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REVIEW ON MULTIPARTICULATE SYSTEM

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ABSTRACT

Novel drug delivery offers new ways to administer the medication Multiparticulate system is one of them. It helps to sustained & controlled the dose of drug. Implementation of Multiparticulate system can be done using oral, mucosal, transdermal & pulsatile type of delivery method. The Pelletization, granulation, microspheres, nanoparticles could be used for formulation of multiparticulates system. Multiparticulate drug delivery systems are the most extensively used dosage than unit dosage forms for their improved bioavailability and reduced chances of dose dumping. It serves many applications over traditional system.

Keywords: Multiparticulate system, Pelletization, nanoparticles, NDDS.

INTRODUCTION

The Multiparticulate system can be defined as, the system in particles of drug coated or covered with specialized polymeric membranes & used for controlled or sustained drug action. It is most important type of NOVEL DRUG DELIEVERY SYSTEM (NDDS). Novel drug delivery system is the system which administers the drug unlike the conventional drug release pattern. NDDS release the drug either by controlling release of drug or by sustaining the drug action. Multiparticulate or multiple unit dosage forms are the discrete, small, repetitive units of drugs particle which may or may not possess similar drug release pattern. They can be tailored for pulsatile, controlled or delayed, targeted drug release depending on polymer employed in design.[1, 2]

Sustained Release: In this system the pharmaceutical dosage form is formulated to retard the release of active drug in a way that its appearance in systemic circulation is delayed or prolonged & its plasma profile is sustained in duration. The onset of its pharmacological action is often delayed, & the duration of its desired effect is sustained. [2]

Controlled Release: The release of active drug is occurred in predetermined manner means the release pattern of active drug is calculated before the administration of dose. The release of the drug from dosage form is occurred in concentration per unit time.

Multiparticulate dosage forms, such a beads, microspheres, or engineered granules, can be used to provide a wide range of drug release patterns to meet an area of drug delivery needs. Multiparticulates can be designed to provide extended release, delayed release, pulsatile or bi-phasic release, or even site-specific release of drugs. [2, 3]

Aim & Objectives:

(1) To formulate the dosage form having more bioavailability than the conventional dosage form like single unit dosage tablet, capsule or liquid dosage form like solution, suspension, elixirs, emulsion, etc.

(2) Design of dosage form existing protective action against variable pH of stomach & intestine.

(3) Preparation of dosage form with increase duration of action tends to increase therapeutic effect.

(4) The main objective of this system is to increase

the patient compliance by reducing the dosing frequency. [2, 3, 4]

Implementation: Implementation or application of Multiparticulate system covers the following area –
Oral route: It is the most accepted route for conventional as well as for novel drug delivery system. In conventional dosage form when drug administered it comes to stomach, disintegrate, dissolve, absorbed& distributed to desired site. Release of active drug occurred at a time. While in multiple unit system; firstly the outer most polymer coat get dissolve & then active drug encapsules (single particle of drug or group of drug particles covered by polymer coat) get released with respect to its polymeric membrane thickness means encapsules having thinner coat get dissolve first & the encapsules having thicker membrane later on. After the dissolution active drug comes to exist its therapeutic effect. [5]

Mucosal Drug Delivery: In mucosal drug delivery the drug is combined with polymer; the intact dosage form then get adhered to mucosal lining when administered. The drug released according to increased density of polymer used. It indicates that the polymer having low density get dissolves first.Until the all amount of drug is released from the tablet it is remain adhere to mucosa of stomach or intestine or colon. [6]

Transdermal Drug Delivery: In this system, dosage form is formulated in the form of patch (strip like device containing active drug which directly in contact with inner layer of skin i.e. subcutaneous tissue). It may be composed of one side open & another is covered with protective membrane. The open part is directly in contact with blood vessel, the drug released is occurred in the controlled rate manner. [7]

Intrauterine Drug Delivery: In this system, the drug is released in the form of sustained form. Drug released also affected by body temperature (Copper-T). Intrauterine devices are used in the family planning programme, hormone replacement therapy. [8]

Pulsatile Drug Delivery: It releases a therapeutic agent at a rhythm that ideally matches the required biological concentration for corresponding disease therapy. The disease, which not require a constant release of drug but require pulse of therapeutic concentration in periodic manner. Various techniques available for the pulsatile drug delivery systems are pH dependantsystem, time dependent system, micro-flora activated systems, and etc.which are formulated on the basis of physiology of disease & properties of drug molecule. [9]

Other Routes: Other routes includes nasal, ocular, systemic, parenteral route.

