



Controlled Release Orally Disintegrating Tablets: A Review

Harsha Kathpalia*, Bhairavi Sule, Ashwini Patil, Anagha Mahadik, Komal Sharma

Vivekanand Education Society's College of Pharmacy, HashuAdvani Memorial Complex, Chembur, Mumbai, India.

*Corresponding author's E-mail: hkathpalia2007@rediffmail.com

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ABSTRACT

An Orally disintegrating tablet (ODT) is a solid dosage form that disintegrates and dissolves in the mouth within 30 seconds or less without aid of water. This novel dosage form not only provides patient compliance but also allow manufacturers to extend the patent protection. In combination with modified release technology ODTs will continue to provide enhanced therapeutic and commercial benefits. Combining ODTs with specialized functional polymers and coating processes can lead to ODTs with sustained-, modified- and customized release profiles. It is even possible to combine different drugs with different release patterns into a single dosage form. Typical of these approaches are microencapsulation and multi-particulate coating technology, which allow formulator to create modified release polymer layer around API particles. These particles are flexible enough for compression without breakage or loss of the modified release properties and small enough to provide good mouth feel. Future challenges for controlled release ODT manufacturers include reducing costs by finding ways to manufacture with conventional equipment, improving mechanical strength and taste masking capabilities.

Keywords: Controlled release, microencapsulation, multi-particulate systems, ODT.

INTRODUCTION

The goal of controlled-release drug delivery systems is to provide the optimum dosage of a drug so as to increase efficacy, reduce side effects and increase patient compliance. Extended release formulations enable less frequent dosing of drugs with short half lives and avoid the 'peaks and troughs' of drug plasma concentrations associated with rapid release formulations.¹ Once-a-day extended-release formulations provide an additional advantage for the pediatric and adult patient population where compliance is an issue.

An Orally Disintegrating Tablet (ODT) is a solid dosage form that disintegrates and/ or dissolves in the mouth (either on or beneath the tongue or in the buccal cavity) without water within 30 seconds or less. The US Food and Drug Administration Center for Drug Evaluation and Research (CDER) defines in the Orange Book an ODT as "A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue".²

Orally disintegrating tablets which melt fast in the mouth are easy to swallow and easy to administer to pediatric population thus increasing patient compliance. This dosage form is also convenient for patients who experience dysphasia that is difficulty in swallowing. In this case, rapidly disintegrating dosage forms are superior over conventional dosage forms in terms of patient compliance.

Controlled release ODT can offer advantages of both, ODT technology and controlled release technology, which provide additional clinical value to patients.

Controlled release ODT should be able to disintegrate completely in mouth without releasing drug until it reaches to its site of absorption whether to stomach or small intestine and releasing drug there at specified rate.

FORMULATION CONSIDERATION FOR CR ODT

Out of many methods of formulating ODTs; direct compression is being used for formulation of controlled release ODT. Drugs which have poor compressibility must be aided with directly compressible excipients in order to formulate into ODT. Excipients to be directly compressible must have good flowability and compressibility. Excipients which undergo plastic deformation are ideal for direct compression. Various diluents of directly compressible grades are available in the market. Microcrystalline cellulose (MCC) is true DC filler and binder. MCC deforms plastically with minimum elastic recovery but has poor or intermediate flowability. This issue is solved to the major extent by PROSOLVSMCC™ which is silicified MCC with good compressibility and flowability.³ Spray drying of excipients gives spherical and uniform sized particles.⁴ Dilution capacity of filler is the maximum proportion of drug that can be compacted into an acceptable compact using that filler. Unlike spray dried lactose, MCC has high dilution capacity. MCC produces compacts with significant hardness at levels of 3-5%. Glidants at levels of 0.1-0.2% must be incorporated for high loading drug which has poor flowability. At higher levels of glidants, weight variation may increase as a result of poor flow.⁵ Few excipients of directly compressible grade are mentioned in Table 1.

In order to achieve tablet disintegration within 30 seconds; superdisintegrants have to be incorporated.



Croscopovidone, croscarmellose sodium, sodium starch glycolate have been used in concentration range of 1- 8 %. Though MCC is water insoluble; it gives faster disintegration due to wicking action. Use of co-processed MCC (Avicel PH 101,102) and mannitol (Pearlitol DC) gives harder, less friable tablets with lower disintegration time than plain MCC and mannitol.⁶ Sugar based diluents like dextrose, mannitol, sorbitol give palatable ODT, also help in disintegration due to high aqueous solubility.

