their small size, large surface area of absorption thus, reduces gastric emptying rate and time [13]. There is no difficulties in flow property, it packs easily and low porosity of about 10% resulting uniform as well as reproducible fill weight of capsules and tablets [21]. Good sphericity, smooth surface properties, narrow size distribution and low friability ensures a drug content uniformity with minimum risk of dose dumping [15]. High toxicity as well as concentration in high dose administration should avoided [15]. The incomplete release of dose does not observed [10].

**Disadvantages:**

The use of PVP K-30 and maize starch indicate that anti-lipidemic fenofibrate release was not consistent and show incomplete release [18]. Microcrystalline cellulose based pellets of poorly soluble hydrochlorothiazide and piroxicam prepared by extrusion-spheronization release less than 40% after 75 min [3]. Pellet preparation is very expensive process, specialized handling person and equipments required for it [13]. Capsule filling with immediate release pellets involves increase in cost [13].

**Formulation variables in immediate release pellets**

- Different excipients are maily used for development of pharmaceutical development of pharmaceutical dosage forms for it's intended site [14].
- Various drug entities doesn't posses the required properties for desired dosage form. So, formulation design and manufacturing of dosage form involves addition of one or more excipients that has role in it [14].
- If immediate release pellets intended for oral route then excipients used in pellets is same that used in tablet and capsule formulations with same functional characteristics [14].
- The excipients used in the immediate release pellets are varied with their chemical and physical properties [14].
- The physicochemical properties of drug and excipients are combine individually to developed a successful pelletized product [14].
- The material variables required for preparation of spherical granules of pellets includes concentration of binder, solvent system, size and shape of non-paeril cores, amount of fillers and size of particles [4].
- The coated pellets have physical and mechanical properties are nearly same with it's core i.e. it should be uniform thickness, non-segregation during capsule filling, drug release rate, film diposition and formulation during coating, packing properties etc. [4].
- Core pellets used as substrates by layering process. The main component of core pelletization is sucrose and has side-effects on diabetics and potential carcinogenicity [4].
- Binder had an important characteristics in wet granulating and drug layering process; it affects the final developed drug properties. All the type of binders are acceptable for pellet preparation, but gelatin and carboxymethyl cellulose were most suitable to friability of pellets [4].
- Niskanen *et al.* (1992) observed the binder concentration as well as particle size of drugs affect the physical and mechanical properties of pellets [4].
- Souto, *et al.* (2005) prepared the croscarmellose sodium and sodium starch glycolate based pellets. He observed that there is no significant change in size and shape of pellets when compared to eachother. But dissolution rate is slightly higher in sodium starch glycolate because of it's swelling capacity [22].

**Formulation variables enlisted below**

1. **Fillers:** Fillers are added in pellet formulation to increase bulk properties. Fillers are water soluble or insoluble in nature. So, the selection of pellets based on intended properties of pellets formulation. The use of fillers based on characteristics of drug, method of preparation and required dose. The amount of fillers used in formulation as high as 90% or as low as 1%. The quantity and physical properties may affect the desired formulation's rate and extent of drug release from pellets. Physicochemical factors of fillers also affects the stability of pellets [14].
2. **Binders:** Binders are use to integrate and bind the powder for pellet formulation by adhesive nature of it. It is essential component for pellet formulation and manufacturing [14].
3. **Lubricants:** Lubricants are used in pellet formulation to reduce the friction between manufacturing equipment and reduce [14].
4. **Separating agent:** During pelletization process separating agents absorbs on surface to promote separation of pellets into individual unit. Pellets promote surface charge during manufacture and may lead to attract one another [14].
5. **Disintegrant:** Disintegrants are suitable to add in formulation to any suitable step of process, particularly to granulation or during lubrication step prior to compression [17]. These are substances which in presence of fluid break up the compacted mass of solid dosage form [14].
6. **pH adjuster:** pH adjuster are those which are used to control the microenvironment of drug molecules in pellets for various reasons. Generally to protect the acid labile compounds from acidic environment by enteric film coating [14].
7. **Surfactants:** Surfactants are generally used in pellet formulation mainly for same reason they used in other various dosage forms. The poorly soluble drug have improved solubility, wettability and enhance dissolution rates. The initial and subsequent growth of pellets depends on formation of liquid bridges to hold particles together that means lowering surface tension may leads to weaken bridges and forming pellets [14].
8. **Spheronization enhancers:** These formulation aids which are used to develop a spherical pellets. These substances are impart binding properties to pellets for it's strength and integrity [14].
9. **Glidants:** These are used to develop a flow characteristics of during layering of pellets. During the binder addition there is need to add glidant in well controlled rate for simultaneous binder application [14].

