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Tableting Of Coated Pellets

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Abstract: Multiparticulate drug delivery systems consist of large number of discrete units, each exhibiting desirable characteristics. They are especially suitable for achieving controlled or delayed release of the drug with lower risk of dose dumping. Various techniques like spheroidal oral drug absorption system (SODAS), programmable oral drug absorption system, pelletized delivery system, and pelletized tablet system were developed for oral delivery of multiparticulates. Pelletized tablet consists of polymer coated drug pellet compressed into a tablet. Tableting of pellet reduces the esophageal residence observed from capsules and improves physico-chemical stability compared with suspensions. Compression of coated pellet is a challenging task as, the polymeric coating may not be able to withstand compression force and drug release may be affected due to separation of coating from the pellet surface during compaction process. Other problems like weight variation, poor hardness and friability were also observed in compression of pellets. They can be overcome by carefully monitoring the process variables like nature of polymer, shape, porosity, and density of pellets, compression force, and content of coated pellets in tabletting blend, wall thickness of pellets and nature of the excipients used. An ideal excipient should prevent direct contact of pellets and act as cushion during compression. Influence of various formulation variables that should be considered and the desired properties of excipients to act as cushioning agents in compression of coated pellets are presented in this article.

Keywords:- Multiparticulates, compression, coated pellets, polymer, one step dry coated technology.

Introduction

Multiparticulate drug delivery systems are mainly dosage forms consisting of large number of small discrete units each exhibiting desirable characteristics. Multiparticulates may be prepared by different methods like pelletization, granulation, spray drying and spray congealing. Drug particles may be entrapped within the multiparticulates (matrix systems) or layered around them (Reservoir systems). They can be modified in many ways to achieve desired drug release profile. Depending on the type of coating material used, sustained release, delayed release, targeted release and pulsatile release can be obtained in addition to improvement of chemical stability, physical characteristics and patient acceptance. The purpose of designing multi particulate drug delivery system is to develop a formulation with all the advantages of single unit formulations. Various techniques like spheroidal oral drug absorption systems (SODAS), programmable oral drug absorption systems, pelletized delivery system, and pelletized tablet systems were developed. In spheroidal oral drug absorption system, the beads are coated with different types of product specific polymers and encapsulated into a hard gelatin capsule. By combining different beads, varying degrees of controlled release profiles can be obtained[1].

Mini tablets programmed to release at various sites in the GIT are incorporated into hard gelatin capsule in programmable oral drug absorption system[2]. In pelletized delivery system, sustained release beads are manufactured by different techniques like pheronization and coated with release modulating polymers. Later, the coated beads are filled into hard gelatin capsules[2]. Polymer coated pellets are compressed into a tablet in pelletized tablets. Pelletized tablets offer various advantages over other systems like high patient compliance, high dose strength administration, and high production rate and less cost over capsules. The other major advantages are reduced risk of local irritation and toxicity, predictable bioavailability, minimized fluctuations in plasma concentration of drug caused by food effects.

Challenges Associated With Compression Of Coated Pellets:

Compression of a coated pellet is a challenging task as the polymeric coating may not withstand the compression force and the drug release may vary due to the unpredictable concentration of deposited polymer left after compaction process and altered surface area during in-vivo dissolution. The optimization of various process variables like compression force required, velocity of the punches, hardness, thickness and porosity of the tablets to be maintained is required.

The surface area of tablet containing pellets can be maintained by compressing material to form a tablet with cup shape. The parameters to be considered during compression of pellets are presented briefly here.