Table 1: Directly compressible excipients

Excipient	Brand name	Manufacturer
Lactose	Tabletose	Meggle Pharma
Starch	Starch 1500	Colorcon
Mannitol	Pearlitol	Roquette Pharma
Microcrystalline cellulose	Avicel	FMC Biopolymer
Dicalcium phosphate	Emcompress	JRS Pharma
Sucrose	Di-pac, Nutab	JRS Pharma
Dextrate	Emdex	JRS Pharma
Sorbitol	Neosorb 60	Roquette Pharma

STRATEGIES TO DEVELOP CONTROLLED RELEASE ODT

Combining ODTs with specialized functional polymers and coating processes can lead to ODTs with sustained, modified and customized release profiles. It is even possible to combine release profiles in a single dose.

Micro-encapsulation

It is the process in which small droplets of liquid or particles of solid material are surrounded or coated by a continuous film of polymeric materials.

Microcapsules for controlled release

Relative ease in design and formulation of microcapsules, make them more interesting to use in controlled drug delivery system.⁷ As a micro-particulate system, it gives sustained release from each individual microcapsule and offer greater uniformity and reproducibility. Additional advantage over monolithic system is reduced incidence of dose dumping. Also multiple particle systems are distributed over a great length of gastro-intestinal tract, which results in lowered local concentrations and hence reduced toxicity or irritancy.

Coating materials used in Microencapsulation

Drug release rate from microcapsule is governed by the polymer used as a coating material. The selection of appropriate coating material decides the physical and chemical properties of the resultant microcapsules/microspheres. The polymer should be capable of forming a film that is cohesive with the core material. It should be chemically compatible, non-reactive with the core material and provide the desired coating properties such as strength, flexibility, optical properties and stability.

A wide variety of coating materials are available for microencapsulation which gives controlled drug release.

a] pH sensitive polymers⁸

pH sensitive or pH responsive polymers are materials which either swell or collapse depending on the pH of their environment. This behavior is exhibited due to the presence of certain functional groups in the polymer chain.

There are two types of pH sensitive polymers:

1. Polyacidic polymers: Possess acidic groups (-COOH, -SO₃H), which swell due to ionization in basic pH thus releasing the drug.

Eg. Polyacrylic acid (Eudragit L, Eudragit S, Eudragit FS)

Adi shefer et al., have worked on pH responsive microspheres of Bovine serum albumin by using Eudragit S 100 which gave controlled release rate in the intestine.⁹

2. Polybasic polymers: Possess basic groups (-NH₂) which swell and release the drug at acidic pH.

Eg. Chitosan

b] Biodegradable polymers

Biodegradable polymers have been used widely as drug delivery systems because of their biocompatibility and biodegradability. Release rate from biodegradable polymer depend upon physico-chemical properties of drug and polymer and kinetics of biodegradation,

Eg. Gelatin, Pectin, Chitosan, Poly(lactide-co-glycolide)

J. Y. Park et al., have formulated microcapsules of soluble active ingredient using cross linked polymer of chitosan and phytic acid.¹⁰ Microcapsules showed good entrapment efficiency while sustained release of soluble active ingredient was achieved for 10 hrs.

c] Hydrophilic/ hydrophobic polymers

Generally hydrophilic polymers, hydrophobic polymers or a combination of both are used for the microencapsulation process.

Eg. Hydrophilic polymer- Hydroxyl ethyl cellulose, Hydroxypropyl methyl cellulose, polyethylene oxide, polyvinyl alcohol

Hydrophobic polymer- Ethyl cellulose, Cellulose acetate phthalate

Thomas C. et al., microencapsulated Verapamil using ethyl cellulose as rate controlling polymer by phase separation method.¹¹ At the phase ratio of 10: 1 of ethyl cellulose: drug loaded microcapsules, 98% drug release was obtained upto 16 hours.

Sunitha S. et al., formulated sustained release microcapsules of Tramadol Hydrochloride using non-aqueous, emulsification- solvent evaporation technique.¹² Polymers like ethyl cellulose, cellulose acetate phthalate were studied at the 1:1, 1:2, 1:3 drug: polymer ratio. Maximum drug release was achieved for ethyl cellulose microcapsules formulated at the 1:3 drug: polymer ratio.