**Potential candidate for immediate release pellets** [17]

- **Anti-diabetic drugs:** Acetohexamide, chlorpropamide, glibenclamide, gliclazide, glipizide
- **Anti-fungal agents:** Amphotericin, butoconazole nitrate, clotrimazole, econazole nitrate, flucytosine, griseofulvin,

ketoconazole, nystatin, sulconazole nitrate, terbinafine HCl, terconazole, tioconazole

- **Diuretics:** Acetazolamide amiloride, bendrofluazide, bumetanide, chlorothiazides, chlorthalidone, spironolactone
- **Gastrointestinal agents:** Bisacodyl, cimetidine, cisapride, diphenoxylate HCl, famotidine, loperamide, mesalazine, omeprazole
- **Lipid regulating agents:** Bezafibrate, clofibrate, fenofibrate, gemfibrozil, probucol

**Drug selection criteria**

- Poorly water soluble drugs have more than 40% identified through combinatorial screening programs. Poor solubility is drug of choice for formulation development [21].
- Drugs having plasma half-life 22.1 hrs. and water insolubility is suitable candidate for immediate release pellets. The drugs with long biological half-life, lower clearance and lower elimination are desirable candidates for immediate release pellets [18].
- Drug should be compatible with excipients. Poorly soluble BCS class – II drugs (hydrochlorothiazide and piroxicam) compatible with modified starch (high amylose, crystalline and resistant starch) by extrusion/spheronization technique [3].
- Non-steroidal anti-inflammatory drugs (NSAID's) like aceclofenac causing irritation to gastrointestinal tract. Aceclofenac is BCS class - II drug having low water solubility and high permeability. So, it is potential candidate with limited bioavailability for immediate release pellets. It should be compatible with solid dispersion technique having mixed surfactants, forms complexation with HP-β-Cyclodextrins (HP-β-CD), chitosan-aceclofenac co-crystals, aceclofenac loaded agarose beads are suitable to selection of NSAID's like aceclofenac. Particle size reduction of poorly soluble drugs is essential for improving solubility thus bioavailability become improved. Drug should avoid gastrointestinal toxicity [10].
- Drug suitable with solid dispersion technique used by limited number of researchers to enhance solubility of $H_2$ – receptor antagonist. Famotidine is $H_2$ – receptor antagonist with low and variable bioavailability to overcome this problem two hydrophilic carriers are made suitable with solid dispersion technique. Drug with enhance wetability and dispersibility is drug of choice for immediate release pellets. Famotidine like drugs undergoes first pass metabolism and bioavailability ranging from 40%-50%. So, drug having high polarity, poor aqueous solubility are improved dissolution rate by increased surface area of drug to enhance solubility of it [5].
- Proton pump inhibitor drugs are very slightly soluble in water, very unstable and easily inactivated in acidic environment of stomach. Those drugs which rapidly degrades at low pH values are choice for immediate release pellets [7].
- Temperature sensitive and bitter drugs are also preferred candidates for pelletization [11].

**Selection criteria for polymers**

1. Ideal characteristics requires in extrusion - spheronization aids for polymers which are water insoluble have longer water absorption and retention capability. Lubrication and surface plasticization require during extrusion - spheronization respectively for it; similar to a reservoir to achieve optimal rheological condition. They have sufficiently larger surface area with cohesiveness for water interaction and formulation component. Polymers have ability to enhance drug release in immediate release pellets [1].
2. Fillers are water soluble and insoluble in nature. The selection of fillers depends on desired dose, physical properties of drug and manufacturing process [14].
3. Binders like sucrose, starch, HPMC, HPC, gelatin, PVP are used to avoid the sticking of drug on seal coated pellets and provide uniform coating on it. Talc is used as a glidant for reducing the static charges to avoid sticking during film coating [13].
4. Polymer selection is also based on drug taste masking by inclusion complex i.e. "host-guest" relationship in which host is complexing agent and guest is active compound. The complexing agent can decrease solubility in oral cavity. β–cyclodextrins is commonly used complexing agent which acts by van-der-waals forces and non-toxic in nature [13].
5. Excipients/Polymers are active in nature and impacts on manufacture, quality, safety and efficacy of drug substances in dosage forms. They have ideal properties; regulating solubility and bioavailability of active ingredients, enhance stability of drug, support active ingredient to maintain it's polymorphic form [9].
6. 2-5% concentration of HPMC is used in total weight of itraconazole immediate release pellets to maximize high quality surface, desired release and size distribution in range [12].
7. Modified starch with suitable binder gives narrow particle size distribution, spherical shape with high process yield. Modified starch is suitable material for poorly soluble drugs by extrusion-spheronization pelletization technique [3].
8. Microcrystalline cellulose (MCC) is most widely used excipient for pellets prepared by extrusion-spheronization. It provides good plasticity to wet mass and well binding property. So, it ensures good extrusion - spheronization but disintegration is important issue of MCC for immediate release pellets. MCC based pellets shows lack of disintegration of poorly water soluble drug in immediate release form which prolongs the drug release [3].
9. In spite of excellent characteristics MCC is not employed as excipient for production of pellets it adsorbs drug onto the surface, number of drugs chemically incompatible with MCC. So, alternative excipients are used like powder cellulose, starches, chitosan, pectinic acid, β – cyclodextrins, sodium alginate, polyethylene oxide and carrageenan [1].
10. Sucrose is main component for core pelletization by layering process [4].
11. Binder is also important in wet granulation and drug layering process; it affect the final drug properties of pellets. All types of binders are acceptable for pellet preparation, but gelatin and carboxymethyl cellulose were more suitable [4].