Nature of Polymer:

The polymer used in preparation of pellet plays an important role in drug release after compression. It must have sufficient elastic properties to prevent rupture of coating polymer and plastic properties to accommodate the changes in shape and deformation during tableting. Ethyl cellulose possesses weak mechanical properties and hence the pellets compacted with ethyl cellulose showed loss of sustained properties. Use of pseudo latexes plasticized ethyl cellulose showed minimal effect on mechanical properties of ethyl cellulose making it brittle with low values of puncture strength and elongation. Compression of ethyl cellulose coated diltiazem hydrochloride tablets showed faster drug release compared to non compressed pellets indicating the loss of release properties.[5]

The coatings prepared from organic solvents of ethyl cellulose were more resistant to compaction compared to that of aqueous solutions. The films formed by using organic solvents showed better mechanical properties. To reduce the damage to coating, compressed pellets can be kept in hot air oven above the glass transition temperature which resulted in covering of ruptures due to compression.[3] Brittle character of ethyl cellulose can be overcome by using multilayered beads consisting of alternating layers of ethyl cellulose, drug or cushioning agent.

Crystals, granules or pellets coated with aqueous acrylic polymer dispersions (Eudragit NE 30D, Eudragit RS/RL 30D) were more flexible than ethyl cellulose films and they can be compressed with little damage to the coating.[3]

Thickness of Polymer Coating:-

In general, a thicker coating can prevent damage due to compression than the thinner coating. The deformation characteristics changed with the increased coating. Ability of pellets to undergo plastic deformation as well as elastic deformation increased with increasing coating level.[3] However, an increased coating level caused decrease in tensile strength, yield pressure and increased elastic recovery on ejection. Increasing the punch velocity resulted in decrease in tensile strength of the compacts and increase in both yield pressure and elastic recovery values. The punch velocity dependence increased with increased coating levels.[3] Irrespective of compaction pressure and coating level, the pellets lost their sustained release properties due to compaction.

Pellet Core:-

Not only the film but also the core of pellet should also have sufficient flexibility. It must possess some degree of elasticity, which can accommodate changes in shape and deformation during tableting. It should deform and recover after compression without damage to the coating. Harder pellets were able to withstand compression

forces as they deformed to a lesser degree.[6] Compactability of lactose rich pellets was better than that of micro crystalline cellulose pellets. The poor compactability of micro crystalline cellulose pellets is due to loss of plasticity during wet granulation process. Lactose/micro crystalline cellulose beads were more compressible and exhibited more fracture than micro crystalline cellulose beads.[7] Dicalcium phosphate/microcrystalline cellulose beads underwent plastic flow more easily than the other two bead formulations, had a higher degree of fracture and were more compressible.

MCC pellets containing the plasticizers such as PEG 6000 in the powder mixture can modulate compression behavior of pellets without marked changes in the main dimensions and porosity of the pellets. MCC based bead formulations incorporating wax is more compressible than those made without wax. Presence of wax made the compact to undergo elastic recovery. Hence the desired compaction profile can be obtained by changing bead formulation.

Porosity:-

Increased pellet porosity increased the degree of deformation of pellets during compression and tensile strength of tablets because of formation of stronger inter-granular bonds. The effect of intragranular porosity on drug release is also high. Compacted pellets of high porosity were densely packed and deformed. So the drug release was unaffected. The drug release was markedly increased when low porosity pellets were compacted due to slight densification and deformation. So the use of highly porous pellets was advantageous, in terms of preserving the drug release profile after compaction, compared with pellets of low porosity.[8]

Porosity of pellets depends upon materials such as granulating fluid used in their formation. Increasing the amount of water in the mixture resulted in harder and less porous tablets and a slower drug release. Pellets prepared using 95% ethanol had excellent compressibility compared with that of water.[3]

The final porosity attained after compaction depends on pressure applied. Unlubricated pellets require higher pressures than lubricated.[3]

Size:-

The size of the pellets also affects compaction properties and drug release from the compacted pellets. At the same coating level, smaller pellets were more fragile than larger pellets. This is due to the reason that increased surface area resulted in reduced film thickness[9] It was also found that increase in particle size resulted in more damage to the coating, as indicated by larger difference between the release profile of tablets and uncompressed pellets.

Shape:-

Shape of the pellets was found to affect the compression behavior and tablet forming ability of granular materials. More irregular shape induced more complex compression behavior of granules i.e., more attrition of the granules was induced and increased deformation was resulted.[4] Isometric shaped pellets offer less contact points and uniform drug release when compared with anisometric shaped particles.