Microencapsulation Techniques

There are various techniques available for the encapsulation of core materials such as, Interfacial polymerization, Co-acervation and phase separation, Spray drying and congealing, Fluid bed coating, Pan coating etc.¹³ Out of these methods fluid bed coating is widely used in industry. Depending on the physical nature of the core substance to be encapsulated the technique used can be varied.

Microencapsulation at laboratory scale

Emulsification-Solvent removal is most convenient method at laboratory scale.

In this method, the polymer is dissolved in volatile organic solvents like dichloromethane or chloroform. Drug is then dissolved or dispersed into polymer solution.¹⁴ This mixture is then emulsified by adding this solution or slurry at a controlled rate to the aqueous phase containing surface active molecule like polyvinyl alcohol or Tween 80. This method is used when drug is water insoluble. If drug is water soluble, above method will result in low yield and low entrapment efficiency. For water soluble drug, the polymer and drug solution is to be dispersed in liquid paraffin. This emulsion is then subjected to either of following method:

- Solvent evaporation: Emulsion maintained at reduced atmospheric pressure, under low agitation due to which solvent gets evaporated
- Solvent extraction: Emulsion transferred to large quantity of water or other quenching medium where solvent diffuses out forming microcapsules.

Rate of solvent removal influences characteristics of microcapsules. Rapid solvent removal forms porous microcapsules and causes hardening of polymer in amorphous state. Out of above two methods, solvent removal by extraction process is faster and forms porous capsules.¹⁵ Higher porosity of microcapsules leads to rapid release of drug compared to nonporous microcapsules.

Microcapsules in ODT

Microcapsules can be formulated as ODT by compression. These particles are flexible enough for compression without breakage or loss of the modified-release properties and small enough to provide good mouth feel. Adjusting the coating parameters such as thickness, composition, porosity of microcapsules and by use of pH modifying agents the desired plasma profile can be achieved efficiently.

Along with the coating polymer, nature and amount of plasticizer in coating solution will determine the strength of coating film upon compression. Relatively high percentage of plasticizer is needed to provide flexibility to coating film which will avoid substantial breakage upon compression. Particular amount of plasticizer will vary depending upon nature of coating polymer and of

plasticizer used. The amount may be determined empirically by testing the drug release from tablets. If medicament is being released too quickly then amount of plasticizer should be increased. Generally plasticizer must be used in amount of 20-25% of coating material and 15-20% weight of active substance.¹⁶

Literature review

a] Rehab S. et al., have worked on sustained release orally-disintegrating tablets containing drug loaded resin microcapsules.¹⁷ Betahistin Dihydrochloride (BHCl)-resin complex was microencapsulated with Eudragit® RS100 using the solvent evaporation technique. Prepared microcapsules were compressed into tablet using Pearlitol® 200 SD, a disintegrant (crospovidone) and a binder. The release characteristics of the original microcapsules were maintained after compression, indicating that the compression process did not induce mechanical damage to the coating.

b] Rotman A. has patented Acetaminophen microcapsules, formulated in modified Uni Glatt powder coater by using spray drying method.¹⁸ Spraying solution was 8% ethyl cellulose in 90:10 acetone: ethanol with castor oil as plasticizer.

Coated microcapsules were then sieved in order to get particle size ranging from 74- 210 microns. 400mg of coated particles and 100 mg of starch mixture was compressed under 1.5 tons to get 500mg ODT. Disintegration time of tablet was 5-10 seconds.

Microencapsulated drug showed in vitro drug release for 24 hrs with half of the drug being released in 10 hrs. After compression, total drug was released up to 16 hrs with half of the drug being released after 5 hrs. This showed that relatively few microcapsules were broken during compression without much affecting desired sustained release profile.

c] Rajendra et al., formulated ODT containing surelease coated Famotidine microcapsules along with viscosity enhancer like Hydroxypropyl methyl cellulose (HPMC K15M) which formed viscous slurry of microcapsules in saliva.¹⁹ This gave pleasant mouth feel, preventing particles from distributing throughout the mouth. It also allowed gliding and swallowing of particles smoothly.

d] J. Y. Kim et al., have prepared sustained release micro-particles of Tamsulosin Hydrochloride with Ethyl cellulose and Eudragit L as encapsulating material.²⁰ ODTs composed of Tamsulosin microparticles, mannitol and crospovidone disintegrated within 30 seconds and showed sustained release profile.