**Pelletization aid**

1. **Powdered cellulose:** Origin of powdered cellulose is same like microcrystalline cellulose just missing partial hydrolysis. It involves high degree of polymerization as well as low crystallinity index. Powdered cellulose contain the chains with different crystalline and amorphous parts. Lindner and Kleinebudde was prepared the pellets by powdered cellulose with binder polymer for wet massing liquid pellets with 30% paracetamol. Pellets prepared from powdered cellulose show high porosity, less spherical shape and faster dissolution as compared to MCC based pellets. It found to be difficult when powdered cellulose use in high concentration because extrusion requires more water and powdered cellulose have low water holding capacity. Alvarez *et al.* compared MCC with powdered cellulose included 50% and 25% furosemide. The observed evaluation of powderd cellulose pellets found highly porous, friability size distribution, roughness and faster drug release as compared to MCC [1].
2. **Starch (e.g. amylopectin, amylase):** Dukic *et al.* was evaluate the modified starch as main excipient by using poorly soluble drugs like hydrochlorothiazide and piroxicam immediate release pellets. UNI-PURE EX modified starch is identified and suitable material for pellet preparation using extrusion-spheronization. It is crystalline in nature obtained by enzymatic de-branching of amylase rich starch. UNI-PURE EX starch with suitable binder contribute to form spherical pellets with narrow particle size distribution and high process yield. UNI-PURE EX modified starch as disintegrant used in medium water soluble theophylline (anhydrous) release should be done in less than 20 min. There are two experimental designs for hydrochlorothiazide (HCTZ). HCTZ (10% and 50% w/w), HPMC (4% and 7% w/w) for two factors water level is low and high and sorbitol having absent and present respectively. The concentration of sorbitol is 10% with UNI-PURE EX starch content in formulation. UNI-PURE EX starch is disintegrating agent due to this disintegrating time of all batches was between 5 and 10 min. *in vitro* drug release profile showed that more than 80% HCTZ concentration. The second model of piroxicam contains piroxicam (2.5% w/w), HPMC (7% w/w) and sorbitol (10% w/w). The pellets prepared by two water levels (high & low). More than 90% of piroxicam was released in dissolution process within 45 min. from starch based pellets. Sorbitol based pellets increase piroxicam release within 30 min. and starch based pellets without sorbitol had shorter disintegration time within 10 min. vs 15 min. for starch based pellets without sorbitol [3].
3. **Chitosan:** Tapia *et al.* showed that pellets are produced by dissolving chitosan in dilute acetic acid added to powdered mixture of MCC. The concentration used for chitosan in pellets is 2-3% w/w. Formulation of diclofenac sodium containing chitosan can slowers drug release rate. Santos *et al.* prepared pellets by using chitosan (4 or 16%) including MCC (50%), povidone, fillers and diclofenac sodium model drug results surface roughess and porous pellets with percent increase in chitosan. This problem was overcome by preparing hydroalcoholic mixture of alcohol/water (v/v) in same proportion but in this technique drug release should not control. Jess and Steckel studied the effect of chitosan in different degree of deacetylation of it on extrusion – spheronization method. Budesonide is used as model drug with granulating liquid (0.2 N acetic acid). Different degree of de-acetylation may affect the rheological properties like viscoelasticity of wet mass and enlarge extrudability. The deacetylation more than 99% of chitosan is suitable for extrusion-spheronization and does not affect drug release property (pseudo-zero order kinetics) was observed. Chitosan based pellets are less porous, rough and effective drug release. It requires granulating liquid and acid for good morphological and mechanical properties as well as increase flexibility and cohesiveness [1].
4. **Pectinic acid:** Pectin is prepared from apple, pomace and citrus peel. It is gel forming polysaccharide containing polygalacturonic acid. Pectin is partially water soluble. It has different grades on the basis of degree of methoxylation and amidation. Choice of pectin as pelletization aid is very important because of high degree of swelling and stickiness to extrudates formed when mixed with pure water; to avoid this problem additives like ethanol, calcium chloride and citric acid may increase pelletization process. Cross linking of calcium ions may reduce the solubility and swelling of pectin in pelletization for spherical pellets formation. Pectinic acid is used for fast drug delivery of poorly water soluble drug and having high drug loading capacity with high mechanical stability. Sriamornsak *et al.* prepared pellets using MCC, calcium acetate and HPMC solution as granulating agent with theophylline as model drug. Interfacial complexation results in insoluble coating of calcium pectinate by soaking pellets in aqueous solution of pectin [1].
5. **β – Cyclodextrins:** The cyclodextrins are cyclic carbohydrates. The β - CD shows cyclic nature with three hydroxyl groups on every glucopyranose unit. Two hydroxyl groups located at glucopyranose unit on $C_2$ and $C_3$ position. This hydroxyl group is secondary alcohol. The third hydroxyl group is primary alcohol having position $C_6$. The structural confirmation of glucopyranose three dimentional unit represents by hollow cone. This three dimentional structure have hydrophobic cavity for aqueous environment. The small cavity present in α-cyclodextrins and largest in γ - cyclodextrins. The external shape of cyclodextrins hydrophilic in nature so, it has aqueous solubility. β-cyclodextrins cavity is appropriate for the drug having small molecular entities. It had maximum theoretical solubility is 8 mg/ml of drug solubilised [9].