Methods of Preparation: Multiparticulate approaches include formulations in the form of pellets, granules, beads, micro particles and nanoparticles. Recently, much emphasis is being laid on the development of Multiparticulate dosage forms in comparison to single unit systems because of their potential benefits.

A)Pelletization: It is the conversion of fine powder into pellets. These oral multiparticulate drug-delivery systems offer biopharmaceutical advantages with respect to predictable and even distribution and transportation in the gastro-intestinal tract.There are different techniques in the preparation of pellets for a drug which includes hot-melt extrusion, extrusion spheronization, spray drying, spray congealing, roto granulation and drug layering. This Multiparticulate drug delivery system can be used in formulations requiring immediate as well as prolonged release. Hence they can be formulated for chewable and disintegrating tablets. Some important techniques for preparation of pellets are; [10, 13]

a)Extrusion-spheronization: Pellets are produced from mixtures of solids and liquids by the involvement of forming and shaping forces. It involves four main steps:
1) Preparation of wet mass called granulation,
2) Shaping the wet mass into cylinders called extrusion,
3) Breaking up the extrudate & rounding of the particles into spheres called spheronization
4) Drying of pellets. [11, 13]

b) Hot-melt extrusion: A novel method used in preparing matrix pellets for controlled release drug delivery system to overcome the disadvantages associated with wet granulation is called as a hot-melt extrusion method where a thermal agent softens or gets melted during the process to obtain matrix pellets. Its advantages are:
1. It is a simple, efficient and continuous process with fewer processing stages 2.
It does not require drying for long duration since it does not involve water or solvent 3.The absence of water prevents drug degradation
4. It reduces the loss of coating material during coating process. [12, 13]

Advantages of Pelletization:

1) Can be used for patients having difficulty in swallowing and dysphasia, children and geriatrics.
2) Different drugs can be blended and formulated in single unit dosage form thus facilitating delivery of 2 or more chemically compatible or incompatible drugs at the same or different site in GIT.
3) Reduces variations in gastric emptying rates and overall transit time.
4) Pellets with different release mechanisms can be mixed to give a new modified release profile. 5) Have excellent flow and packaging properties.
6) When formulated as modified release dosage form, pellets are less susceptible to dose dumping.
7) Have greater absorption since they disperse freely in GIT.
8) Produces spheroids with high loading capacity of active ingredient without producing extensively large particles.
9) GI irritation are limited spread as the particles spread in the intestine since particles less than 2-3 mm pass pylorus rather than filling level of the stomach.
10) Reduce peak plasma fluctuations and minimize potential side effects without lowering drug bioavailability. [13]

Problems Faced During Pelletization: The size, shape and flow of pellets must be consistent in all batches, since variation in these factors will lead to difference in physiochemical properties of final dosage form. [13]

B) Formulation of beads: These are the preparations, which are prepared by coating drug powder on preformed core called nonpareil seeds (slurry of starch, sucrose & lactose). The rough, core granules are rounded for hours on a coating pan & classified according to size. The drug seeds for drug loaded granules are then coated with slowly dissolving materials, e.g. waxes, polymeric substances, or mixture of both. [14]

C) Granulation: It is the process of conversion of powder to small particles ranging from0.2-0.4mm in size. Granulation helps to modify the flow properties, compression characteristics, packing arrangement, dissolution-disintegration parameters of powder drug. Depending on the methods granulation could be divided in two types, wet granulation & dry granulation. In wet granulation compact mass of powder drug is prepared with the help of addition of liquid or water& then it is sieved to required size granules. In dry granulation, granules are formed without addition of liquid substances. Effectiveness of granules affected by, type & volume of binder used, less or more time required for preparation of wet mass, amount of force applied & rate of drying of granules. The most popular novel granulation techniques are;

1) Pneumatic dry granulation
2) Freeze granulation
3) Foamed binder technology
4) Melt granulation technology
5) Steam Granulation
6) Moisture activated dry granulation
7) Thermal adhesion granulation process. [15, 16, 17]

1) Pneumatic dry granulation: It produces porous granules with the application of pneumatic drying. Granules prepared with this method can be used in sustained release, fast dissolving & coated dosage forms & also suitable for heat & moisture sensitive drugs.