Thus it can be concluded that well formulated microcapsules can be compressed into ODT to achieve desired drug release profile.

Multi-particulate systems

Multiple-unit dosage forms comprise of number of discrete particles called pellets that are combined into



one dosage unit. As being multi-particulates, it shares all the advantages as mentioned for microcapsules.

Final dosage form of pellets can either be capsule or tablet. Though filling into capsule is more common, the production costs for capsules are high and their production rate is low compared with those of tablets. Hence compression of subunits into tablets is more preferred nowadays.

Pellets into ODT

Pellets when coated with rate controlling polymer give controlled drug release. Coated pellets behave differently than powders under compression. Powders undergo plastic deformation upon compression hence form strong compacts. But pellets due to their spherical shape undergo elastic deformation and fragmentation giving compacts of low mechanical strength.²¹

One of the disadvantages of ODTs is that they are more friable than conventional tablets and hence require special packaging. Thus it is important to form sturdy ODTs containing coated pellets without changing drug release profile upon compression.

Following parameters have to be optimized:

A] Parameters related to the properties of core pellets

Properties of pellets are dependent on the formulation method selected, processing conditions, drying method, granulating liquid used and the pellet composition.²²

a. Size of pellets

Size of pellets influences the compaction behavior and drug release from compressed tablets. Smaller pellets demonstrated more strength than larger ones; hence smaller pellets were less affected by compaction pressure.²² When smaller and larger pellets were coated, at the same coating level, smaller pellets were more fragile than larger pellets. This was attributed to the reduced film thickness of the smaller pellets because of the larger surface area.²³

b. Porosity of pellets

Higher the porosity of core pellet, more deformation and more densification takes place upon compression. The change in drug release upon compression is inversely related to the original porosity of the reservoir pellets.^{21,24}

c. Composition of pellets

Pellets usually undergo elastic deformation so that they deform and recover after compression without damage to the coating. But some degree of plasticity which can be achieved by microcrystalline cellulose and some waxy materials is important to improve compression characteristics of the pellets.

Iloanusi et al., investigated compression behavior of pellets containing microcrystalline cellulose with and without waxy materials. MCC based pellets containing wax demonstrated more compressibility than those made

without wax. Pellets formulated with wax underwent plastic deformation upon compression while pellets without wax underwent higher elastic recovery.²⁵ Generally, compacts formed by plastic deformation have higher strength than compacts that undergo elastic deformation and brittle fragmentation.

B] Parameters related to coating polymer

a. Type and amount of coating polymer

Selection of coating polymer is important to avoid rupture of coating upon compression. The polymer should have sufficient strength, ductility and thickness to withstand the forces generated during compression without rupturing. Type of coating system also affects the film strength. Polymer should be elastically deformable and should have at least 75% elongation at break to avoid rupture of coated film upon compression.²⁶ Films exhibiting a relatively high elastic modulus and apparent Newtonian viscosity provide the highest protection to the pellet core on compression.²⁷

During compaction of enteric coated pellets it was observed that increasing the amount of coating material (Eudragit® L 30 D-55/Eudragit FS 30 D) increased the tablet mechanical strength.²⁸ Generally a thicker coating can withstand damage better than thinner one. Coating used should adapt to the densification and deformation of the pellets and remained tightly adhering to the pellet cores, even after compaction.

Also, solvent-based coatings have been found to be more flexible and have a higher degree of mechanical stability than aqueous based ones and therefore are less affected by compression.²⁹

b. Type and amount of plasticizer

Plasticizers are liquids of low glass transition temperatures (T_g), around -50 to -150°C. They lower the T_g of polymer below room temperature rendering it softer and more flexible. The concentration of plasticizer required is dependent upon the type of plasticizer used. Exceeding concentration of plasticizer than the optimum, results in sticky agglomerates.