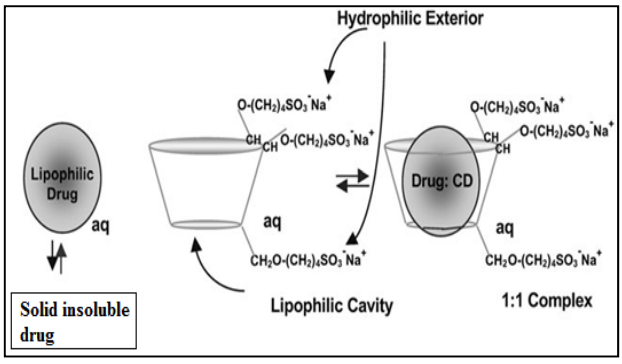


**Fig 1:** Equilibrium solubilization of a water-insoluble drug by a CD. Abbreviations: CD: cyclodextrin; aq.: aqueous.

Gazzaniga *et al.* states that β - cyclodextrins is used as pelletizing agent by extrusion - spheronization technique. Pellets of drug and β - CD complex with MCC (< 20%). MCC is used to avoid poor quality of extrudates while water acts as wetting agent. Santos *et al.* formed immediate release pellets of diclofenac sodium as model drug with mixture of MCC, xanthan gum and β - CD. The studied release mechanism showed irregular drug diffusion-erosion conflict each other during drug release from tablets. Gainotti *et al.* studied β - CD (90%) as extrusion - spheronization aid. Poorly soluble drug requires 90% of β - CD for inclusion complex useful for pellets preparation to accelerate poorly soluble drug release pattern [1].

6. **Sodium alginate (e.g. Alginic acid, sodium alginate powder):** Alginates are anionic polysaccharide extracted from brown seaweed. It is sodium salt of alginic acid and residues of D - mannuronic acid and L - guluronic acid composed polyuronic acids. The block structure and molecular weight of it investigated and amount of sequence, composition regulate physical properties of alginates. Alginates have capable to form gel in presence of metal ions and it is non-toxic, biodegradable and biocompatible. Sriamornsak *et al.* studied the results of calcium salt using sodium alginate. Pellets produced by using sodium alginate is of good quality and use of calcium acetate improve the drug release. Calcium salt is used as an aid for pellet preparation which reduces the quality of MCC required for pelletization and MCC will removed from formulation [1].
7. **Carrageenan:** Kilor *et al.* used the κ - carrageenan with combination of sodium starch glycolate resulting the fast disintegration of immediate release pellets of poorly water soluble drug aceclofenac. Origin of κ - carrageenan is from red-seaweed's cell wall. κ – carrageenan is used as alternative to MCC as pelletizing agent to prepare aceclofenac immediate release pellets [10]. Kilor *et al.* prepared pellets by using composition of MCC, κ – carrageenan, maize starch and lactose using extrusion-spheronization method. In this composition MCC/ κ – carrageenan acts as pelletizing agent and maize starch/lactose acts as fillers using aceclofenac as model drug. κ – carrageenan had good binding characteristics and yields 99.99% pellets when used as pelletizing agent. 30% of κ – carrageenan in formulation results disintegration time 4 min. as compared to MCC base pellets it is 18 min. κ – carrageenan had high wettability, swelling index and diffusion rate respectively; so it disintegrate rapidly [10].