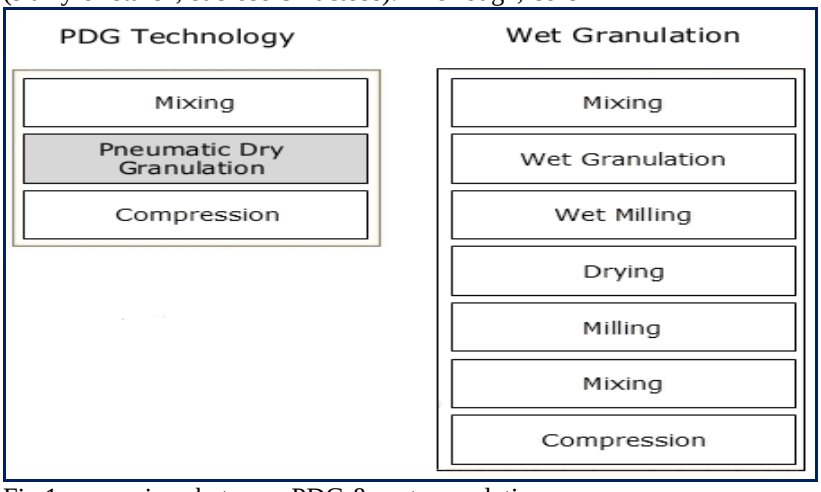

Fig.1 comparison between PDG & wet granulation

Advantages:
i) High drug loading is possible.
ii) As compare to wet granulation speed of manufacturing is more & cost is less.
iii) Helpful in sterile production as dust level is low.iv) Final products are stable.
v) Less quantity of waste material & disintegration of tabletare more.[15, 16]

2) Freeze granulation: In this technique suspension of powder is sprayed in liquid nitrogen, the smaller droplets get immediately frozen, frozen granules subjected to freeze drying, granules get dry without any segregation effect of air drying. Advantages:
i) Control granule density
ii) Oxidation of important constituents prevented by mild drying.
iii) Complete packing of voids & small as well as large quantities of same quality could be formed.
iv) Equipment is easy to clean.
v) Organic solvents can be recycled using distillation process. [16].

