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Multiple Unit Particle Systems (MUPS), a Versatile Strategy for Controlled Drug Delivery: Focus on Formulation and Process Concerns

Kallakunta VR, Sarabu S and Tiwari RV*

Department of Pharmaceutics and Drug Delivery, School of Pharmacy, The University of Mississippi, University, Mississippi 38677, USA

Abstract

In oral drug delivery modified release dosage forms (MRD) plays an important role in regulating the drug delivery to improve the quality of therapy. One excellent technique to formulate MRDs is multiple unit particle systems (MUPS), where the dosage form is distributed over multiple units rather than a single unit. This unique feature of MUPS makes them a suitable candidate for the delivery of different types of drug molecules for a variety of therapeutic purposes. The current techniques like fluidized bed granulation and, extrusion and spheronization are promising in maintaining uniformity of dosage form and successful drug delivery at the desired site or maintaining the desired time profile of drug delivery. Apart from formulation strategies more focus is required in process optimization and scale-up issues to broaden the range of application of MUPS to different drug candidates and drug delivery systems.

Keywords: Multiple unit particle systems (MUPS); Granulation; Bioavailability; Pellets

Introduction

In oral drug delivery modified release dosage forms (MRD) are the well suited option for controlled drug release in gastro-intestinal tract (GIT) instead of the conventional immediate release dosage forms (IRD). The MRDs are meant for the altering drug release and absorption with an intention to deliver the drug to different regions of GIT or for timely release of the dose. These dosage forms also help in maintaining the required plasma level of the drug over a long period of time. A simple way of formulating MRDs is multiple unit particle systems (MUPS) which contains pellets and all the units are integrated to form a single unit. MUPS may exist as pellets, powders, crystals, non-pareil sugar spheres, mini-tablets, coated particles etc. [1]. The particle size of less than 2 mm facilitates uniform drug absorption of the drug over the large surface area in GIT and more uniform drug absorption profile is assured compared to conventional unit dosage forms. This kind of particular distribution of dosage form assures more consistency in bioavailability by avoiding the problem of dose dumping [2]. These MUPS can be formulated into commonly used dosage forms like tablets and capsules, which makes them more economical and stable in terms of shelf life of the final dosage form [3]. The type of coating process required for MUPS can be done generally by using a fluidized bed coaster where the initial drug coat will be performed on pellets followed by further functional coatings depending on the formulation of dosage forms. Figure 1 represents a MUPS based tablet in which MUPS are admixed with other excipients and compressed into a tablet. Generally, MUPS are divided into 2 types of systems one is comprised of coated pellets and the other one is with uncoated pellets. The coated pellets will be acting as a reservoir system and uncoated pellets follow a general matrix pattern. In both cases, excipients should be separated from particular systems and should not interfere with the functionality of particles.

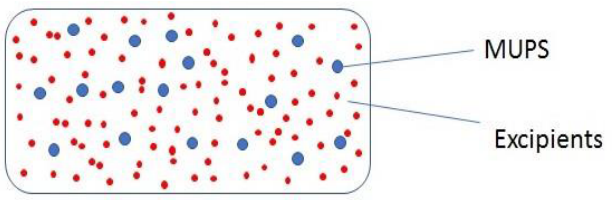

Figure 1: A general representation of MUPS tablet.

a) Coated pellets: Basically the coated particles are prepared by coating the required polymer on the spheres in a layer wise manner. The functionality of the dosage form depends on the type of functional coating on pellets (Figure 2). For e.g. Surelease® (Ethyl cellulose dispersion with 25% solid content for sustained release), Eudragit EPO® (methacrylic based polymer soluble above pH 5) [4].

b) Uncoated pellets: These pellets are usually produced by extrusion and spheronization process and the behavior of matrix depend on the excipients incorporated. Waxes like glyceryl behenate or agents like xanthum gum can be incorporated in the pellet matrix depending on the desired drug release profile [5,6].

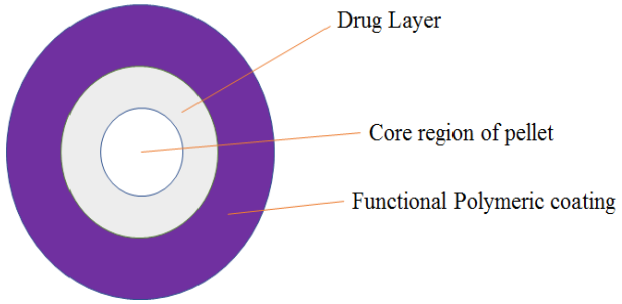

Figure 2: Schematic representation of different layers of a single unit in MUPS.