   At least 5% of κ – carrageenan is sufficient to produce pellets without MCC. Addition of more water for binding aid produces stability problems with sensitive drugs [1].

**Drug diffusion systems**

- **Diffusion controlled systems:** Diffusion controlled systems are divided in two types one is reservoir systems and matrix systems.

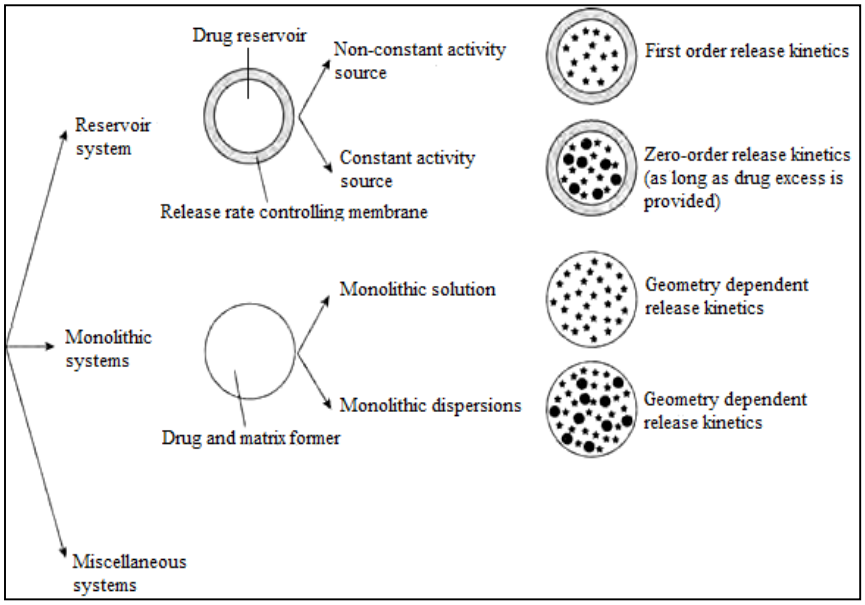


**Fig 2:** Schematic classification of diffusion controlled drug delivery systems

**1. Reservoir systems**

- It is also known as membrane-controlled drug delivery system. In this system the core containing a drug should enclosed with and encapsulated in specific shape of rate-controlling membrane having definite thickness. The core drug will dissociate and dissolve in it's surrounding medium by membrane diffusion [2].
- The core of drug reservoir consists of specific shape like spherical, cylindrical or disc like shape and core is surrounded by non-biodegradable polymer. The physicochemical properties and compatibility of drug-polymer controls the diffusion rate of drug release in blood stream. The drug release rate in uniform concentration depends on reservoir thickness. Once the drug release completely, whole reservoir system discharge from body and if reservoir system is disturbed the drug dumping may occurs [20].
- The core drug in reservoir system does not affect by pH; it independently release from system. The different drug release rate must be readily achieved by reservoir system. Reservoir system offers the various drugs strength without development of new dosage form [16].

- Variables used in reservoir systems are polymer and pore former for film coat, drug load and solubility. The polymers generally used for membrane are ethylcellulose (surelease or aquacoat) and acrylic copolymers (Eudragit RL30D, RS30D and NE30D) as well as water-soluble polymer like HPMC and polyethylene glycol are choice of polymer formers for uniform coating the Wurster coater is commonly used. During storage condition; dissolution of reservoir system changed [16].

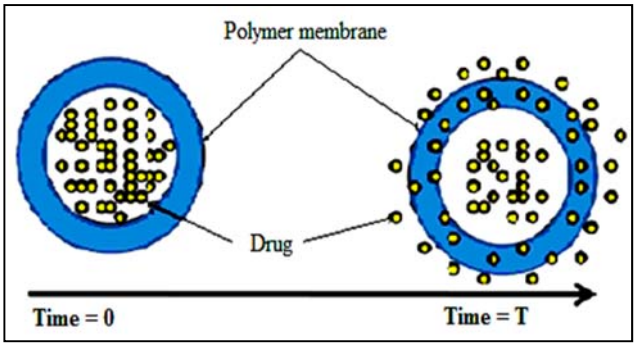


**Fig 3:** Schematic representation of reservoir system

On the basis of physical properties there are two types of reservoir systems:

a) Non-swelling reservoir system
b) Swelling-controlled reservoir system

**a) Non-swelling reservoir system:** Those polymer membrane which can't swell in aqueous medium. The polymer used in this system regulates thickness, porosity, insolubility and slow dissolution. Non-swellable reservoir system include pellets, granules, crystals, drug particles and minitablets. e.g. ethylcellulose and polymethacrylates

**b) Swelling-controlled reservoir system:** Those polymers which delayed the drug release because it require to swell and hydrate in aqueous medium to activate the barriers after that constant drug release proceed. e.g. HPMC [2].