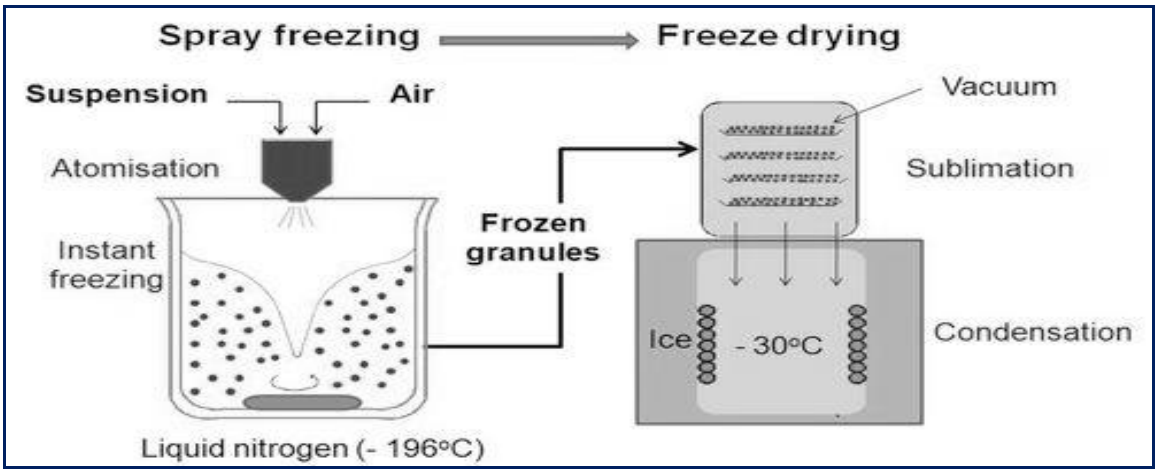

Fig.2 Freeze Drying

3) Foamed binder technology: It requires short time period for processing as water requirement is reduced. In this technique there is incorporation of air in liquid soluble binders such as methylcellulose &hydroxyl propylmethyl cellulose (HPMC). Appearance of resulting foam is like shaving cream.
Advantages:

I. It provides higher surface area & spread rapidly.
II. Easy to handle during processing.
III. Processing variables such as spray patterns, droplet size, and droplet distribution are eliminated. [17]

4) Melt granulation technology: In this technique, molten binder is used or binder get melt during processing. Granules are formed through given steps;
i. Wetting and nucleation: In this step binder comes in contact with drug powder & forms liquid bridges, agglomeration starts.It also involves two steps;
a) Immersion- deposition of fine solid particles on molted binder particles.
b) Distribution-unlike to immersion melted binder solution deposited on fine solid particles.
ii. Coalescence step: it is simple agglomeration step.
iii. Attrition and breakage: It is the fragmentation of formed granules by solidifying the molten mass by tray cooling at ambient temperature.

Advantages:
i. Not requirement of solvent or water
ii.Time consuming drying process eliminated.
iii. Uniform dispersion of fine particles
iv. Stability at varying pH & moisture levels
v. safe application in humans [15, 16, 17]

5) Steam Granulation: in this process there is use of steam instead of water as binding agent. It follow the steam injection method, in which steam is employed at 150^0C., resulting in formation of overheating & excessive wetting turns to formation of lumps & granulating product.
Advantages:
i) Distribution uniformity is high.
ii) Increases diffusion rate into powder.
iii) Granules are more spherical in shape.
iv) Increased dissolution rate from granules as surface area is increased.
v) Tablet processing rate is less resulted in more tablet formation [15, 16, 17]

6) Moisture activated dry granulation:
It uses the moisture absorbing MCC so there is no need to drying as it involves moisture for activation of granules. Wet agglomeration of the powder mixture followed by moisture absorption is the two major steps. Described in the given flow chart;