Density:-

Density of pellet is required to achieve prolonged gastric residence. The critical density to achieve prolonged gastric residence may lie between 2.4 to 2.8g/cm^3.[4]
Density and size of the pellets play an important role for achieving content and weight uniformity. Segregation may occur when pellets are compressed using excipients with smaller particle size and density.

Use of pellets with a narrow size distribution along with excipients of similar size, shape and density can prevent segregation.[10]

Hardness of Pellets:-

Harder pellets coated with Eudragit L30 D-55 were able to resist the compression forces better when compared with softer, more porous pellets, which deform easier and therefore resulted in a higher degree of film rupture.

Compression Force:-

It is one of the critical parameter that must be optimized. A compaction force of 15KN was required to obtain tablets with a smooth surface. Lower compression forces may result in tablets with granular appearance. The compaction induced pellet deformation was practically complete at 6KN and no change in dissolution rate was observed upon increasing the compression force to 20KN for the pellets of theophylline prepared using Eudragit NE 30 –D.[11] Compression force is decided by Hiestand indices.

Tableting Excipients:-

Several excipients have to be used to assist the compaction process and to prevent rupture and damage of the coated pellets during compression. When, reservoir pellets are compacted without including any excipients, disintegration of the tablet cannot be ensured and matrix tablets are often formed.

An ideal excipient should prevent the direct contact of pellets and act as cushion during compression. It should fill the void space to prevent adhesion and fusion of coated pellets during compression. The filler excipient can be either primary powder particles or in the form of secondary agglomerates such as granules or pellets. The use of agglomerates is preferred because of low risk of segregation owing to difference in particle size.

The physical integrity of tablet components can be maintained by using a polar organic solvent for the preparation of cushioning beads of micro crystalline cellulose (MCC). More compressibility can be achieved by the use of freeze dried MCC. Along with MCC beads, when a hydro carbon wax was incorporated with it, damage of the coat can be minimized. Inclusion of approximately 30% of excipients in the tablet formulation is most often needed to fill the void space between the coated pellets, and to prevent separation of the coatings, so that no significant changes observed in damaging to coatings or drug release[4].

With respect to excipient particle size, particles smaller than 20µm were found to protect the coating irrespective of excipient material used, while larger excipient particles increased the dissolution rate on compaction.[4] It was found that small MCC particles increased dissolution rate.

Differences between the particle size and density of pellets and that of excipient particles lead to segregation of the pellets from the powder blend. The segregation may also result due to vibration and centrifugal force of rotary compression machine. This may result in weight variation and content uniformity problems.

One Step Dry-Coated Tablet Technology (OSDRC):

This technique involves three compression stages. In the first stage, a small amount is compressed which forms the outer layer. In the second stage, first outer layer/core layer complex is formed and in third stage, whole tablet containing upper outer and side outer layer is formed. The first and last layers contain diluents with good formability characteristics while the core layer contains pellets. So the segregation problem does not arise and therefore weight variation and content uniformity problems can be nullified.

Another different approach is to layer the cushioning agents as extra coating layers to the reservoir pellets. One such layer is poly ethylene oxide. It hydrates and forms a sealant for the cracks formed in the rupture polymer coating.

Conclusion:-

Various formulation and process parameters have to be optimized in order to obtain coated tableted pellets having the same release properties as that of the non compacted pellets. The type of polymer selected for the coating of pellets plays an important role in compression. The polymer selected should be in such a way that it should have sufficient elastic and plastic properties so that it can resist the compression force. Pellet core should

also withstand the compression force. The properties of polymer and physico chemical properties of pellets should be controlled during compression of pellets to ensure desired drug release from the tableted pellets. The geometry of tablet is also an important parameter to be considered to develop controlled release from tablets compressed with pellets. Layered tablets can be considered to release the drug immediately and to maintain the drug in systemic circulation up to desired period of time.

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