**On the basis of chemical properties reservoir system divided in two types are as follows:**

a) pH-dependent reservoir system
b) pH-independent reservoir system

**a) pH-dependent reservoir system:** These systems are designed for those drugs which irritates to gastric mucosa. So, the core drug is coated by insoluble polymer like ethylcellulose and intestinal fluid soluble HPMC polymer. The coated polymer make resistance against stomach environment pH 1 - 3 then coated drug travelled to small intestine by dissolving protective coat at pH > 5. The formed microporous membrane allows release of drug from core.

e.g. potassium chloride delivery which irritates to gastric epithelium [2].

The poorly soluble drug release had made possible by using hydrophilic polymer to achieve zero-order release [16].

pH-dependent swelling system are based on polymer swelling and shrinking should be weakly acidic or basic group. It acts swelling and shrinking on pH changing. This pH-dependent property controls the drug release from pH-sensitive polymer [2].

**b) pH-Independent reservoir system:** pH-independent system can't affect by food and have robust performance. This system will affect by various physiological and biopharmaceutical factors like GI transit time, ionic strength, regional permeability, secretion of bile salts, GI tract metabolism, transporters etc. The developed theophylline formulation by independent reservoir system showed significant as well as opposite food effects. The buffering systems are commonly used to overcome those problems. Buffering systems are commonly used to overcome these problems. Buffering agents are limited buffering and loading small molecule capacity [16].

**2. Matrix systems**

- In matrix system drug is uniformly distributed throughout all the polymer. The drug release from polymer matrix is uniform and there is no dose dumping observed during accidental case. A matrix containing dissolved drug dissolved drug upto or below saturation level of solubility in polymer. Macroscopic channels within a polymer matrix not exist to drug molecules leaching. The reservoir system compared matrix system, it has lower permeability as compared to polymer matrix system [20].
- The matrix system is conventional, bilayer or trilayer matrix system [2].
- The reservoir system is more complicated than matrix system. In matrix system finely powdered drug is dissolved upto or below saturation solubility with pre-polymer. This mixture is added to the mould. There is no need to form barrier layer over the core like reservoir system [20].

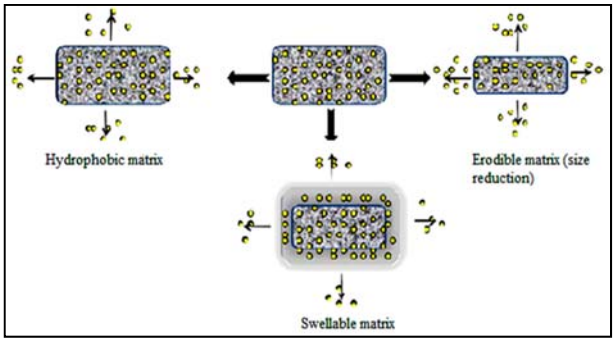


**Fig 4:** Schematic representation of drug release from different type of matrix system

**On the basis of physical properties of matrix systems it divides in two types:**

a) Hydrophilic matrix
b) Hydrophobic matrix

**a) Hydrophilic matrix:** Those systems where the drug loaded polymer is water-swellable or erodible hydrocolloid e.g. high molecular weight HPMC, HPC, HEC, xanthan gum, sodium alginate, guar gum, locust bean gum, PEO (polyethylene oxide) and crosslinked polymers of acrylic acid. These are porous system [2].

Hydroxyalkyl methacrylates as hydrophilic matrix have various advantages like they have minimal foreign tissue response and non-toxic, they are highly permeable to charged species, hydrophilic and hydrophobic solutes. On the basis of copolymer as composition, cross linked density with hydrophilic polymer variate permeability of drugs. Such polymer offers increased mechanical strength [20].

Depending on swelling behaviour there are two types of matrices:

1. Free swelling matrix
2. Restricted swelling matrix

Free swelling matrix is that the polymer swelling is not disturbed and restricted-swelling is that in which impermeable polymer is used on the surface of system which restrict hydration of swellable matrix [2].

**b) Hydrophobic matrix:** This is the system in which water insoluble polymer used and many times polymer is not essential for drug release. e.g. waxes, glycerides, fatty acids, polymeric materials like ethyl cellulose and methacrylate copolymer etc. [16].