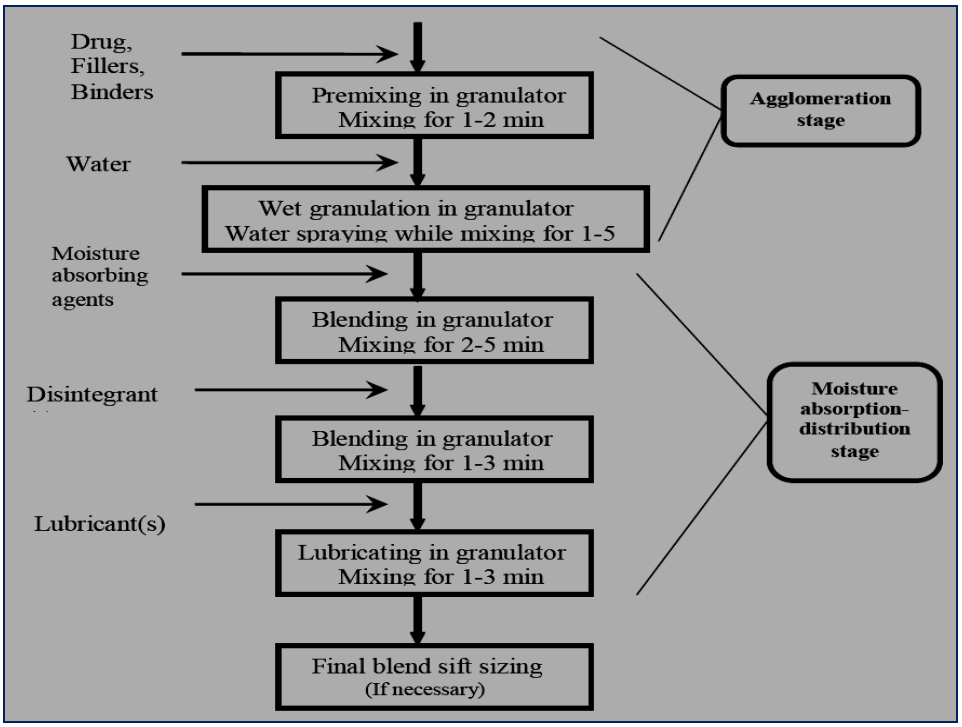

Fig.3: Flow diagram of moisture activated dry granulation process [15, 16, 17]

7. Thermal Adhesion Granulation Process (TAGP)
With this technique one can formulate the tablet like direct compressible tablet. In this technique condition of low moisture contents or low concentration of appropriate solvent is followed, it can be done by using mixture of one or more diluent & active agents, binder & disintegrating agent if required. [15, 16, 17]

Some examples related to multiparticulate drug delivery:

1) Formulation and evaluation of intragastric floating multiparticulate system of Aceclofenac was a successful attempt to improve the micromeritic properties of pure drug, with the help of solvent emulsification technique the floating time of the tablet was increased. [18]
2) An attempt of design and development of oral mucoadhesive Multiparticulate formulation of atenolol, using ionic gelation technique to increase the swelling index & mucoadhesive property as well. [19]
3) Formulations containing theophylline or cimetidine granulated with Eudragit RS 30D were developed and beads were produced by extrusion-spheronization, solubility of active drug used increased. [20]

Conclusion: This Multiparticulate drug delivery system can be used in formulations requiring immediate as well as prolonged release. Hence they can be formulated for chewable and disintegrating tablets. Multiparticulate drug delivery systems are the most extensively used dosage than unit dosage forms for their improved bioavailability because of increased surface area, reduced inter-subject variation, good distribution and transportation and reduced chances of dose dumping. Multiparticulate formulations can have several advantages over single-unit controlled release dosage forms. They tend to exhibit more uniform gastric emptying as compared to single-unit dosage forms, which can be important for dosage forms with time-based release mechanisms. Multiparticulate also have significantly lower risk of dose-dumping than do single unit dosage forms, because the dose is distributed among many provide more complex and customized release profiles, such as bi-phasic release using drug delivery units rather than being constrained to one unit.