The ductility of coating film can be improved by the addition of plasticizers. Felton et al., found that the tensile strength of film coated pellets increased with increasing plasticizer content. As the degree of plasticization of the polymer increased, the film coating became more elastic and was able to deform during compression.³⁰

Free films of Eudragit RS 30D and Eudragit RL 30D in 4:1 ratio and with different concentrations of Triethyl Citrate (10%, 20%, 30% w/w based on dry polymer) as plasticizer were prepared and tested for their mechanical properties by applying 1 kN load.²⁶ It was found that at 10% concentration of plasticizer, lowest elongation of film was observed, as stated earlier the elongation of coating film should be more than 75%. At higher concentration (30%)

sticky films were observed. Hence it was concluded that 20% of Triethyl citrate is the optimum concentration.

c. Parameters related to excipients used in ODT formulation

c.(i). Particle size of excipients: Particles of diluents used in ODT must be of size to fill the inter-pellet voids completely. Filling of these void spaces is necessary to prevent adhesion and fusion of the coated pellets during compression which may cause breaking of coated film. Particle size distribution must be narrow to avoid weight variation and content uniformity problems.

c.(ii). Cushioning agent: To protect the coated pellets from damage during compression, cushioning agents can be incorporated. Cushioning agents are mostly plastically deformable materials those that take up the pressure of compaction by re-arranging themselves within the tablet structure thereby providing protection to the coated pellets. The protective effect of an excipient is dependent on the particle size. Most commonly used cushioning agents are microcrystalline cellulose and polyethylene glycol.

Lin et al., studied sugar multi-particulates layered with Chlorpheniramine maleate followed by an ethylcellulose coat which were tableted using various lactose grades like micronized lactose produced by jet milling, spray-dried lactose and polymer-co-processed lactose, as fillers. Drug release from compacted multi-particulate tablets was used to evaluate the cushioning effect of the fillers. The results showed that the cushioning effect of lactose principally depended on its particle size.³¹

Literature review

a] Study was carried out to formulate sustained-release ibuprofen tablets which upon oral ingestion rapidly disintegrated into sustained-release pellets in which the integrity of the pellet core and/or coat was preserved.²⁶

Method-

- Preparation of cured pellets- Cured pellets containing 60% ibuprofen, 27% Eudragit RS/RL (1:1), 10% Avicel and 3% PVP K30 were prepared.
- Coating of the pellets - 10 % w/v of coating formulation containing Eudragit RS 30D and Eudragit RL 30D in 4:1 ratio was prepared. Triethyl citrate was added to the dispersion as plasticizer (20% w/w related to dry polymer) and Talc (2% w/v) was added as an anti-adherent. The coating was performed using a fluidized bed coater (Wurster coater).
- It was demonstrated that the compression force, pellet to filler ratio and composition of filler blend did not influence the ibuprofen release rate from their disintegrating compacts. However tablet hardness, disintegration time and friability were markedly influenced by compression force and pellet ratio.

b] G. Venkatesh et al., have investigated sustained release pellets which were compressed into ODT.¹⁶

- Preparation of immediate release beads: Dicyclomine Hydrochloride solution in 95% ethanol: water (75:25) containing polyvinyl pyrrolidone (PVP K30) was coated onto Inert MCC seeds, using bottom spray Wurster coater.
- Preparation of Sustained release pellets: The immediate release drug loaded beads were then coated in fluid bed coater with solution of Ethyl cellulose containing tri ethyl citrate in acetone: water (90:10) at a coating weight of 15%.
- Preparation of ODT- 40 mg and 80 mg Dicyclomine Hydrochloride controlled release ODTs were prepared by compression of sustained release beads and pharmaceutically acceptable ingredients. Various superdisintegrants were tried like crospovidone, sodium starch glycolate, croscarmellose sodium etc.

Formulated ODTs had similar drug release profile as that of the uncompressed pellets. Also the ODTs had enough mechanical stability and rapidly disintegrated in oral cavity producing smooth easy to swallow dispersion.

c] Rajendra et al., formulated ODT containing pellets.¹⁹ Pseudoephedrine Hydrochloride pellets were formulated by drug solution layering on sugar spheres. Pellets were then coated with Hydroxypropyl methylcellulose phthalate (HP 50). Coated pellets compressed into ODT along with Hydroxypropyl methylcellulose (HPMC K15M) as viscosity enhancer.

d] Diffucaps®

This technology of Aptalis facilitates the development of controlled-release delivery systems for once- or twice-daily dosing of single drug or drug combinations that exhibit extreme pH-dependent solubility profiles.³²

Diffucaps is a multi-particulate bead system comprised of multiple layers of drug, excipients and release-controlling polymers. The beads contain a layer of organic acid or alkaline buffer to control the solubility of a drug by creating an optimal pH microenvironment for drugs that exhibit poor solubility in intestinal pH, in environments with pH greater than 8.0 or in physiological fluids. Alternatively, the beads can contain a solid-solution of drug and crystallization inhibitor to enhance bioavailability by maintaining the drug in its amorphous state. Diffucaps beads are <1.5 mm in diameter and can be filled into capsules or compressed into orally disintegrating tablets.