***Corresonding author:** Tiwari RV, Department of Pharmaceutics and Drug Delivery, School of Pharmacy, The University of Mississippi, University, Mississippi 38677, USA, Tel: +1 662-915-7211; E-mail: roshanvt@gmail.com

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Applications of MUPS in different drug delivery systems

MUPS is a versatile technology for preparation of different types of dosage forms intended for spatial and temporal drug release, especially enteric release, colon targeting and circadian controlled drug release, etc. MUPS are advantageous over normal conventional tablets which follow the all or none effect where as MUPS assure the availability of drug at the required site or the time and maintain the concentration of drug levels as per the intention of formulation [7-9].

In GRDDS (gastro-retentive drug delivery systems), the main aim is to maintain the drug in the stomach or upper GIT for the required period of time. In the floating type of GRDDS the particles will float on the gastric fluids for a definite period and the drug will be released at the proximity of the absorption window for the drug. A MUPS based floating drug delivery system was developed for Dipyridamole with the help of water soluble excipients like lactose, mannitol, which dissolve in aqueous gastric medium and the porous matrix provides buoyancy for the dosage form and functional polymers ethyl cellulose and Eudragit NE 30D® which help in the prolonged drug release up to 12 h [10]. In another study of Zolpidem tartrate floating pellets, the two functional coatings were sprayed on drug layered sugar spheres. The inner effervescent layer containing sodium bicarbonate (12% weight gain on drug layered spheres) which was plasticized into HPMC (hydroxyl propyl methyl cellulose) with the help of PEG (poly ethylene glycol 6000 (10% weight of HPMC weight) providing the floating ability for the system [11]. A study of bio-adhesive GRDDS was reported by Zhanga et al., 2016 in which Ofloxacin bio -adhesive system was formulated with the help of Carbomer® 934P. In this formulation release was retarded by a mixture of polymers Surelease® E-7-10940 and Eudragit NE 30D® in 2:2 ratio and weight gain of functional polymers was 15% of the core pelletscoating [12].

The premature drug release in the stomach may degrade drugs which are acid labile and some molecules may be potent gastric irritants [13]. The enteric coatings can be performed on the drug-layered pellets by using anionic polymers of methacrylates and methacrylic acid like Eudragit L30D® 55 (dissolves at pH >5.5) or Eudragit FS30D ® (dissolves at pH> 7) which prevent the drug release in the stomach and extend the drug release for the rest of the period. In a study reported by Rok et al., 2011 enteric release coting was performed with Eudragit L30D® 55 (14-25% weight gain on core pellets) with a plasticizer combination of triethyl citrate (TEC) (10-20% weight of dry polymer [14]. Polymers like Eudragit L100® can be used for targeted release in colon area for drugs like celecoxib as these polymeric coating dissolves in pH above 6 [15]. These specific kinds of coatings enable the control over the drug release in specific regions that adds more therapeutic value to the treatment. Moreover, in combinations of 2 or more drugs MUPS provide an advantage of maintaining different time profiles for the release of different drugs which provides a better option for combinatorial formulations. Metformin has a lower half-life of 4 h compared to Sitagliptin phosphate (half-life of 12.4 h). To develop a formulation for sustained drug delivery up to 12 h, metformin was formulated as enteric coated, sustained releasing part where as Sitagliptin phosphate was incorporated as IR pellets. This combination provided a sustained release without any dose dumping for this combination [16]. Circadian timing of drug release is the critical factor in patient survival in severe conditions like asthma and angina pectoris. In these conditions, drug release should be pulsatile and untimely release can be fatal which makes MUPS a potential options for this kind of delivery systems [17]. Such example is Isosorbide 5 mono-nitrate coated micro crystalline cellulose pellets and these pellets were further coated with Eudragit NE 30D® (at 8, 13 and 15% weight gain of polymer) to maintain a lag period of 4 h before drug release and the drug release was extended up to 10 h) [18]. This pulsatile release of the drug can be a crucial tool in the treatment of heart patients in whom the frequency of attack is higher between midnight to early in the morning [19].