REFERENCES

1. N.S. Dey, S Majumdar and MEB Rao Review Article on Multiparticulate Drug Delivery Systems for Controlled Release, Tropical Journal of Pharmaceutical Research, September 2008; 7 (3): 1067-1075.
2. Ioan Tomufiv And Sorin E. Leucufia Development And In Vitro Evaluation Of Multiparticulate Sustained Release Carbamazepine Formulation Acta Poloniae Pharmaceutica And Drug Research, 2012 Vol. 69 No. 5 Pp. 951and 964.
3. Shailesh L. Patwekar, Mahesh. K. Baramade Research Article Controlled Release Approach To Novel Multiparticulate Drug Delivery System, International Journal Of Pharmacy And Pharmaceutical Sciences 2012 Vol 4, Issue 3,Issn- 0975-1491.
4. Bipin Gandhi And Jagdish Baheti Review Article Multiparticulates Drug Delivery Systems, International Journal Of Pharmaceutical And Chemical Sciences ISSN: 2277-5005.
5. Tanmoy Ghosh, Amitava Ghosh Drug Delivery Through Osmotic Systems – An Overview Journal Of Applied Pharmaceutical Science 2011 01 (02); 2011: 38-49.
6. Madan Jyotsana, Banode Sagar, Dangi Mahesh Review Article Mucosal Drug Delivery System International Journal Of Research In Ayurveda & Pharmacy, Sep-Oct 2010 Volume 1, Issue 1, 63-70.
7. Latheeshjlal L, P. Phanitejaswini, Y. Soujanya, U. Swapna, V. Sarika, G. Moulika, Transdermal Drug Delivery Systems: An Overview International Journal of PharmTech Research CODEN (USA): Oct-Dec 2011 IJPRIF ISSN : 0974-4304 Vol.3, No.4, pp 2140-2148.
8. Debjit Bhowmik , Chiranjib , Biswajit , Vinod Dubey , K. K. Tripathi , K. P. Sampath Kumar Recent advances in Intrauterine Drug Delivery System Annals of Biological Research 2010, 1 (1): 70-75.
9. Hema Jaiswal and Farogh Ahsan , Juber Akhtar , Badruddeen Pulsatile Drug Delivery System: A Boon In Patient Compliance European Journal of Biomedical AND Pharmaceutical sciences ISSN 2349-8870 Year: 2015 Volume: 2 Issue: 7 139-148.
10. Bipin R Gandhi, Bhatu P Badgujar, Ankit V Kasliwal Research Article Development And In Vitro Evaluation Of Multiparticulate System Using Novel Coating Material For Controlled Drug Delivery System International Journal Of Pharmacy And Pharmaceutical Sciences 2011 Issn- 0975-1491 Vol 3, Issue 3.
11. Shyamala Bhaskaran and Lakshmi. P.K Extrusion Spheronization –A Review International Journal of PharmTech Research CODEN (USA): , Oct-Dec 2010.IJPRIF ISSN : 0974-4304 Vol.2, No.4, pp 2429-2433.
12. Ankit Patel, Deepak Sahu et. Al A Review of Hot Melt Extrusion Technique International Journal of Innovative Research in Science, Engineering and Technology June 2013 Vol. 2, Issue 6.
13. Jagan Mohan Kandukuri, Venkatesham Allenki , Chandra Mohan Eaga, Vasu Keshetty, Kiran Kumar Jannu Review Article Pelletization Techniques for Oral Drug Delivery International Journal of Pharmaceutical Sciences and Drug Research 2009; 1(2): 63-70.
14. Durga Jaiswal, Arundhati Bhattacharya , Indranil Kumar Yadav, Hari Pratap Singh , Dinesh Chandra And D.A. Jain Research Article Formulation And Evaluation Of Oil Entrapped Floating Alginate International Journal Of Pharmacy And Pharmaceutical Sciences, , Nov.-Dec. 2009 Vol. 1, Suppl 1.
15. Balakrishna Koppukonda , Venkatareddy K, T. Venkateswara Rao Advanced granulation technologies: a review Indian Journal of Research in Pharmacy and Biotechnology ISSN: 2321-5674(Print); 2320 – 3471.
16. Sayyed Sarfaraz Ali Riyasat Ali , Dr. O. G. Bhusnure, R. S. Pentewar, S. B. Gholve, S. V. Gapat, V. K. Morkande, An Overview: Emphasis On Novel Granulation Technologies World Journal Of Pharmaceutical Research Volume 4, Issue 11, 612-630.
17. Himanshu.K.Solanki , Tarashankar Basuri, Jalaram H.Thakkar, Chirag A. Patel Review Article Recent Advances In Granulation Technology International Journal Of Pharmaceutical Sciences Review And Research Volume 5, Issue 3, November – December 2010; Article-008.
18. Keerthi Kancharla, B.V.Basavaraj, S.Bharath, R.Deveswaran and V.Madhavan Formulation and evaluation of intragastric floating multiparticulate system of Aceclofenac Scholars Research Library Der Pharmacia Lettre, 2011, 3(2): 238-245.
19. hadab Md, Gourav K. Singh, Alka Ahuja, Roop K. Khar, Sanjula Baboota, Jasjeet K. Sahni, Javed Ali review Mucoadhesive Microspheres as a Controlled Drug Delivery System for Gastroretention Systematic Reviews in Pharmacy, January-December 2012.Vol 3 ,Issue 1
20. M. Harisha Kumari, K. Samatha, Anna Balaji And M.S. Uma Shankar Recent Novel Advandcements In Pellet Formulation: A Review International Journal Of Pharmaceutical Sciences And Research 3803 Ijpsr (2013), Vol. 4, Issue 10