e] G. Venkatesh et al., investigated Diffucaps technology for formulating Controlled release ODT of Melperon Hydrochloride.³³ The drug was loaded onto sugar spheres followed by seal coating with Hydroxypropyl cellulose (Klucel LF). Alkaline buffer of dibasic sodium phosphate anhydrous was spray coated onto Melperon immediate release beads to create basic microenvironment. Ethyl

cellulose was coated on alkaline buffer-coated immediate release beads. The resulting sustained release (SR) beads were dried to evaporate the residual solvents and sieved through 30 and 80 meshes. Rapidly dispersing microgranules were prepared with D-mannitol and crospovidone. Melperone Hydrochloride SR ODTs were formulated by blending the SR beads and rapidly dispersing microgranules in the ratio of 2: 3, with other excipients. Diffucaps technology was used to prolong the drug release by creating a microenvironment of pH 8 at which drug shows poor solubility.

Lipospheres

Lipospheres are water insoluble nano- and micro-particulates of particle size ranging from 0.2-100 micron in diameter.³⁴ Lipospheres are composed of outer phospholipid layer surrounding the solid inner core. The inner core is comprised of drug alone or drug along with solid carrier. Solid carriers are inert hydrophobic biocompatible materials with a melting range between 30-120°C. For example, waxes, fatty acid esters like ethyl stearate; high molecular weight fatty alcohols like cetostearyl alcohol, cetyl alcohol etc.^{35, 36} One or more layers of phospholipids are embedded into the surface of solid core. A phospholipid is a phosphorylated diacylglyceride molecule or its derivative. Other molecules like lecithin, phosphatidic acid, sphingomyelin can also be used to coat solid core.

Controlled release lipospheres

The release rate of the drug from the liposphere is dependent in part upon the composition of the core, as well as the outer phospholipid layer, and can be altered by varying the composition appropriately.

Lipospheres have been explored as parenteral, topical and oral drug delivery system for local anesthetics, anti inflammatory, antibiotics.

Domb A. et al., have formulated Lidocaine lipospheres using Tristearin as solid carrier, which sustained the drug release upto 24 hrs.³⁵

Lipospheres in ODT

Aceclofenac sustained release lipospheres were formulated using Compritol 888 ATO with cetylalcohol.³⁷ Formulation prepared by using cetyl alcohol: drug at 1:1, ratio showed in vitro drug release till 24 hrs. Sustained release lipospheres were combined into ODT by lyophilization method.

Combining lipospheres into ODT is not yet explored much. There is scope for investigating ODT containing lipospheres.

Miscellaneous Techniques

Miscellaneous Techniques used for Controlled release ODT are provided in table 2.

Table 2: Miscellaneous Techniques used for Controlled release ODT

Drug	Technique for sustained release	Polymers used
Ketoprofen	Spray dried SR granules ³⁸	EudragitRS-30D, Starch 1500 and Polyethylene glycol 6000
Dextromethorphan	Complexation with Ion exchange resin (Amberlite®IRP69) ³⁹	Drug-resin complex coated with Kollicoat SR®30D (Polyvinyl acetate aqueous dispersion)
Nicorandil	Dry emulsion ⁴⁰	Dry emulsion was prepared with Myristyl alcohol and Stearyl alcohol

CONCLUSION

With the rapid acceptance of ODTs by patients and pharmaceutical companies, the market for this dosage form is promising and the product pipeline continues to grow rapidly. Technologies, such as multi particulate coating and micro-encapsulation can be combined with ODTs to provide enhanced therapeutic and commercial benefits. Use of various functional polymers and coating processes can lead to ODTs with controlled release profiles. The microcapsules and pellets are flexible enough for compression without breakage or loss of the modified-release properties and small enough to provide good mouth-feel. Adjusting the coating parameters like thickness, composition, porosity, pH modifying agents, and number of layers, formulator can change the desired plasma profile, which provides additional clinical value to patients.

Future challenges for controlled release ODT manufacturers include reducing costs by finding ways to manufacture with conventional equipment, using versatile packaging and improving mechanical strength of coated particulates to withstand compression forces at the same time getting the desired controlled release profile.

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