Technologies suitable to MUPS and process constraints

The formulation and process issues like formation of a homogeneous film on pellet and further coatings need the optimization of many parameters, which depends on polymer, plasticizer, desired release profiles, the amount of the polymeric coating coated and compression behavior of pellets. The integrity of the film can be modified by choosing right polymer or plasticizer. In a reported study acetyl salicylic acid and indomethacin pellets coated with Eudragit L30D® 55 shown compression induced cracks when exposed to simulated gastric fluid and the problem was solved by adding another flexible polymer Eudragit® NE30D [20]. Similar kind of results were published for Lansprazole pellets where Eudragit® L30D55: Eudragit® NE30D ratio was maintained at 9:1 ratio and triethyl citrate (TEC) was incorporated as a plasticizer at 20% w/w concentration [21]. The physico-chemical properties of the plasticizer are also very crucial as they can affect the drug release. The plasticizer which forms an integral part of functional coating controls the elasticity and permeability of the polymeric layer on the core pellets. The reports suggest that the amount of verapamil hydrochloride released varied from the MUPS which have a Kollicoat® SR 30D as a functional polymer and triethyl citrate (TEC), dibutyl sebacate (DBS) and propylene glycol as plasticizers at 10% w/w proportion. The drug diffused out with higher pace in propylene glycol based formulations, whereas diffusion was slow in the case of TEC and DBS. This behavior can be attributed because of the lower aqueous solubility of TEC and DBS [22]. Table 1 includes some examples of approved, marketed products by USFDA [23].

There are some technologies other than fluid bed granulation were reported to produce MUPS. These includes, wet granulation followed by extrusion and spheronisation [24], hot melt extrusion [25] etc. The other important factor is the compression of MUPS into tablets where the integrity of film should not be damaged. The particles are more prone to damage in tablet die during compression, and smaller particle size helps to avoid the damage to the coat as the particles hides in the porous matrix of excipients [16]. One more strategy to avoid fracture during compression is the incorporation of cushioning agents like PEG, glyceryl behenate which deform on compression and porous grades of excipients like MCC 200, MCC KG-802 [26-28]. Recently prilling was reported as a technique to produce MUPS by Vervaeck et al., 2014. In this study lipids [stearic acid/behenic acid) were mixed with PEG and the mixture is in a molten state, pressurized through a nozzle with needle to form droplets [28].

Conclusion

MUPS offer many advantages in terms of drug delivery and stability of dosage forms. Main constrains in formulation and process are to be balanced to get a desired release profile. Selection of polymers, plasticizer, and optimization of process conditions are crucial in the coating process. In case of compression of MUPS into tablet, the ratio of pellets and other excipients, incorporation of cushioning agents and compression force are the key factors to be focused. Selection of appropriate excipients and optimization of processing conditions is vital in the formulation of MUPS and a balance between all these factors could make MUPS a potential drug delivery option for a variety of molecules.

Brand Name	Drug	Manufacturer	Dosage form	Description	Year of Approval
PRILOSEC®	Omeprazole Magnesium Eq 20 mg of base	AstraZeneca Pharmaceuticals Lp	Tablets	Delayed release dosage form	2003
ORACEA™	Doxycycline-40 mg	Galderma Laboratories Lp	Capsules	Delayed release dosage form	2006
NAPRELAN®	Naproxen sodium 750 mg	Alvogen Malta Operations Ltd	Tablets (IPDAS®-Intestinal protective drug absorption system)	Rapidly disintegrating tablet system combining an IR component and a SR component of micro particles	1996
TOPROL-XL®	Metoprolol succinate 200mg	AstraZeneca Pharmaceuticals Lp	Tablets	Extended Release	1992
CLARINEX-D® 24 HOUR	Desloratidine- 5mg and Pseudoephedrine sulphate -240mg	Merck Sharp and Dohme Corp	Tablets	Extended release tablets	2005
NEXIUM®	Esomeprazole Magnesium Eq to 40 mg of base	AstraZeneca Pharmaceuticals Lp	Capsule	Delayed release pellets	2001
PREVACID®	Lansoprazole- 30 mg	Takeda Pharmaceuticals USA Inc.	Tablet	Delayed release, orally disintegrating	2002
PREVACID 24 HR®	Lansoprazole- 15 mg	GlaxoSmithKline Consumer Healthcare	Capsule	Delayed release pellets	2009

Table 1: Some examples of marketed products of MUPS approved by USFDA.

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