As mentioned above all the examples of hydrophobic matrix are slowly soluble, erodible or digestible other than polymeric materials because they are non-digestible [2].

It was important to use lactose if drug release rate will be improved. Hydrophobic matrix system are generally not suitable for poorly soluble or insoluble drugs. The inadequate concentration gradient may affect incomplete drug release during GI transit time [16].

**Depending on the drug incorporation manner hydrophobic matrices are divided as follows:**

1. Porous (heterogeneous matrix)
2. Non-porous (homogeneous matrix)

**1. Porous (heterogeneous matrix):** Those systems in which drug and matrix microparticles are mixed together and dispersed in polymer solution by evaporation of solvent [2].

The drug release rate mechanism can be expressed by fick's first and second law of diffusion. When initial drug load with polymer (less than 10%) beyond saturation point. So, drug diffusion coefficient within polymer matrix and initial drug load. The additional variable should be incorporated in this system. When initial drug load is increased more than 10% w/w at a certain point drug particles form continuous pores within matrix. The least resistant path formed for drug to diffused within channels for leaching from matrix. The diffusion characteristics of those systems are known as 'porous' or 'granular' matrices [20].

**2. Non-porous (homogeneous matrix):** The drug is incorporated in melted release retarding matrix material by mass stirring, mixing and congealing. When the drug load is equal to or less than saturation level of drug then it's release rate depends on diffusion coefficient of drug in polymer and it's initial load. This diffusion is depends on drug property and polymer matrix system variables such systems can described as homogeneous matrix [20].

There are two types of non-porous matrix systems are possible i.e. dissolved drug non-porous system and dispersed drug non-porous system. In dissolved drug non-porous system drug is dissolved in molten mass of release retarding matrix material and dispersed drug non-porous system is that the quantity of drug used is greater than it's solubility in molten matrix polymer [2].

**Characterization of pellets**

**1. Particle size distribution:** The size distribution of particles are made narrow as possible with minimum coating thickness variation. Sieve shaker is most widely used method for determination of particle size. Vernier calliper and microscopic methods are basic for size distribution study. Optical microscopy and scanning electron microscope are also used for determination of pellets [8].

**2. Surface area:** The surface area characteristics includes size, shape, porosity and surface roughness are characterized by different techniques like gas adsorption and air permeability. For measurement of batch to batch variation air permeability is efficient method. The resistance produced by compacted material plug to air flow is principle behind surface area determination. In gas adsorption method the evacuated bulb contain substrate which adsorbs specific volume of nitrogen at different pressure and it is plotted p/v ($p^o$- p) vs p/$p^o$ as linear plot. Where, p – pressure, $p^o$ - saturation vapour pressure of liquefied nitrogen, V – volume of gas adsorbed ($cm^3$). The slope intercept gives the value of b and $V_m$. The specific surface ($S_w$) equation solved by equation ($S_w = 4.35 \times V_m$). This method is known as BET method [8].

**3. Flow property:** Flow property of pellets were determined by USP tap density apparatus for calculation of hausner's ratio and fixed funnel method is used for angle of repose [18].

**4. Hardness and friability:** Hardness and friability testing is necessary task for handling, shipping, storage and coating. For hardness Kaul pellet hardness tester used and Erweka type tablet friabilator or Turbula mixer used for fixed period of time; the glass beads are used with pellets for abrasion [23].

**5. Porosity:** The drug release rate will affected by the porosity of pellets. The Scanning Electron Microscopy (SEM), mercury porosimetry and combination of optical microscopy with scanning electron microscopy used together [23].

**6. Tensile strength:** The 5 kg load cell is used in tensile strength tester apparatus. Tensile strength is calculated by applying recorded value to failure load and radius of pellets [23].

**Conclusion**

From the study of immediate release pellets it is concluded that the poorly water soluble drugs with different categories are developed as immediate release pellets by using different techniques but in that extrusion - spheronization is commonly used. The selection of suitable excipients and manufacturing techniques is also matters the disintegration, dissolution and surface morphology of immediate release pellets. Microcrystalline based pellets shows lack of disintegration and prolong drug release. So, different alternatives are used to change drug diffusion and release kinetics. Microcrystalline based pellets of hydrochlorothiazide and piroxicam prepared by extrusion - spheronization technique shows < 40% release after 75 min. but in contrast omeprazole immediate release pellets successfully prepared by combination of milling, extrusion - spheronization and powder coating. It results 96% release as compare to physically mixed pellets.

**Acknowledgement**

The authors would like to thank the Hon. Principal, Dr. S. J. Surana, SES's, R. C. Patel Institute of Pharmaceutical Education and Research. A special gratitude to Dr. H.S. Mahajan, Head, Department of Pharmaceutics and Quality assurance for his continuous support and encouragement throughout this work.

**References**


1. Bhaskar R *et al*. Non - MCC Polymer as a Pelletization Aid: A Review. The Pharma Innovation Journal. 2015; 4(7):100-105.
2. Brahmankar DM Jaiswal SB. Biopharmaceutics and Pharmacokinetics-A Treatise, Vallabh prakashan, Delhi. 2009; 32 (2):417-419:425-426.
3. Dukic-ott A *et al*. Immediate release of poorly soluble drugs from starch-based pellets prepared via extrusion/spheronization. European Journal of Pharmaceutics and Biopharmaceutics. 2007; 67:715-717:721.
4. Harun AR *et al*. Centrifugal granulating process for preparing drug-layered pellets based on microcrystalline cellulose beads. Pharmaceutical Technology Division University of Helsinki, Finland, 2001; 5:17.
5. Ibrahim MA, El-Badry M. Formulation of immediate release pellets containing famotidine solid dispersions. Saudi Pharmaceutical Journal. 2014; 22:149:150:155.
6. Jawahar N, Patel HA. Multiple Unit Particulates Systems (MUPS): A Novel pellets for oral dosage forms. Journal of Pharmaceutical science and research. 2012; 4(9):1915.
7. Juhong G *et al*. Sodium bicarbonate-coated omeprazole immediate release pellets to improve bioavailability by improving stability in gastric acid. Asian Journal of Pharmaceutical Sciences. 2011; 6(3-4):123-124.
8. Kandukuri JM. Pelletization Techniques for Oral Drug Delivery. International Journal of Pharmaceutical Sciences and drug research. 2009; 1(2):69.
9. Katdare A, Chaubal MV. Excipient Development for Pharmaceutical, Biotechnology and Drug Delivery Systems. Published by Taylor and Francis Group informa healthcare. 2006; 10:1:54:55.
10. Kilor VA *et al*. Development and characterization of Enteric-coated Immediate-Release Pellets of Aceclofenac by extrusion/spheronization technique using κ-carrageenan as a pelletizing agent. American Association of Pharmaceutical Scientists (AAPS) PharmSci Tech. 2010; 11(1):336-340.
11. Krause Thommes J, Breitkreutz MJ. Immediate release pellets with lipid binders obtained by solvent-free cold extrusion. European Journal of Pharmaceutics and Biopharmaceutics. 2009; 71:138-144.
12. Kumar AC *et al*. Development of Itraconazole Immediate Release Pellets by using HPMC loaded in gelatin capsules. International Journal of Biological and Pharmaceutical Research. 2012; 3(7):904-905.
13. Kumari MH *et al*. Recent novel advancements in pellets formulation:A Review. International Journal of Pharmaceutical Sciences and Research. 2013; 4(10):3803-3805:3810-3811:3814.
14. Kumar V *et al*. Multiple Unit Dosage Form – Pellet and Pelletization Techniques: An Overview. International journal of Research in Ayurveda and Pharmacy. 2011; 2(1):124-125.
15. Kushare SU *et al*. Development and Evaluation of a novel modified release pellets based system for the delivery of desloratadine and pseudoephedrine hydrochloride. Asian Journal of Pharmaceutics. 2011, 203.
16. Li X, Jasti BR. Design of Controlled Release Drug Delivery Systems. Published by McGraw-Hill companies. 2006; 116-117:120-122.
17. Neeraj B *et al*. A Review on Immediate Release Drug Delivery System. International Research Journal of Pharmaceutical and Applied Sciences. 2014; 4(1):78-80:85.
18. Noor A *et al*. Formulation, Development and *in vitro* Evaluation of immediate release fenofibrate pellets. Asian Journal of Complementory and Alternative Medicine. 2014; 2(3):1-4.
19. Punia S *et al*. Pelletization Techniques: A Literature Review. International Research Journal of Pharmacy. 2012; 3(3):44.
20. Ranade VV. Drug Delivery Systems. Lippincott publishing company Philadelphia. 2004; 30(2):25-26.
21. Rani YR. Formulation and *In vivo* evaluation of Immediate Release Glimepride coated pellets using $3^2$ full factorial design by novel liquid layering technology. Journal of Pharmacy Research. 2014; 8(5):642-643.
22. Souto C *et al*. A comparative study of the utility of two superdisintegrants in microcrystalline cellulose pellets prepared by extrusion – spheronization. European Journal of Pharmaceutics and Biopharmaceutics. 2005; 61(94):98.
23. Vats T *et al*. Pelletization Techniques: A Review. Journal of Pharmaceutical Science and Bioscientific Research (JPSBR). 2015; 5(3):247-248.